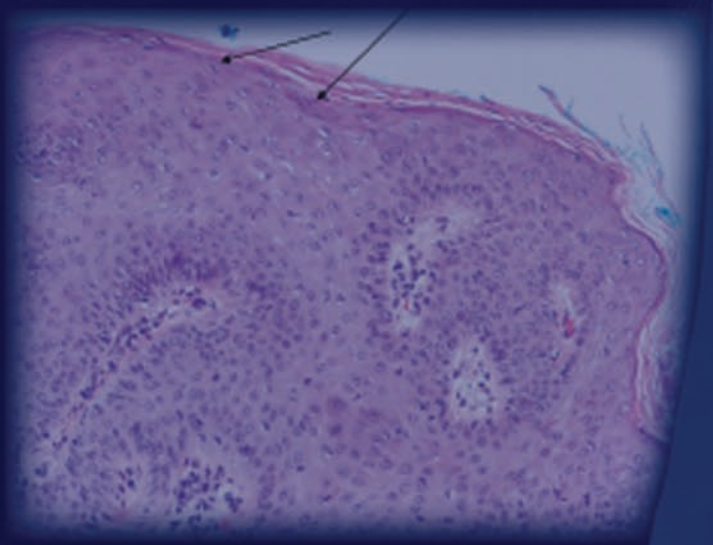
SECOND EDITION

THE VULVA

Physiology and Clinical Management



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The Vulva

Physiology and Clinical Management

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For my adored Mother and Father: your countless sacrifices have formed my world and given me the gift of purpose and strength of will to succeed. Wherever you are, I am nourished and guided by your never-ending love.

Miranda A. Farage

Contents

Foreword

This is a much-needed book for the patient with vulvovaginal symptomatology who too often faces the prospect of an incomplete evaluation and misdirected therapies. There are many reasons for this. Physicians with practice time constraints magnified by an office full of waiting patients too often begin their physical examination with the introduction of the vaginal speculum, bypassing the vulva. In addition, the record of diagnostic accuracy of vaginal infections by physicians shows a high error rate, and inaccurate diagnoses lead to inappropriate therapeutic interventions, which only prolong and sometimes intensify a patient's symptomatology. Finally, to a large extent, the care of patients with vulvovaginal problems requires dermatologic insights that are too often lacking for many practitioners.

The editors of this second edition, Miranda A. Farage and Howard I. Maibach, attempt to address these shortcomings, and I applaud their efforts. They have selected experts who have both the knowledge and the ability to organize their prose that captures reader attention and accomplishes reader understanding. The underlying philosophy of this book is to provide an in-depth exposé of the anatomy and physiology of the vulva: a basis for the understanding of the pathophysiology and one that sets a goal to be achieved with appropriate therapy. This is followed by an exposition of the myriad presentations of patients with a wide range of vulvovaginal diseases and current scientifically accepted treatment regimens. There is an excellent analysis of the menstrual cycle, lochia, and the range of health care products that are now available to women. Since medicine is not practiced in a vacuum, the influences of race and societal norms on women are provided in detail. Finally, there is a fascinating section that provides an in-depth review of newer investigational techniques that will influence the future care of women.

This second edition is for all readers. For me, it is a cover-to-cover joy to read. For others, it will be a valuable office reference to be opened every day in order to address the problems of individual patient care. My congratulations to both the editors and the authors. Obviously, this is a labor of love that hits the mark.

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Preface

Few books are devoted exclusively to the vulva. We have been in pursuit to break the menstrual and genital area taboos that still exist today on a global basis and move to scientific empowerments. Researchers studying the vulva and clinicians treating patients with vulvar conditions know that there is a paucity of information about the vulva in the medical/scientific literature. Consequently, the unique physiology of the vulva, its normal and diseased states, pertinent cultural and hygiene practices that affect vulvar health, menstrual cycles, and the direction of current investigative research are not widely recognized. This insufficient body of information is responsible for the existing deficiencies in knowledge of the vulva, education and training of physicians about vulvar conditions, and appropriate diagnosis and treatment of vulvar pathology. In addition, the assumption that vulva skin is exactly like the skin of external body surfaces is wrong. Vulvar tissue has many unique physiological properties and characteristics that differentiate it from the skin and tissue of other body sites.

We attempt to redress these deficiencies with this second edition volume, *The Vulva*, and strengthening the compilation of up-to-date clinical, physiological, sensorial, disease states, symptomology and research information collected in one comprehensive 2nd edition work.

The Vulva, *Second Edition*, was updated primarily for medical and scientific audiences to underscore unique aspects of vulvar physiology, menstruation, to highlight possible ethnic differences, to review vulvar diseases, to alert researchers and clinicians to cultural and hygiene practices that affect vulvar health, to share the latest techniques in investigative research on vulvar tissue, and most importantly to break the taboo and move the science forward. *The Vulva* includes chapters on vulvar anatomy, physiology, microbiology, age-related changes, ethnicity, diseases, symptoms, current therapies, global cultural and hygiene practices, vulvar care, personal products used on the vulva, and toxicological and bioengineering research methods applied to vulvar research.

The information included in this second edition book presents the current knowledge and understanding of vulvology and its clinical management. Although this work attempts to be a comprehensive and up-to-date resource, we acknowledge that research on the vulva still lags other fields study. Researchers and clinicians who have contributed to this volume hope to continue promoting a better understanding of the unique physiology of the vulva and to encourage needed research.

This book is intended to continue to increase awareness of the unique health concerns of the genital and vulva areas and to be a valuable resource on the vulva region for the medical and scientific communities.

The editors welcome any suggestions and ideas for the third edition.

Miranda A. Farage and Howard I. Maibach

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Many appreciations and thanks are gratefully owed to the many people who contributed knowingly and indirectly to this book.

The following readers generously offered their time and expertise to peer-review relevant chapters: Drs. Kenneth W. Miller, G. Collier, Ms. Lisa Lennon, Drs. Tom Osborn, Brian Gray, Ray Warren, Mr. Ron Visscher, Mr. J. Cooper, Mr. Kevin Johnson, and Dr. Ninah Enane-Anderson. Their collective recommendations have vastly improved the texts assembled here. Many thanks go to the efforts, valuable time, and help of all the contributors of this book.

This book represents the fruits of a jointly conceived and executed venture and has benefited from partners. Our deepest gratefulness and appreciations go to Dr. Sharon Mitchell and Dr. Ninah Enane-Anderson for their genuine support and encouragements. No praise is excessive from Ms. Lisa Lennon's help and efforts for which she has our heartfelt gratitude. Our deepest and most sincere debt is owed to an exceptional person who shepherded the book from start to finish, Dr. Kenneth W. Miller without whose belief, support, help, encouragement, guidance and understanding, this book would not have seen the light of day.

We would also like to single out Mr. Robert Peden, acquisitions editor, for a special recognition. His great efforts, time, discipline, and dedication helped moved this book forward on a timely and organized manner.

Above all, our everlasting gratitude, thanks and love go to our families, children, and spouses who supported, helped, and encouraged us all the way with their incredible patience. Your continuous care, unconditional love, and sacrifice made all this possible, and easier to achieve.

Miranda A. Farage and Howard I. Maibach

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PART 1

Anatomy and Physiology

1

Anatomy of the vulva

Aikaterini Deliveliotou and George Creatsas

INTRODUCTION

The vulva, or pudendum, is a collective term for the external female genital organs that are visible in the perineal area. Knowledge of the basic anatomy of the vulva is necessary in order to understand its physiology and appropriately recognize the wide spectrum of vulvar pathology. To achieve these goals, the vulvar embryology is first presented, before describing the anatomy of the vulva in women of reproductive age. Lifetime changes in the vulva from birth to adulthood are described in Chapter 3.

EMBRYOLOGY OF VULVA

Early in the fifth week of embryonic life, the cloaca is divided by the urorectal septum, which gives rise to the perineum. Folds of tissue form on either side of the cloaca: the anterior folds are urogenital and the posterior folds are anal. The anterior folds meet at the midline to form the genital tubercle. The genital tubercle enlarges. In the male embryo, under the influence of androgens, the genital tubercle becomes the penis; in the female embryo, growth slows and it becomes the clitoris. On either side of the tubercle, the urogenital folds form the labia minora. In the indifferent stage, the labioscrotal swellings develop on either side of the urogenital folds. In the male embryo, under the influence of androgens, they differentiate into the scrotum; in the female, lacking androgenic stimulation, they remain largely unfused to become the labia majora. The definitive urogenital sinus gives rise to the vaginal vestibule, into which the urethra, vagina, and greater vestibular glands open.

ANATOMY OF THE VULVA

The vulva consists of the mons pubis, the labia majora, the labia minora, the clitoris, the hymen, the vestibule of the vagina, the urethral orifice, Skene's glands, Bartholin's glands, and the vestibular bulbs (Figure 1.1).

Anatomy of the Vulva

The anterior and posterior boundaries of the vulva extend from the mons pubis to the anus, respectively; its lateral boundaries lie at the genitocrural folds. The vulvar epithelium exhibits regional differences in tissue structure based on embryonic derivation. The skin-bearing mons pubis, perineum, and labia are derived from the embryonic ectoderm. Vulvar skin, like skin at other sites, has a keratinized, stratified, squamous epithelial structure with hair follicles, sebaceous glands, and sweat glands. The thickness of the degree of keratinization of vulvar skin decreases progressively from the labia majora, over the clitoris, to the labia minora. The vulvar vestibule, derived from the embryonic endoderm, is nonkeratinized. Chapter 2 describes in detail the regional tissue structure of the vulva.

Mons Pubis

The mons pubis (mons Veneris) is the rounded eminence in front of the pubic symphysis, which is formed by a collection of adipose tissue beneath the integument. During puberty, it becomes covered with hair up to its junction with the abdominal wall. The hair pattern, or escutcheon, of most women is triangular. Genetic and racial differences produce a variety of normal hair patterns, with approximately one in four women having a modified escutcheon with a diamond pattern.

Labia Majora

The labia majora are a pair of prominent longitudinal, cutaneous folds of fibro-adipose tissue that are homologous to the scrotum in the male. The structures bear epidermal tissue resembling the dartos tunic of the scrotum, as well as adipose tissue, areolar tissue, blood vessels, nerves, and glands. The labia majora also include the terminal extension of the round ligament and, occasionally, a peritoneal diverticulum, the canal of Nuck.

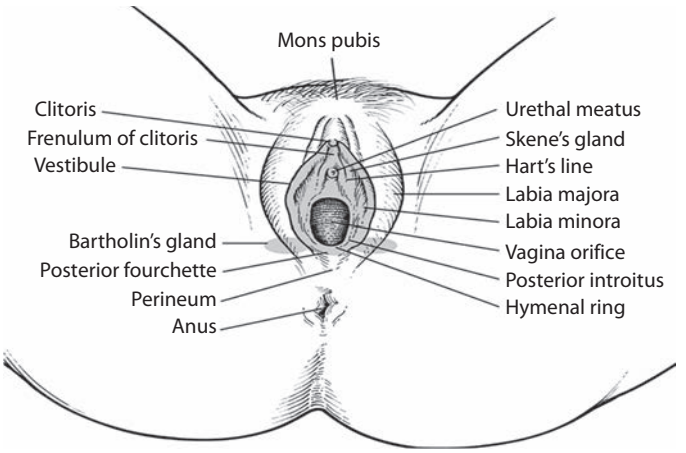

Figure 1.1 Anatomy of the adult vulva. (With kind permission from Libertas Academica Ltd, from Farage MA et al. *Clin Med Womens Health* 2010; 3: 1–13.)

The size of the labia majora is related to fat content. Each is approximately 7–8 cm in length and 2–3 cm in width. The labia majora extend downward and backward from the mons pubis, thus forming the lateral boundaries of a fissure or cleft (the pudendal cleft or rima) into which the vagina and urethra open.

Each labium majus has two surfaces: the outer surface is pigmented, rugose, and bears pubic hair, sebaceous glands, apocrine glands, and eccrine glands. The inner surface is smooth; it bears sebaceous, apocrine, and eccrine glands but no hair follicles. Vulvar apocrine glands are similar to those of the breast and axillary areas.

The labia majora are thicker in front. Anterior to the clitoris, they join to form the anterior boundary of the pudendal cleft, known as the anterior labial commissure. The labia majora do not surround the pudendal cleft fully; laterally, they remain approximately parallel to it and posteriorly, they gradually merge with the neighboring integument below the juncture of the labia minora (fourchette). The posterior ends of the labia majora and the connecting skin between them form the posterior boundary of the pudendum, known as the posterior labial commissure. The interval between the posterior commissure and the anus is 2.5–3 cm in length and constitutes the perineum.

Labia Minora

The labia minora (nymphae) are two small cutaneous folds that are situated between the labia majora and the vaginal orifice. The labia minora are homologous to the penile urethra and part of the skin of the penis in males. Laterally, they extend obliquely from the clitoris toward the rear for approximately 4 cm on either side of the vaginal orifice. They are shorter and thinner than the labia majora. At the clitoris, the anterior portion of each labium minus divides into two segments. Each upper segment passes anteriorly to the clitoris to meet its fellow of the opposite side, forming a fold, the preputium clitoridis, which overhangs the glans of the clitoris. Each lower segment passes beneath the clitoris, joining with its fellow to form the frenulum, which is attached to the inferior surface of the clitoris. The posterior portions of the labia minora surround the vestibule of the vagina. Their posterior juncture is the fourchette.

Histologically, the labia minora are composed of dense connective tissue, erectile tissue, and elastic fibers. Unlike the labia majora, they do not contain adipose tissue. The skin of the opposed surfaces of the labia minora has numerous sebaceous glands but no hair follicles or sweat glands. Among women of reproductive age, there is significant variation in the size of the labia minora. They are relatively more prominent in children and postmenopausal women.

Clitoris

The clitoris is a short, cylindrical, erectile structure that is 2–3 cm in length at the superior portion of the vestibule. It is the female homologue of the penis. It is situated beneath the anterior labial commissure, partially hidden between the anterior segments of the labia minora. The clitoris consists of a base of two crura that attach to the periosteum of the symphysis pubis. Like the penis, the clitoris has a suspensory ligament and two small muscles, the ischiocavernosi, which are inserted into the crura of the clitoris. The body of the clitoris consists of two cylindrical corpora cavernosa composed of thin-walled, vascular channels that function as erectile tissue. The distal third of the clitoris is a small rounded tubercle (glans clitoridis) that consists of spongy erectile tissue with many nerve endings. Usually, only the glans is visible, with the body of the clitoris positioned beneath the skin surface. The normal glans clitoridis in adult women has a width of less than 1 cm, with an average length of 1.5–2 cm. Age, weight, and oral contraceptive use do not change its anatomic dimensions. Childbearing may influence the size of the clitoris.

Hymen

The hymen is a thin fold of mucous membrane situated at the entrance to the vagina. Between the hymen and the frenulum of the labia minora is a shallow depression, the navicular fossa. The inner edges of the hymen may be in contact with each other, such that the vaginal orifice appears as a cleft between them. The hymen is usually perforated, with many variations in its structure and shape. The most common forms are that of a ring, which is broadest posteriorly, or that of a semilunar fold, with a hollow margin turned toward the pubes. The hymen is rarely cribriform or has inner edges that form a membranous fringe. It can be completely absent or can appear as a complete septum across the lower end of the vagina, a condition known as an imperforate hymen. Small tags or nodules of firm fibrous material, termed carunculae myrtiformes, are the remnants of the hymen in sexually active women. However, the hymen can persist after the first sexual intercourse, so its presence cannot be considered a sign of virginity. Histologically, the hymen is covered by stratified squamous epithelium on both sides and consists of fibrous tissue with a few small blood vessels.

Vestibule

The vestibule is derived from the endoderm, the lowest portion of the embryonic urogenital sinus. It is the cleft posterior to the glans clitoridis and between the labia minora. It can be visualized by holding the labia minora apart. The vestibule extends from the clitoris to the posterior fourchette. Hart's line marks the juncture of the nonkeratinized epithelium of the vulvar vestibule and the keratinized epithelium of the inner surface of the labia minora. The urethral and vaginal orifices as well as the ducts of the greater vestibular glands open into the vestibule. The remnants of the hymen and numerous small mucinous glands are located within the area of the vestibule.

Urethra

The female urethra, a membranous conduit for urine, runs from the urinary bladder to the vestibule and measures 3.5–5 cm in length. The mucosa of the distal third of the urethra is lined with stratified squamous epithelium, whereas the proximal two-thirds are lined with stratified transitional epithelium. The external urethral orifice is 4–6 mm in diameter and is immediately anterior to the vaginal orifice, approximately 2–3 cm beneath the glans clitoridis. Its mucosal edges grossly appear slightly everted, forming a short, sagittal cleft.

Vaginal Orifice

The vaginal orifice is a median slit below and posterior to the opening of the urethra; the hymen surrounds it, so that its size varies inversely with that of the hymen. It opens into the vagina, a neuromuscular vault connecting to the cervix of the

uterus that unsheathes the penis during sexual intercourse, and allows passage of the newborn infant during birth.

Skene's Glands

Skene's or paraurethral glands are homologous to the prostate in the male. They are branched, tubular glands, adjacent to the distal urethra. Usually, Skene's ducts run parallel to the long axis of the urethra for approximately 1 cm before opening into the distal urethra. Sometimes they open into the area just outside the urethral orifice. The duct of the Skene's gland presents an opening on its posterior surface. Skene's glands are the largest of the paraurethral glands; however, many smaller glands empty into the urethra.

Bartholin's Glands

The greater vestibular glands, or Bartholin's glands, are the homologues of the bulbourethral glands (Cowper's glands) in the male. They consist of two small, roundish, reddish–yellow bodies. Bartholin's glands are situated on the posterolateral aspect of the vaginal orifice, in contact with the posterior end of each lateral mass of the bulb of the vestibule. Histologically, the gland is composed of cuboidal epithelium. The duct from each gland is approximately 2 cm in length and is lined by transitional epithelium. Bartholin's ducts open immediately lateral to the hymen into the groove between the hymen and the labia minora. Their mucus secretion helps maintain adequate lubrication. Infection of these glands can result in an abscess.

Vestibular Bulbs

The vestibular bulbs are the homologues of the bulb and adjoining part of the corpus cavernosum urethrae of the male. They consist of two elongated masses of erectile tissue situated on either side of the vaginal orifice and are united to each other in front by a narrow median band termed the pars intermedia. Each lateral mass measures approximately 2.5 cm in length. The distal ends of the vestibular bulbs are adjacent to Bartholin's glands, whereas the proximal ends are tapered and joined to one another by the pars intermedia. Their deep surfaces are in contact with the inferior fascia of the urogenital diaphragm. Each bulb is immediately below the bulbocavernosus muscle.

Muscles of the Vulva

Three types of muscle exist in the vulva:

1. The ischiocavernosus muscle compresses the crura and lowers the clitoris. It originates from the ischial tuberosity and inserts at the ischiopubic bone.
2. The bulbocavernosus muscle compresses the vestibular bulb and dorsal vein of the clitoris. It originates from the perineal body and inserts into the posterior aspect of the clitoris; some fibers pass above the dorsal vein of the clitoris in a sling-like fashion.
3. The superficial transverse perineal muscle holds the perineal body fixed. It originates from the ischial tuberosity and inserts at the central perineal tendon.

Blood Supply of the Vulva

The vulva derives its blood supply from the femoral artery via the external and internal pudendal arteries. Venous drainage occurs via the internal pudendal veins.

Lymphatic Drainage of the Vulva

The vulva drains primarily to the superficial and deep inguinal nodes and along the dorsal vein of the clitoris, directly to the iliac nodes.

Innervation of the Vulva

The innervation of the vulva derives from branches of several nerves, including the ilioinguinal nerve, the genital branch of the genitofemoral nerve, the perineal branch of the lateral femoral cutaneous nerve of the thigh, and the perineal branch of the pudendal nerve.

CONCLUSION

This chapter provided a review of the embryology and anatomy of the vulva in women of reproductive age. This knowledge is necessary in order to understand the vulva's physiology and recognize the wide spectrum of vulvar pathology.

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2

Tissue structure and physiology of the vulva*

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INTRODUCTION

The vulva is composed of specialized tissue with regional differences in embryonic derivation, structure, and morphology. The vulva comprises the mons pubis, the labia majora and minora, the clitoris, the vulvar vestibule surrounding the urethral orifice and vaginal introitus, and the hymen, a membrane at the juncture of the vulvar vestibule and the vagina. This chapter describes variations in epithelial structure, blood flow, hormonal and immune responsiveness, barrier function, permeability, irritant susceptibility, and microbial colonization of the vulva in women of reproductive age (Table 2.1).

VARIATIONS IN EPITHELIAL STRUCTURE

The lower urogenital tract is the only portion of the female anatomy derived from all three embryologic layers (ectoderm, endoderm, and mesoderm) (Table 2.2). In the vulva, cutaneous epithelium derived from the embryonic ectoderm is juxtaposed closely with nonkeratinized epithelium derived from the embryonic endoderm (6,17).

The embryonic ectoderm gives rise to the keratinized cutaneous epithelium of the mons pubis, labia majora, clitoris, labia minora, and perineum. Like skin at other anatomical sites, the epidermis of the mons pubis, labia majora, and perineum has a keratinized, stratified squamous structure with sweat glands, sebaceous glands, and hair follicles (Figure 2.1) (18). The cutaneous thickness and the degree of keratinization are relatively high on the mons pubis and labia majora, but decrease over the anterior portions of the clitoris and decline progressively from the outer surface to the inner surface of the labia minora (19).

The cutaneous epithelium consists of four layers:

1. A basal germinative layer (stratum basale), which rests on the basal lamina between the epidermis and the dermis
2. A spinous or prickle cell layer, forming the bulk of the epidermal thickness (stratum spinosum)
3. A granular layer (stratum granulosum)
4. A surface layer of flattened, keratinized cells embedded in hydrophobic intercellular lipid (stratum corneum)

Three specialized cells—melanocytes, Langerhans cells, and Merkel cells—also reside in the epidermis. Melanocytes represent a tenth to a fifth of the cells in the cutaneous basal layer (20). They convert tyrosine to melanin pigment, which protects the basal cells from ultraviolet damage. Melanocytes respond regionally to hormones: at puberty, pigmentation of the mons pubis and labia majora increases; during pregnancy, steroid hormones stimulate melanogenesis in the areola, nipples, and perineum and on the midline of the anterior abdominal wall.

Langerhans cells are dendritic cells found in the epidermis, in thymic and mucosal tissues, and in lymph nodes. Their chief functions are to sample antigens at the epithelial surface, process them, and present them to circulating T lymphocytes, the activation of which initiates the cell-mediated immune response.

Merkel cells are found in the basal epidermal layer. Their cell bodies form synapse-like contacts with the terminal endings of myelinated nerve fibers. They release neurotransmitters in response to sensory excitation (21). Merkel cells serve as skin mechanoreceptors that shape sensitivity to soft touch.

The nonkeratinized epithelium of the vulvar vestibule is the only portion of the female genital tract of endodermal origin (17,22). The epithelial structure of the vulvar vestibule resembles that of the vagina and buccal mucosa (Figure 2.2) (17,23). Its superficial stratum bears large, moderately flattened cells lacking keratin but containing glycogen granules and, frequently, pyknotic nuclei. Differentiation of the inner epithelial layers is indistinct: loosely packed, polyhedral cells alter in size and organelle density as they migrate upward from the generative basal layer, but do not form clearly demarcated strata as observed in the skin. Langerhans cells are present in the epithelium of the vulvar vestibule.

The vaginal mucosa, like the vestibule, is a nonkeratinized squamous epithelium.

BLOOD FLOW AND INNERVATION

The vulva is a highly vascularized and well-innervated structure (24). Arterial blood supplies the vulva bilaterally and derives from branches of the internal iliac and femoral arteries; venous drainage eventually reaches the femoral and internal iliac veins.

Blood flow in labia majora skin is more than twice that in forearm skin (Table 2.3) (25). Studies of vulvar skin have demonstrated increased blood flow in response to histamine at doses to which forearm skin is unresponsive (26).

Genital blood flow and innervation are central to the sexual response. The surge in genital and vaginal blood flow that accompanies sexual arousal results in genital vasocongestion, engorgement, and heightened lubrication (27,28). A nitric oxide/cyclic guanosine monophosphate pathway mediates smooth muscle relaxation and clitoral and vaginal blood flow during

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Table 2.1 Qualitative Differences between Exposed Skin and Vulvovaginal Epithelia

Characteristic	Exposed skin	Vulvar skin	Vulvar vestibule	Vaginal epithelium
Embryonic derivation	Ectodermal		Endodermal	Mesodermal (estrogen dependent)
Tissue structure	Keratinized, stratified squamous epithelium		Nonkeratinized epithelium with less distinct stratification	
Blood flow	Depends on anatomical site	Higher blood flow than exposed forearm skin	No data	
Hydration	Depends on anatomical site	More hydrated than forearm skin (1,2)	Hydrated by cervicovaginal secretions	
Occlusion	Depends on anatomical site	Greater occlusion than forearm skin	Greater occlusion than exposed skin	
Friction	Depends on anatomical site	Higher coefficient of friction than forearm skin (3)	Not determined	
Hormonal influences	Menstrual cycle variability in water barrier function and susceptibility to irritants (4,5)	Thickness unchanged over the course of menstrual cycle (6) Menstrual cycle variability in barrier function and irritant susceptibility unknown	Not determined	Menstrual cycle variability in epithelial thickness, glycogen content, and nuclear pyknosis (7,8)
Permeability	Varies by site; influenced by skin thickness (9)	Permeability affected by increased hydration and occlusion (10,11)	Significantly more permeable than keratinized skin (12)	
Immune cell densities	Diverse population of immune cells	Langerhans cells most common No difference in Langerhans' cell density between keratinized and nonkeratinized regions (13)		Langerhans' cell densities lowest at fornix, highest at introitus (14)
Microbiology	Diverse population includes *S. aureus*, coagulase-negative staphylococci, streptococci, diphtheroids, yeasts, etc.	Microflora affected by hydration, occlusion, and vaginal and perineal cross-colonization. Higher densities of *S. aureus,* streptococci, lactobacilli, and *Candida* than exposed skin (15)	Microflora influenced by cervicovaginal secretions and perineal and urethral cross-colonization	Highly diverse, mixed aerobic and anaerobic microflora. Acid-producing microbes are dominant in healthy women (16)

Table 2.2 Embryologic Derivation of the Female Lower Urogenital Tract

Origin	Structures
Ectoderm	Skin of the labia majora and part of the labia minora
Endoderm	Vulvar vestibule
	Bladder (except trigone)
	Anterior urethral wall
Mesoderm	Hymenal membrane
	Posterior urethral wall
	Bladder trigone

sexual arousal (28). The sex steroid hormones not only maintain epithelial tissue structure and function, but also sustain genital blood flow and vaginal lubrication in response to pelvic nerve stimulation. Estrogen exerts its vascular effects by regulating endothelial nitric oxide production (29).

The vulva has both somatic and autonomic innervation. Motor components mediate pelvic muscle contraction and vascular engorgement of clitoral and vaginal tissue. Sensory components convey touch, pain, itch, temperature, wetness, distention of the anal canal and vagina, and sensations related to sexual arousal. In the clitoris, nerve fibers from the small and large trunks of the dorsal nerve form extensive plexuses in the deeper regions of the dermis and subcutaneous layers (24). In the upper regions of the dermis, the nerve fibers display terminal fibrils with endings that penetrate the epidermis. These epidermal nerve endings vary from simple axon terminals to highly branched and encapsulated structures. Although such structures are found in other regions of the vulva, they decrease in number in a lateral direction from the clitoris.

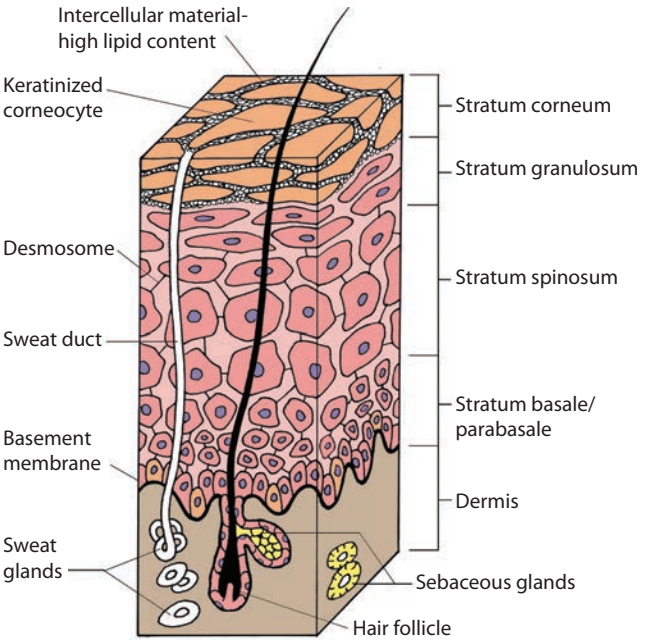

Figure 2.1 Epithelial structure of vulvar skin. (From Farage MA, Maibach HI. *Contact Dermatitis* 2004; 51(4): 201–9. Adapted with permission.)

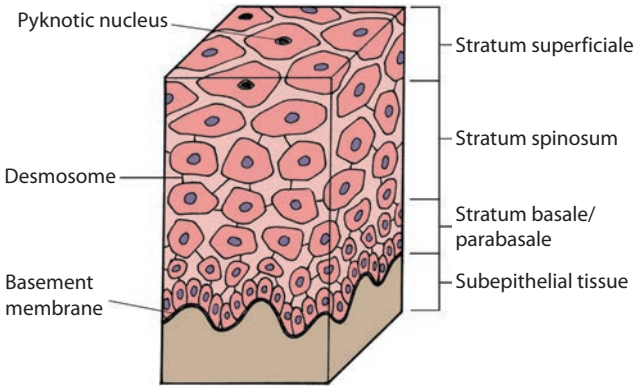

Figure 2.2 Epithelial structure of the vulvar vestibule. (From Farage MA, Maibach HI. *Contact Dermatitis* 2004; 51(4): 201–9. Adapted with permission.)

Innervation of the labia majora differs from that of the rest of the vulva: although both superficial and deep neural nets are present, superficial nerves are reduced markedly. Most nerve endings in the labia majora are parafollicular and do not extend into the epidermis (24).

HORMONAL RESPONSIVENESS

Vulvar skin has a higher concentration of epidermal androgen receptors than skin at nongenital sites (30). At puberty, androgens direct the maturation of vulvar sebaceous glands and hair follicles (31).

The vaginal epithelium has a high level of estrogen receptors and is responsive to ovarian hormone cycling. At midcycle, vaginal epithelial cell proliferation, glycogen content, and nuclear pyknosis increase in response to estrogen. A small but statistically significant increase in vaginal epithelial cell layers has been found at midcycle (8), but no significant difference in epithelial thickness has been observed between follicular and luteal phases (8,32). In postmenopausal women, the lack of ovarian estradiol secretion is associated with long-term thinning of the epithelium, reduced vaginal secretions, and increased pH (33), a condition known as vaginal atrophy.

The concentration of estrogen receptors decreases progressively from the vagina to the vulva, with the lowest levels on keratinized vulvar skin (30). The thickness of the vulvar epithelium remains constant over the course of the menstrual cycle, but its surface cells are predominantly orthokeratotic (lacking nuclei) at the beginning and end of the cycle, and increasingly parakeratotic (bearing a degenerated nucleus) at midcycle (6,7). Progesterone receptors are not found on vulvar skin; they are restricted to the transitional epithelium of the inner aspect of the labia minora and to the nonkeratinized epithelia of the vagina and vulvar vestibule (30).

IMMUNE CELL POPULATIONS

Immune cell infiltration of the vulva is most evident during the reproductive years (31). Langerhans cells are the most common immune cell type in the vulva; intraepithelial and perivascular lymphocytes are found infrequently (13). Langerhans cells are part of the dendritic cell system. They serve as sentinels, sampling antigen at the epithelial surface, then transporting and presenting it in immunogenic form to responsive T

Table 2.3 Quantitative Comparison of Biophysical Variables, Permeability, and Irritant Susceptibilities in Forearm and Labia Majora Skin

Parameter assessed (units)	Forearm	Vulva	Statistical significance (N = number of subjects)	Reference
Transepidermal water loss (g/m² · h)	3.5 ± 0.3	14.5 ± 1.3	$p < 0.001$[a] (N = 44)	(3)
Friction coefficient (μ, unitless)	0.48 ± 0.01	0.66 ± 0.03	$p < 0.001$[a] (N = 44)	(3)
Blood flow (absorbance units)	22.0 ± 3.0	59.5 ± 7.4	$p < 0.001$[a] (N = 9)	(25)
Hydrocortisone penetration (% of applied dose absorbed in 24 hours)	2.8 ± 2.4	8.1 ± 4.1	$p < 0.01$[b] (N = 9)	(11)
Testosterone penetration (% of applied dose absorbed in 24 hours)	20.2 ± 8.1	25.2 ± 6.8	NS[b,c] (N = 9)	(11)
Frequency of irritant reactions to 20% maleic acid solution (%)	62	76	– (N = 21)	(53)
Mean intensity of irritant reactions to 20% maleic acid at 24 hours postapplication (0–3 visual scale)	0.86 ± 0.36	1.29 ± 0.83	$p = 0.036$[a] (N = 21)	(53)
Frequency of irritant reactions to 17% benzalkonium chloride solution (%)	9	57	Not determined (N = 21)	(53)
Mean intensity of irritant reactions to 17% benzalkonium chloride solution at 24 hours postapplication (0–3 visual scale)	0.19 ± 0.33	1.00 ± 0.88	$p = 0.0003$[a] (N = 21)	(53)
Irritant reactions to 1% sodium lauryl sulfate at day 2 postapplication (proportion of scores >1 on a 0–4 scale)	9/10	0/10	$p < 0.05$[d] (N = 10)	(54,55)

[a] Student *t* test.
[b] One-way analysis of variance followed by Neuman–Keuls multiple range test.
[c] Not significant.
[d] Wald–Wolfowitz two-sample test.

lymphocytes in regional lymph nodes. In women, Langerhans cells play a major role in vaginally transmitted HIV infection. They are the first cells to encounter HIV particles, transferring them to their primary targets, the $CD4^+$ T lymphocytes (34). In the murine model, vaginal Langerhans cells are heterogeneous, and at least four populations have been identified by immunohistochemistry and flow cytometry (35). Whether these distinct populations are endowed with specific functions in the immune responses of the vagina is not known at this time.

A gradient in Langerhans cell density exists along the lower female genital tract. In Rhesus macaques, for example, cell densities are lowest at the vaginal fornix and highest at the introitus (14). Human studies demonstrate a higher density of Langerhans cells in the vulva than in the vagina, with no difference between keratinized and nonkeratinized regions (13). The deficit in Langerhans cells in the vagina relative to concentrations in the vulva may be one of several vaginal adaptations to the antigenic challenges posed by resident microbiota and foreign proteins encountered during intercourse. Seminal fluid also contains a variety of inhibitors that suppress immune function in the vagina and cervix.

Langerhans cell densities were estimated at 19 per 100 basal cells in the vulvar epithelium, 13 per 100 basal cells in the cervix, and 6 per 100 basal cells in the vagina. By contrast, lymphocytes predominate in the vagina. The $CD8^+$ subtype is the most common vaginal immune cell, the $CD4^+$ subtype constitutes the second largest population of vaginal immune cells, and tissue macrophages represent the third largest population (32).

Growing evidence suggests that immune responsiveness is modulated differentially along the reproductive tract. Transplantation studies suggest that the cervix is immunologically privileged in order to protect the fetus from maternal alloresponses to antigens in ejaculate (36). Cervical mucus, which protects the entry to the uterus, contains secretory antibodies, particularly IgA. These secretory antibodies inactivate antigens by forming nonabsorbable complexes with them. Cervical mucus is bacteriocidal in the presence of lysozyme and complement, and can agglutinate bacteria and opsonize them for phagocytosis by macrophages.

Different regions of the genital tract exhibit distinct responses to antigens. Antigen application to vulvar skin can result in sensitization; indeed, allergic contact dermatitis to topical agents is a prime contributor to persistent vulvar discomfort (37–39). By contrast, antigen application to nonkeratinized mucosa may induce tolerance. This phenomenon, best characterized in the oral mucosa, is not due to the phenotype of resident Langerhans cells, but results from altered responses at the level of the draining lymph nodes (40,41). Studies in animal models demonstrate that tolerance induction also occurs in the vagina, where the phenomenon is hormonally regulated (42). In mice, vaginally induced tolerance occurred only during the estrogen-dominant phase of the estrus cycle when sperm exposure would occur.

The number and distribution of vaginal immune cells are relatively stable throughout the menstrual cycle (8,32,43), although the thickness of the epithelium peaks at midcycle. However, administration of exogenous contraceptive hormones affects the functional capacity and distribution of vaginal immune cell populations. An increase in the density of vaginal Langerhans cells was observed in response to vaginally administered progesterone (44). The synthetic, long-acting progestin contraceptive depot medroxyprogesterone acetate (DMPA) increased vaginal densities of T cells and of immune cells bearing HLA-DR (a major histocompatibility complex class II receptor) and CCR5 (a chemokine receptor used by HIV to enter and infect host cells) (43). In a study of women using either DMPA, levonorgestrel, or combined oral contraceptives, DMPA caused a selective increase in $CD8^+$ T lymphocytes, levonorgestrel increased the $CD4^+$:$CD8^+$ ratio, and the combined oral contraceptive caused no cell population changes (32).

NuvaRing is a sustained-release, combined contraceptive ring inserted vaginally. It delivers a low dose of synthetic estrogen and etonogestrel (a progestin) to protect against pregnancy for 1 month. NuvaRing and combined oral contraceptive users, but not DMPA users, had lower densities of Langerhans cells in the vaginal epithelium. DMPA users had lower systemic levels of interferon-α (IFN-α). They also exhibited lower cervicovaginal fluid levels of IFN-α, the chemokine CXCL10, monocyte chemotactic protein-1, and granulocyte-colony stimulating factor (45).

Lastly, antimicrobial peptides and proteins, which are secreted by the epithelial tissues of the female genital tract, are increasingly being recognized for their microbicidal and immune modulating properties (reviewed in (46–48)). Among these are secretory leukocyte protease inhibitor, human β-defensin-2), surfactant protein A (SP-A), the cytokines interleukin (IL)-1α and IL-6, and transforming growth factor-β (49,50). SP-A, for example, is produced by a specific vaginal epithelial cell population in the intermediate layer and is also found in vaginal lavage fluid (50). Antimicrobial proteins have a broad spectrum of activity not only against bacteria, but also against fungi and viruses. They suppress bacterially induced cytokine production and induce macrophage chemotaxis and dendritic cell activation in the mucosal tissue.

TISSUE HYDRATION AND BARRIER FUNCTION

Vulvar tissue is more hydrated and has a lower barrier function than exposed skin, as assessed by transepidermal water loss (TEWL), a measure of skin hydration and water barrier function. Water diffuses across the stratum corneum of the labia majora at an elevated rate compared to its rate of diffusion across the stratum corneum of forearm skin (Table 2.3) (1,2). To a degree, this reflects elevated skin hydration due to occlusion. However, vulvar skin also presents an intrinsically lower barrier to water loss: steady-state TEWL values remain higher on the vulva than on the forearm after equilibration with the environment or after the prolonged drying of both sites with a desiccant (2,51). The comparatively greater hydration of occluded vulvar skin raises its friction coefficient (Table 2.3), which may make vulvar skin more susceptible to mechanical damage (3).

PERMEABILITY

Predicting tissue permeability is complex. The phenomenon depends on the extent to which the penetrant partitions into the tissue, the rate at which the penetrant diffuses through the tissue, and the distance to be traversed (52). Consequently, vulvar penetration of exogenous agents is influenced by regional differences in epithelial structure and lipid composition, the physicochemical characteristics of the penetrants, and the nature of the applied vehicle.

Permeability of Labia Majora Skin

Table 2.4 illustrates skin permeability to hydrocortisone by anatomic site (9). Vulvar skin is substantially more permeable

Table 2.4 Relative Permeability to Hydrocortisone (% of Dose Absorbed) by Anatomical Site[a]

Site	Permeability relative to forearm skin
Forearm (ventral)	1.0×
Forearm (dorsal)	1.1×
Foot arch (plantar)	0.14×
Ankle (lateral)	0.42×
Palm	0.83×
Back	1.7×
Scalp	3.5×
Axilla	3.6×
Forehead	6.0×
Vulva (labia majora)[b]	2.8–7.0×
Jaw angle	13.0×
Scrotum	42×

[a] Adapted from Feldmann RJ, Maibach HI. *J Invest Dermatol* 1967; 48: 181–3.

[b] From Britz MB, Maibach HI, Anjo DM. *Arch Dermatol Res* 1980; 267(3): 313–6; Oriba HA, Bucks DA, Maibach HI. *Br J Dermatol* 1996; 134(2): 229–33.

than forearm skin to this agent (10,11). Probable contributing factors include elevated vulvar skin hydration, the higher concentration of hair follicles and sweat glands on vulvar skin, and increased cutaneous blood flow. Tissue penetration rates also depend on the properties of the penetrant. For example, there is no difference in the rate of testosterone penetration through vulvar and forearm skin (Table 2.3) (10,11). However, the skin at both sites is far more permeable to testosterone than to hydrocortisone. This is probably due to the greater hydrophobicity of testosterone and because of the presence of androgen receptors in the skin.

Permeability of the Vulvar Vestibule and Vaginal Epithelium

Nonkeratinized epithelia are more generally permeable to external penetrants. This has been described best in oral tissue, which, like the vulva, displays regional differences in structure and keratinization (56,57). The nonkeratinized buccal mucosa, which resembles the vaginal epithelium morphologically, is 10-fold more permeable to water than is keratinized skin (58). Buccal mucosa is more permeable than the skin to horseradish peroxidase, although absolute penetration rates of this large molecule are lower than those of water (57).

The heightened permeability of nonkeratinized tissue results from several factors. First, the absence of a stratum corneum removes a principal barrier to entry of external agents. Second, the more loosely packed cell layers create a structure with less resistance to paracellular movement, the principal route by which most penetrants traverse tissues (59,60). Third, such tissues have a less-structured lipid barrier with lower resistance to molecular diffusion (61,62).

Finally, thinner epithelia (such as the buccal mucosa and vulvar vestibule) present a shorter path length to be traversed.

Nonkeratinized tissue is also more vulnerable to breaches in tissue integrity, which can augment tissue penetration. For example, buccal tissue was 40-fold more permeable than keratinized skin to the organic base nicotine, an irritant that increases the penetration of coadministered compounds (63,64). The heightened permeability of the vulvar vestibule can be inferred from studies on vaginal and buccal epithelia, which serve as surrogate tissues. Vaginal and buccal epithelia have similar ultrastructural features and lipid compositions. Moreover, comparable tissue penetration rates at coadministration have been observed for a range of model penetrants, including water, estradiol, vasopressin, and low-molecular-weight dextrans (12,65–67). Like the epithelia, the thin, nonkeratinized vulvar vestibule may be more permeable than keratinized skin and more vulnerable to the effects of externally applied agents.

SKIN IRRITATION

Vulvar skin differs from exposed skin in its susceptibility to applied irritants. However, irritant effects are difficult to predict. The available evidence suggests that elevated skin hydration plays a role in vulvar susceptibility to polar irritants. For example, vulvar skin was more reactive than forearm skin to high aqueous concentrations of maleic acid (20% concentration) and benzalkonium chloride (17% concentration) (Table 2.3) (53). Because polar or charged materials do not penetrate the hydrophobic lipid barrier of the stratum corneum readily, the comparatively greater hydration of vulvar skin may have facilitated skin penetration of the polar irritants at this site.

The surfactant sodium lauryl sulfate (SLS) caused a different response. Vulvar skin was less reactive than forearm skin to low concentrations of this agent (Table 2.3) (54,55,68). This result may relate to the structure of the penetrant: the surfactant molecule bears both a charged head and a hydrophobic tail. Notably, hydrophobic molecules partition far more readily into the lipid barrier of the stratum corneum than do charged materials, and lipid partitioning is more favored when the applied medium is relatively polar. In the case of aqueous SLS, skin penetration of the charged head would be highly disfavored; therefore, lipid partitioning of the hydrophobic surfactant tail may have been a driving force for the heightened effects on less hydrated, forearm skin.

An effect of the menstrual cycle on vulvar skin reactions has not been documented. However, evidence from other anatomical sites suggests that skin barrier function and reactivity to irritants may exhibit cyclical variability. Water barrier function on the back and forearm (as measured by baseline TEWL values) was significantly lower on days just prior to menstruation compared to days just prior to ovulation (5). In women, forearm skin exhibited stronger reactions to SLS on day 1 than during days 9–11 of the menstrual cycle, while no difference was detected in a male control group evaluated over the same period (4).

MICROBIOLOGY

Historical studies of vulvar and vaginal microbial colonization have employed traditional culture techniques. Using these techniques, higher cell densities of *Staphylococcus aureus*, coagulase-negative staphylococci, streptococci, diphtheroids, lactobacilli, and yeasts have been measured on the labia majora than on exposed skin (Table 2.5) (15).

Culture-independent methods have recently been applied to characterize vulvar microbiota. A pilot study in five women found a diverse microbiota on the vulva, including populations known to be commensals of the microbiota of the skin, colon, and vagina (69). A greater diversity of microbes inhabited the labia majora compared with the labia minora, although both sites had appreciable numbers of lactobacilli and strict anaerobes. No single species was common to all women. A study in 10 Japanese women compared the microbiota on the labia minora before and during menstruation. Twenty-two genera

Table 2.5 Microbial Cell Densities (CFU/cm²) on Vulvar and Forearm Skin

Organism	Vulva	Forearm
S. aureus	4.1×10^4	1.4×10
Coagulase-negative staphylococci	5.7×10^5	1.8×10^2
Streptococci	3.7×10^2	0.48×10
Lipophilic diphtheroids	7.9×10^5	1.1×10^2
Non-lipophilic diphtheroids	4.6×10^5	1.1×10
Gram-negative rods	1.8×10^3	0.12×10
Lactobacillus species	4.6×10^5	0.96×10
Yeasts	8.2×10	0.8×10

Source: Adapted from Aly R, Britz MB, Maibach HI. *Br J Dermatol* 1979; 101(4): 445–8.
Abbreviation: CFU: colony-forming unit.

were represented (70). The genus *Lactobacillus* predominated in 7 out of the 10 women and *Atopobium vaginae* and *Gardnerella vaginalis* predominated in two others. Six of 10 women exhibited a significantly different profile of vulvar microbiota during menstruation.

Although the afore-referenced pilot studies with culture-independent methods failed to detect *S. aureus*, traditional culture methods suggest that the vulva is the primary site of genital carriage of this microbe; isolation frequencies as high as 60%–70% have been found using traditional selective culture techniques (15). Despite an epidemiological association between vulvar and vaginal carriage of *S. aureus* (71,72), selective culture techniques have detected lower isolation frequencies in the vagina (in the range of 3%–12%) (73–75). However, studies with fluorescence *in situ* hybridization revealed the presence of *S. aureus* in 100% of 44 vaginal specimens obtained from 15 women, while standard microbial culture methods produced positive results in only 34% of the same specimens (76). A study of 47 pregnant and 16 non-pregnant women utilizing selective culture techniques found isolation frequencies of 0%–8.5% in the pregnant women over the course of gestation; *S. aureus* was not detected in the group of non-pregnant women, but the differences in isolation frequencies of this organism between groups were not statistically significant (77).

Microbes derived from the intestinal tract form part of the endogenous vulvovaginal flora. Nonpathogenic levels of such organisms can reside on the perineum, on the external labia majora, and in the vagina. Pathogenic strains of *Escherichia coli* cause urinary tract infections, but the mere presence of *E. coli* microbes on the vulva does not lead to urethral and bladder colonization; host factors and sexual activity play more important roles in determining individual susceptibility to infection (78–80). The most important risk factor for recurrent urinary tract infection in women of reproductive age is sexual intercourse (81,82), which promotes colonization of the introitus and urethra in susceptible women (83–85).

Candida species are found in the endogenous vulvovaginal microflora. These fungi exist as blastopheric spores or as germinative mycelia. The spore form can be associated with symptom-free vulvovaginal colonization, but adhesion, germination, and epithelial invasion are necessary for pathogenesis. Host predisposing factors play a role in the development of frank vulvovaginal candidiasis (VVC). Healthy women appear to possess an innate and noninflammatory form of local immunity that prevents symptomatic infection (86); suppression of this innate immunity is suspected of playing a role in recurrent VVC (87,88). Genetic polymorphisms in mannose binding lectins—surface recognition molecules involved in the immune defense against microorganisms—also play a role in individual susceptibility to *Candida* infection (89,90). Elevated estrogen is another risk factor for symptomatic VVC. Use of high-estrogen oral contraceptives, for example, is linked epidemiologically to an elevated VVC risk (91). Acute episodes of VVC are more common during pregnancy and during the luteal phase of the menstrual cycle, when both estrogen and progesterone levels are elevated; experimental studies indicate that this link relates solely to the elevation of estrogen (92). The mechanism by which estrogen promotes symptomatic infection has not been elucidated fully. Estrogen raises the vaginal concentration of glycogen, which may serve as a nutritional source, and the hormone may act as a growth-promoting signal for some *Candida* strains (93).

People with diabetes mellitus and pregnant women are at elevated risk of developing symptomatic VVC. In these higher-risk groups, the degree of glycemic control plays a role in the prevalence of *Candida* colonization at various body sites (94). In addition, *Candida* adherence to vaginal epithelial cells is enhanced in people with diabetes and during pregnancy (95).

Some studies link antibiotic therapy, which suppresses protective acid-producing microbes in the vagina, to an increased risk of subsequent VVC episodes (96); however, not all studies are consistent in their results, and the association of antibiotic use with clinical candidiasis remains controversial (97).

CONCLUSION

The vulva is a highly specialized tissue with regional distinctions in embryologic derivation and tissue structure. Unique physiological characteristics have been documented in blood flow, innervation, hormonal and immune responsiveness, skin friction, tissue hydration, permeability, and microbial populations. Most of these distinctions appear to represent adaptations to reproductive function. The characteristics of elevated skin friction and skin hydration, coupled with differences in tissue permeability, may also mediate vulvar susceptibility to various exogenous irritants and infectious agents.

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Changes in the vulva and vagina throughout life*

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INTRODUCTION

The vulva and vagina change over the course of life. The most salient changes are hormonally mediated and are linked to the onset of puberty, the menstrual cycle, pregnancy, and menopause. This chapter reviews the morphology and physiology of the vulva and the vagina from infancy to old age (Table 3.1) (1–12).

INFANCY AND EARLY CHILDHOOD

The vulva and vagina of the newborn exhibit the effects of residual maternal estrogens (Figure 3.1). At birth, the labia majora appear plump. The labia minora are well developed and may protrude beyond the labia majora. Similarly, the clitoris may appear disproportionately large. The vaginal introitus is visible but small (typically 4–5 mm in girls under the age of 5 years). The hymen may appear thick and fibriated, a hymenal configuration common in girls under the age of 3 years. Bartholin's glands are visible and Skene's (paraurethral) glands are well formed. The urethral opening is not easily discerned. The vaginal epithelium is glycogen rich and is colonized with lactic acid-producing microbes, such as *Lactobacillus* species, within the first 24 hours of birth (3). A physiologic, white mucoid vaginal discharge may be present. As residual levels of maternal estrogen diminish, this discharge may become tinged with blood from withdrawal endometrial bleeding (1,13).

These estrogenic effects dissipate between the fourth and eighth postnatal weeks. The labia majora lose fat and the prominence of the clitoris and labia minora diminishes (Figure 3.2). The vaginal epithelium loses its stratification and glycogen content and becomes much thinner. The vaginal pH becomes neutral or alkaline, presumably because of a relative deficiency of acid-producing vaginal microbes (4,14). Vulvar skin thickness decreases and the mons pubis and labia majora lose some of the subcutaneous fat present at birth (15,16). Although the full complement of vulvar hair follicles and sebaceous glands is thought to be present from birth, these structures do not mature until the adrenal glands are activated at puberty. The prepubescent labia minora have barely discernible vellus hair follicles that are lost at puberty when the follicles of the labia majora and mons pubis terminally differentiate (15). The appearance of the prepubescent hymen is variable. Two common forms in girls more than 3 years of age are:

1. The annular hymen that surrounds the introitus in a regular fashion
2. The crescentic hymen, a crescent-shaped conformation present along the posterior vaginal orifice only, the ends of which are attached to the lateral vaginal wall

Labial adhesions occur more commonly in younger prepubertal girls (aged 3 months to 6 years, with a peak incidence at 13–23 months of age), creating a flat vulvar appearance (2). This acquired condition is the result of low estrogen levels in the prepubertal child and possibly of a chronic inflammatory process. First-line treatment with estrogen cream is recommended.

A failure to respond to medical therapy requires consideration of other options, which include in-office treatment with manual separation after topical anesthesia or, rarely, separation under sedation in an outpatient setting or surgical suite (17,18).

PUBERTY

Pubertal changes in the vulva and vagina are induced by adrenal and gonadal maturation. Puberty generally begins between 8 and 13 years of age. The physical changes associated with puberty are an accelerated growth rate, the appearance of pubic hair (pubarche), the appearance of axillary hair, breast development (telarche), and the onset of menstruation (menarche). The timing and stages of development of secondary sex characteristics were first defined in Marshall and Tanner's seminal study of 192 girls in a British orphanage (19).

Maturation of the adrenal glands and androgen secretion (adrenarche) begins at about 6 years of age, approximately 2 years before pituitary–gonadal maturation and the production of ovarian steroid hormones (gonadarche). Because adrenarche and gonadarche proceed independently, the appearance of pubic hair does not provide information about pituitary–ovarian maturation. Pubic hair development elicited by androgens proceeds in five stages, as described by Tanner (Figure 3.3) (19):

1. No pubic hair.
2. Sparse hair appears on the labia majora and the mons pubis along the midline.
3. Thickness and coarseness of the hair increase, with coverage of the lobes of the labia majora and increased lateral growth from the midline of the mons pubis.
4. Hair growth increases such that only the upper lateral corners of the mature triangular configuration are deficient.
5. Adult pattern, attained between the ages of 12 and 17 years, with a characteristic horizontal upper margin on the mons pubis just above the limit of the genitofemoral folds.

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Table 3.1 The Vulva and Vagina from Infancy to Old Age

Life stage[a]	Pertinent physiology	Vulvar characteristics	Vaginal features
Newborn	Effects of residual, transplacental maternal estrogens	• Plump labia majora • Well-developed labia minora • Immature hair follicles and sebaceous glands	• Stratified squamous epithelium high in glycogen content • Lactic acid-producing microbes colonize the vagina shortly after birth • White or blood-tinged vaginal discharge may be present (1)
Early childhood	Lack of stimulation by adrenal or gonadal steroid hormones	• Mons pubis and labia majora lose fat • Benign labial adhesions, if present, normalize without treatment (2)	• The vaginal epithelium thins, is less stratified, and has a low glycogen content • Vaginal pH is neutral or alkaline • Cell densities of lactic acid-producing microbes decrease
Puberty	Adrenal and gonadal maturation ensue. Secondary sex characteristics are acquired and menstruation begins (3)	• Subcutaneous fat is deposited in the mons pubis and labia majora • The vulvar epithelium thickens • The labia minora and clitoris become more prominent • Pubic hair emerges	• The vaginal epithelium thickens and stratifies • Cyclical changes in intracellular glycogen content ensue • Cervicovaginal secretions are produced • Cell densities of lactic acid-producing microbes rise (4)
Reproductive years	The menstrual cycle	• The morphology of the vulva is mature • Vulvar skin thickness remains constant throughout the menstrual cycle (6) • Parakeratosis of the vulvar stratum corneum rises at midcycle (5,6)	• Vaginal epithelial thickness, parakeratosis, and glycogen content rise at midcycle (5,6) • Lactic acid-producing microbes are numerically dominant in healthy women (7,8) • Menstrual cyclicity becomes established (9,10) • Cervicovaginal secretions become thicker, clearer, and more elastic prior to ovulation
Pregnancy	Blood volume increases. The menstrual cycle ceases during gestation	• Hair may darken along the midline of the abdomen • Increased blood flow heightens vulvar coloration • Susceptibility to vulvar varicose veins increases (12) • Connective tissue relaxes • Flattening of the fourchette and perineal trauma may occur during delivery	• Connective tissue relaxes and vaginal muscle fibers thicken • The risk of *Candida* infection increases (11) • Following delivery, the morphology and dimensions of the vaginal tract are re-established
Postmenopause	Follicular function and the menstrual cycle cease. The prevalence of urinary and fecal incontinence rises. Physical health, immune function, tissue regeneration capacity, and cognition may be compromised with increasing age	• Pubic hair becomes sparse • Subcutaneous fat is lost • Vulvar tissue atrophies • The risk of perineal dermatitis rises in older women with incontinence	• The vaginal epithelium atrophies • Cervicovaginal secretions become sparse • Vaginal pH rises; colonization by enteric microflora may increase • Atrophic vaginitis is common

Source: Adapted from Farage M, Maibach H. *Arch Gynecol Obstet* 2006; 273(4): 195–202.

[a] Because of inter-individual variations, the age definition of each life stage is approximate. The newborn period lies between birth and 1 month of age; early childhood refers to between 1 and 8 years of age. Puberty usually occurs between 8 and 15 years, although the age criteria for premature puberty are controversial. The reproductive years begin at menarche (mean age of approximately 12 years) and continue through the perimenopause. Menopause is defined as beginning 1 year following the final menstrual period; menstruation ceases at a median age of 50 years in Western industrialized countries.

In most ethnic groups (except for women of Asian or Native American heritage), hair coverage extends from the labia to the upper aspects of the thighs.

Gonadal maturation usually occurs during the 2 years preceding menarche. During the maturation process, follicular development causes estrogen production to rise. The vaginal epithelium thickens and intracellular glycogen production begins. The cervix and vagina increase in size, the vaginal fornices develop, cervicovaginal secretions are produced, and vaginal fluid becomes acidic.

Vulvar morphology matures at this time. Fat deposition occurs in the mons pubis and labia majora. The vulvar epithelium increases in thickness (16), labial skin becomes rugose, the clitoris becomes more prominent, the vestibular glands become

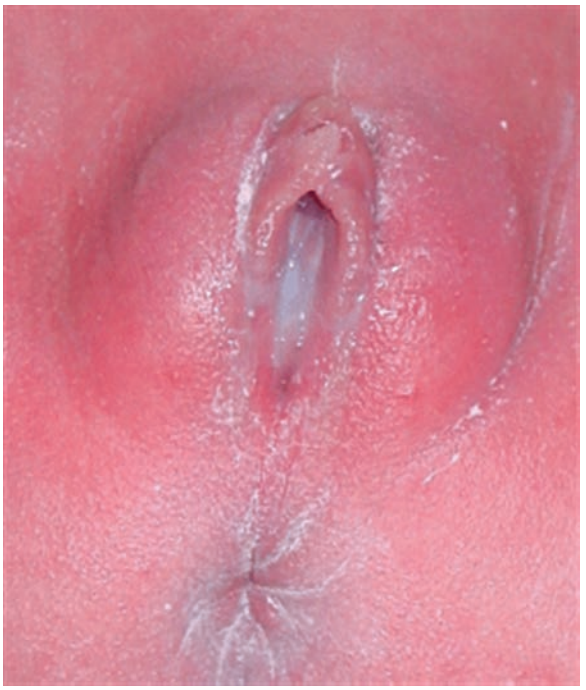

Figure 3.1 Anatomy of the newborn vulva.

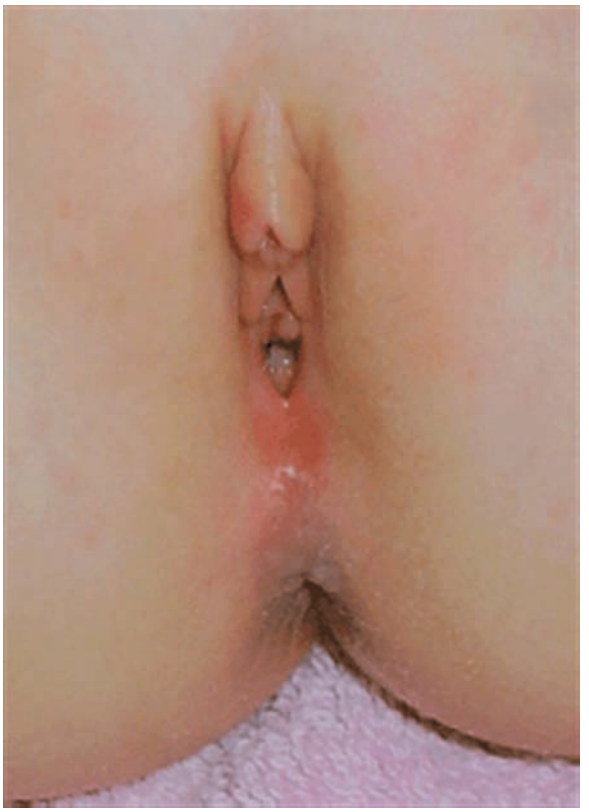

Figure 3.2 Anatomy of the prepubescent vulva.

active, the introitus increases in diameter, and the urethral orifice is more discernible. Vaginal discharge may be evident between the anterior folds.

Breast development, influenced by estrogens, is also described by the five Tanner stages, from no development (Stage 1) to the mature adult breast (Stage 5) (19). Menarche occurs near the end of the Tanner sequence of breast changes, typically sometime between the ages of 11 and 15 years (3). The mean age of menarche worldwide is between 12 and 13 years (20). The sequence from the first appearance of pubic hair through to breast development and menarche takes approximately 4 years. Normative menstrual cycle length is established by the sixth gynecologic year (i.e., the sixth year following menarche), usually around the chronologic age of 19 years, although this may occur anytime between the ages of 17 and 21 years, depending on menarcheal age (9,10,18,21,22).

Idiopathic Precocious Puberty

Historically, puberty had been defined as precocious in girls when secondary sex characteristics (particularly breast development) appeared prior to the age of 8 years. However, an apparent advance in the age of onset of pubertal changes has been observed in the USA and in girls from developing countries who have migrated to Western Europe for foreign adoption (reviewed in (23)). Two large studies in the USA found that pubertal signs may appear before the age of 8 years, especially in African–American as compared to Caucasian girls (Tables 3.2 and 3.3) (24–26). Between the 1970s and 1990s, the average age of menarche in the USA fell from 12.75 years to 12.54 years (26).

Controversy surrounds the clinical significance of these findings. Most cases of early pubertal development are idiopathic and probably do not represent precocious puberty unless bone maturation and developmental characteristics are so accelerated that diminished adult height is likely (27,28). However, because true endocrine pathology may be overlooked if early pubertal signs are dismissed, vigilant longitudinal follow-up of

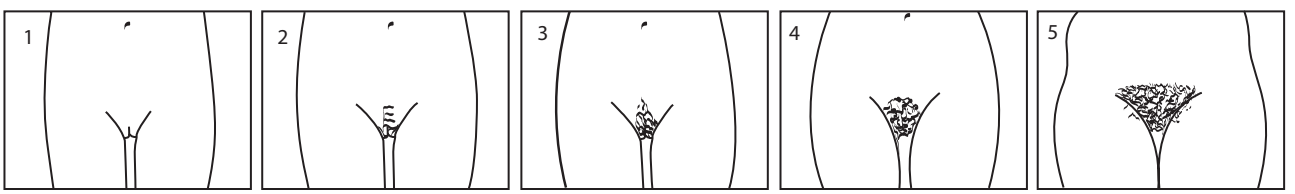

Figure 3.3 Tanner stages of pubic hair development. (Adapted from Farage M, Maibach H. *Arch Gynecol Obstet* 2006; 273(4): 195–202.)

Table 3.2 Mean Onset of Secondary Sex Characteristics (Tanner Stage 2) and Menarche in Caucasian and African–American Girls from North American Suburban Medical Practices (1997)[a]

Ethnicity	Mean age of onset (years)			% with pubertal signs by age 8
	Menarche	Breast development	Pubic hair	
African–American	12.16 (SD 1.21)	8.87 (SD 1.93)	8.78 (SD 2.00)	48.3
Caucasian	12.88 (SD 1.20)	9.96 (SD 1.82)	10.52 (SD 1.67)	14.7

[a] References 19,24,68.

Table 3.3 Mean Age of Menarche and Median Age of Onset of Secondary Sex Characteristics (Tanner Stage 2) (19) by Race from the U.S. Third National Health and Nutrition Examination Survey (NHANES III) (1988–1994)

Ethnicity	Age (years)		
	Menarche[a]	Breast development[b]	Pubic hair[b]
African–American	12.14 (SE: 11.87–12.39)	9.48 (FL: 9.14–9.76)	9.43 (FL: 9.05–9.74)
Caucasian	12.60 (SE: 12.48–12.71)	10.38 (FL: 10.11–10.65)	10.57 (FL: 10.29–10.85)

Source: Adapted from Farage M, Maibach H. *Arch Gynecol Obstet* 2006; 273(4): 195–202.
[a] Mean age of menarche. From Anderson SE, Dallal GE, Must A. *Pediatrics* 2003; 111: 844–850.
[b] Median age at which 50% of the sample entered Stage 2 of pubertal development. FL based on probit analysis for multiple race comparisons at the 95% confidence level. From Sun SS et al. *Pediatrics* 2002; 110: 911–919.
Abbreviation: FL: fiducial limit.

girls with early pubertal onset is advised (29). Several risk factors (genetics, low birth weight, higher body mass index, and exposure to endocrine disruptors) are correlated statistically with earlier pubertal onset, but the biological mechanisms of accelerated onset are unknown (26,30–40).

REPRODUCTIVE YEARS

Changes in the vulva and vagina during the reproductive years are linked to the menstrual cycle and pregnancy.

Vulvar and Vaginal Effects of the Menstrual Cycle

Vulvar epithelial thickness is at its highest in the reproductive years (Figure 3.4). Vulvar skin thickness remains constant over the menstrual cycle, but its surface cells are predominantly orthokeratotic (lacking nuclei) at the beginning and end of the cycle, and increasingly parakeratotic (bearing a degenerated nucleus) at midcycle (5). These cytological changes are thought to be mediated by estrogen: parakeratosis of vulvar epithelial cells is rare in postmenopausal women, but its incidence rises dramatically in response to systemic estrogen supplementation (5). The vaginal epithelium is sensitive to ovarian steroid hormone cycling. Estrogen stimulation causes the thickness, glycogen content, and parakeratosis of the vaginal epithelium to peak approximately at midcycle (Figure 3.5) (6).

During menstruation, vaginal pH rises to as high as 6 on day 2 and drops to approximately 5 by day 4 (41). The impact of the menstrual cycle on the microbial ecology of the vagina is not well understood. Studies using traditional culture techniques suggest that *Lactobacillus* species predominate in the vaginal flora of healthy women and that their cell densities remain relatively constant over the menstrual cycle (7). However, such techniques typically identify only the most readily cultivated microbial populations, which may represent but a subset of the extant community. Emerging data obtained by analysis of total microbial community DNA indicate that lactic acid-producing genera such as *Atopobium*, *Megasphaera*, and *Leptotrichia*, rather than *Lactobacillus*, are numerically dominant in some women (8). Consequently, genera besides *Lactobacillus* may contribute to the acidity of vaginal tract, but the impact of the menstrual cycle on these genera has not been studied.

Vulvar and Vaginal Effects of Pregnancy and Delivery

During pregnancy, an increase in total blood volume heightens the coloration of the vulva and the vagina. The connective tissue of the vulva, vagina, and perineum relaxes and the muscle fibers of the vaginal wall increase in size in preparation for delivery. Progesterone elevates venous distensibility, which may cause varicose veins in the vulva (12). Pregnancy

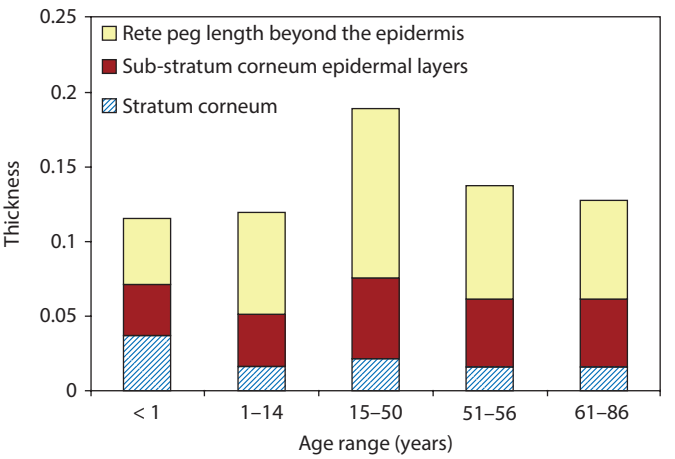

Figure 3.4 Epithelial thickness of the labia majora with age. (Based on data in Jones IS. *Clin Exp Dermatol* 1983; 8: 513–521.)

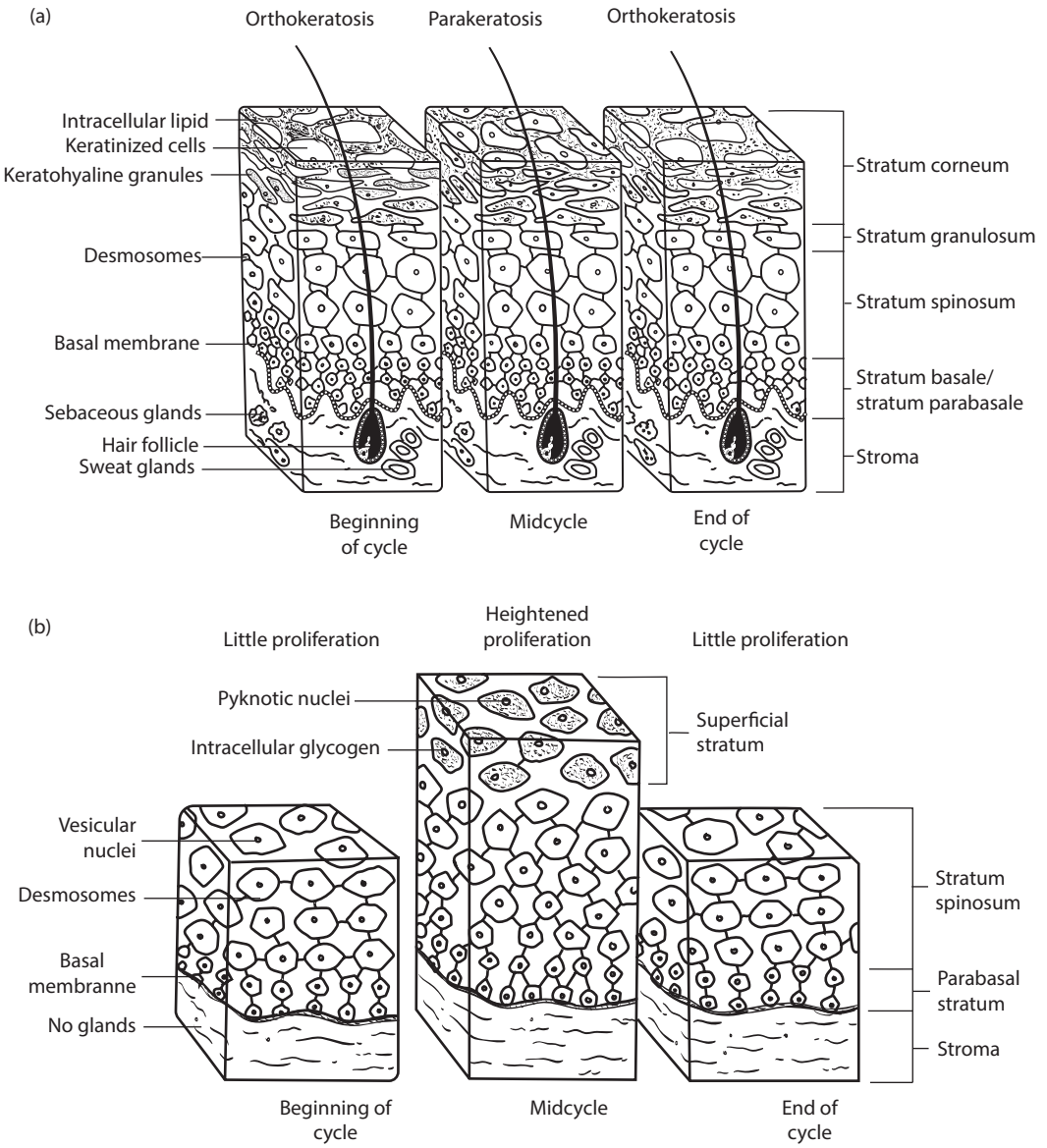

Figure 3.5 Menstrual cycle variations in (a) vulvar skin and (b) vaginal mucosa. (Adapted from Nauth H. Anatomy and physiology of the vulva. In: Elsner P, Marius J, eds. *Vulvovaginitis*. Vol 1. New York, NY: Marcel Dekker, 1993.)

is associated with a 10- to 20-fold increased incidence of vulvovaginal candidiasis (11).

During delivery, the perineal and the vaginal musculature relax and the vaginal rugae flatten to allow expansion of the vaginal tract, accommodating passage for the infant. Injury to the perineum can occur spontaneously or because of episiotomy. After delivery, the vaginal introitus is wider and the fourchette appears more flattened. Over the next 6–12 weeks, the morphology and dimensions of the vaginal tract are reestablished (42).

MENOPAUSE AND OLDER AGE

Menopause is the permanent cessation of menstruation due to the loss of follicular activity. A constellation of symptoms emerges during the perimenopause, the transition period to menopause. The most notable is menstrual cycle irregularity, reflecting an increase in the number of anovulatory cycles and cycles with a prolonged follicular phase. Some women experience cramps, bloating, or breast tenderness; symptoms of estrogen depletion, such as vasomotor symptoms (hot flashes), migraine, and vaginal dryness, can ensue. The perimenopause commences typically after the age of 45 years and lasts approximately 4 years. Menstruation ceases at a median age of 50 years in Western industrialized societies (43). Menopause is considered to be established 1 year after the final menstrual period (44,45).

Following menopause, pubic hair grays and becomes sparse, the labia majora lose subcutaneous fat, and the labia minora, vestibule, and vaginal epithelium atrophy (16,46). At the cytological level, estrogen-induced parakeratosis of vulvar stratum corneum is highest in the third decade of life, but rarely seen by the eighth decade (47).

Postmenopausal atrophic vulvovaginitis is a common condition. Vaginal secretions decrease, reducing lubrication and increasing coital discomfort (48–53). Thinned tissue is irritated more easily and may be more susceptible to infection. The vaginal pH rises and the prevalence of colonization by enteric organisms associated with urinary tract infections increases (54). In addition to these physiologically induced changes, certain vulvar dermatoses, such as lichen sclerosus, are more prevalent in peri- and post-menopausal women (55).

Vulvar skin differs from exposed skin in the characteristics of skin hydration, friction, permeability, and visually discernible irritation (reviewed in (56)). It is commonly assumed that aged skin is intrinsically less hydrated, less elastic, more permeable, and more susceptible to irritation. As discussed later in this chapter, however, assessments of the vulvar skin of pre- and post-menopausal women by means of bioengineering techniques did not reveal large age-related changes in these characteristics (Table 3.4).

For example, the skin of the labia majora is more hydrated than forearm skin as measured by transepidermal water loss, and its coefficient of friction is higher (57,58). Although small age-related changes in these parameters were measured on the forearm of pre- and post-menopausal women, the impact of the menopause on the water barrier function and the friction coefficient of vulvar skin was negligible (Table 3.4) (58).

Vulvar skin is more permeable to hydrocortisone than forearm skin, but comparable testosterone penetration rates have been measured at both sites. In postmenopausal women, skin permeability to hydrocortisone drops on the forearm but not on the vulva, and no age-related differences in testosterone penetration were found at either site (Table 3.4) (59). (For perspective, penetration of testosterone but not hydrocortisone may be mediated by androgen receptors.) Exposed forearm skin was more susceptible than vulvar skin to the model irritant, aqueous sodium lauryl sulfate (1% w/v). This agent caused intense erythema on the forearms of premenopausal women, but no visually discernable response on the vulva in either pre- or post-menopausal women (Table 3.4) (60).

Although large age-related differences in skin vulvar permeability and intrinsic susceptibility to irritants have not been demonstrated, dermatitis of the vulva, perineum, and buttocks can be a substantial problem in older people with incontinence. A mechanistic understanding of the etiology of incontinence dermatitis was first developed from studies on diapered infants and then extended to older adults. Chapter 36 provides a detailed explanation of the mechanistic factors that contribute to incontinence dermatitis. The etiology is multifactorial. In brief, exposure to urinary moisture under occlusion makes the skin more susceptible to friction damage; urinary ammonia elevates the local pH, which alters skin barrier function and activates fecal enzymes; these enzymes further compromise skin integrity and increase skin susceptibility to microbial infection (61–66). Incontinence dermatitis is particularly debilitating in older adults because urine and feces exert their effects against a background of atrophied tissue, immobility, a potentially weakened immune response, and often compromised physical health and cognition. Several factors exacerbate the deleterious effects of skin wetness, occlusion, and fecal enzyme action in elders. Although the

Table 3.4 Physiologic Skin Parameters in Pre- and Post-Menopausal Women

Parameter	Site	Age group[a]	Measured value	Significance[b]	Reference
Water barrier function (TEWL, g/m²·h)	Forearm	Premenopausal	3.7 + 0.4	p = 0.05	(58)
		Postmenopausal	2.6 + 0.3		
	Vulva	Premenopausal	14.8 + 1.5	NS	(58)
		Postmenopausal	13.5 + 1.8		
Skin hydration (capacitance, AU)	Forearm	Premenopausal	93.3 + 2.3	NS	(58)
		Postmenopausal	91.9 + 2.8		
	Vulva	Premenopausal	116.8 + 4.1	NS	(58)
		Postmenopausal	118.0 + 8.2		
Friction coefficient μ	Forearm	Premenopausal	0.49 + 0.02	p < 0.05	(58)
		Postmenopausal	0.45 + 0.01		
	Vulva	Premenopausal	0.60 + 0.04	NS	(58)
		Postmenopausal	0.60 + 0.06		
Hydrocortisone penetration (% dose absorbed)	Forearm	Premenopausal	2.8 + 2.4	NS	(59)
		Postmenopausal	1.5 + 1.1		
	Vulva	Premenopausal	8.1 + 4.1	p < 0.01	(59)
		Postmenopausal	4.4 + 2.8		
Testosterone penetration (% dose absorbed)	Forearm	Premenopausal	20.2 + 8.1	NS	(59)
		Postmenopausal	14.7 + 4.2		
	Vulva	Premenopausal	26.7 + 8.0	NS	(59)
		Postmenopausal	24.6 + 5.5		
Number of positive visual erythema scores (on day 2, after 24-hour exposure to 1% sodium lauryl sulfate)	Forearm	Premenopausal	9	p = 0.03	(60)
		Postmenopausal	5		
	Vulva	Premenopausal	0	NS	(60)
		Postmenopausal	0		

Source: Adapted from Farage M, Maibach H. *Arch Gynecol Obstet* 2006; 273(4): 195–202.

[a] Group sizes (water barrier function, skin hydration and friction parameters): premenopausal—34 subjects; postmenopausal—10 subjects. Group sizes (hydrocortisone and testosterone penetration): nine subjects in each group. Visual erythema score to sodium lauryl sulfate application: 10 subjects per age group.

[b] Level of statistical significance of age group difference.

Abbreviation: TEWL: transepidermal water loss.

baseline skin wetness level does not differ significantly in aged skin, the excess hydration induced by occlusion is significantly greater and dissipated more slowly in older skin than in young skin (67). Although the coefficient of friction of vulvar skin is unchanged in older women, reduced mobility subjects atrophied genital tissue to higher shear forces than those encountered by infants. Moreover, atrophied genital tissue may be more susceptible to pH changes and enzymatic action, while immune function and tissue regeneration capacity may also be compromised. Lastly, elders may not receive the same degree of attentiveness as infants, and those with impaired cognition may be unable to alert caregivers to incontinent episodes. These factors underscore the need for vigilant care and proper hygiene to help maintain healthy urogenital skin in older women with incontinence.

CONCLUSION

In summary, the vulva and vagina undergo characteristic age-related changes in morphology and physiology over the course of a lifetime. At birth, these tissues exhibit the effects of residual maternal estrogens. During puberty, the vulva and vagina mature under the influence of adrenal and gonadal steroid hormones. During the reproductive years, the vagina responds to ovarian steroid hormone cycling and both tissues adapt to the needs of pregnancy and delivery. Following menopause, the vulva and vagina atrophy. A rise in the prevalence of incontinence among older women increases the risk of vulvar and perineal dermatitis. Vigilant care is needed to avoid dermatitis in the older person with incontinence, as the condition is particularly debilitating at this stage of life.

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Microbial ecology of the vulva

Catherine C. Davis and Ronald W. Berg

INTRODUCTION

Although there is a considerable body of literature regarding the composition of the vaginal microbiota, remarkably little is known of the microbiota of the vulva. A comprehensive understanding is hindered by the anatomical reality that the vulva is likely not a single ecological niche, but rather a structure that includes many unique and diverse microbial habitats. From an ecological perspective, the vulva can be best thought of as a transitional zone between the arid desert of external skin surfaces and the tropical rainforest of the vagina. Thus, the microbial ecology of the vulva is not a single entity but a complex construction, the nature of which is likely to be revealed in interwoven yet distinctive parts, depending on: (i) the anatomical areas sampled; (ii) the methodology used to analyze the samples; and (iii) the ability to describe the evenness, composition, and richness of the microbial communities.

ANATOMICAL STRUCTURE OF THE VULVA

The vulva consists of the mons pubis, the labia majora and minora, the clitoris, and the vestibule of the vagina. The external urethral orifice is situated in the vestibule, as are the ducts of the mucus-secreting paraurethral and Bartholin's glands.

The mons pubis and the outer aspects of the labia majora are covered with hairy skin that is similar to that of the scalp and axillae. The labia majora contain numerous sebaceous glands, along with apocrine glands and eccrine sweat glands. The labia minora, in contrast, are free from hair, and are covered with stratified squamous epithelium, which can have a thin layer of keratinized cells at its surface. Sebaceous glands are present, but as the skin is glabrous, these glands open directly at the surface. Eccrine sweat glands are found occasionally on the labia minora, but apocrine glands are absent. The clitoris is covered with a thin, nonkeratinized, stratified squamous epithelium and contains nerve bundles and erectile tissue. From the innermost surface of the labia majora to the vagina, the epidermis gradually changes from the keratinized epithelium typical of other external body surfaces to the mucosal epithelium typical of the vagina and other mucous membranes. The vulvar vestibule extends laterally from the hymenal ring to a line of more keratinized skin on the labia minora (Hart's line). The overall structural diversity of the vulva is summarized in Table 4.1. An organ with this degree of structural diversity is unlikely to harbor a single microbial ecosystem, as the diverse habitats that result create unique ecological pressures that are likely to shape unique populations of microorganisms.

FACTORS CONTROLLING MICROBIAL GROWTH AND DIVERSITY

Although the environment of the vulva has some unique properties as compared to other skin sites, there are a number of ecological factors in common with other sites that can affect microbial populations. Relatively few studies have addressed vulvar skin directly, but there is a wealth of information from these other similar sites that can be instructive in understanding the factors that control vulvar microbial ecology.

Moisture

It has long been known that the availability of water is the primary rate-limiting factor for growth of bacteria on skin. The largest populations of microorganisms are found in those regions where high humidity results in high skin hydration; for example, the perineum, axillae, and between the toes. The primary source of water on the skin is eccrine sweat. Transepidermal water loss (TEWL) can also contribute to skin hydration, particularly if the skin is occluded to limit evaporation. Studies have shown that TEWL is higher on labia majora skin than on forearm skin (1) or inner thigh skin adjacent to the vulva (2). Other sources of moisture unique to the vulvar area include vaginal secretions and urine. Increased skin hydration has been shown to result in both increases in microbial density and changes in the relative ratios of microorganisms (3,4). Adult forearms occluded tightly with plastic film showed increases in microbial populations from a baseline of approximately 10^2 colony-forming units (CFU)/cm^2 to almost 10^8 CFU/cm^2 over the course of several days. The relative populations of micrococci decreased, Gram-negative rods emerged, and lipophilic diphtheroids became the dominant microbiota. Although occlusion of the vulvar area resulting from tight-fitting clothing or nonbreathable fabrics is unlikely to approach the level provided by plastic film, it is readily apparent that increased moisture availability can have a dramatic effect on the quantitative and qualitative nature of microbial populations on skin.

pH

Most bacteria that inhabit the skin can grow under all pH conditions normally found on diverse skin sites, but many bacteria possess individual pH optima for growth; therefore, small changes in pH have the potential to provide an ecological advantage to those finding more favorable conditions with regard to hydrogen ion concentration. Studies have shown that increased skin hydration resulting from occlusion is accompanied by an increase in pH from its normal slightly acidic condition to near neutrality (5). pH can also exert an effect on

Table 4.1 Anatomical Features of Vulvar Skin Relevant to Microbial Ecology

Structure	Epithelium type	Hair	Eccrine sweat glands	Apocrine sweat glands	Sebaceous glands
Mons pubis	Keratinized	+	+	–	+
Clitoris	Nonkeratinized	–	–	–	–
Labia majora	Keratinized	+	+	+	+
Labia minora	Nonkeratinized	–	±	–	+
Vestibule—outside Hart's line	Keratinized	–	–	–	+
Vestibule—inside Hart's line	Nonkeratinized	–	–	–	–

microbial populations by altering the antimicrobial properties of fatty acids on the skin. The protonated form of the acid is generally better able to penetrate microbial cells than the unprotonated form, so as the pH approaches the pKa of the acid, antimicrobial activity increases. Because microorganisms can vary in their susceptibility to the antimicrobial effects of fatty acids, relatively small changes in pH can influence the numbers and kinds of organisms that thrive in a population.

Microbial Nutrients and Inhibitors

Nutrients on the skin surface are derived mainly from eccrine sweat, apocrine and sebaceous gland secretions, and the stratum corneum. These materials supply a rich mixture of proteins, peptides, amino acids, carbohydrates, nucleic acids, lipoidal material, and inorganic salts that provide ample nutrition to support large microbial populations. However, the epithelium also secretes a range of antimicrobial compounds that are able to kill microorganisms or inhibit their growth. The differential activity against various microbes provides additional ecological pressure to shape the resulting population. In areas where sebaceous glands are present, skin surface lipids are quantitatively the most important class of substances occurring on adult human skin. Sebum, as synthesized in the sebaceous gland, contains little or no free fatty acid (6). However, sebum triglycerides are hydrolyzed subsequently to liberate these acids. Generally, this hydrolysis is accepted to be the work of bacterial lipases, especially those of lipophilic diphtheroids (7). The antimicrobial properties of fatty acids have been known for many years. For example, the saturated free fatty acid fraction of skin lipids was shown to inhibit the growth of *Streptococcus pyogenes*, *Staphylococcus aureus*, and skin micrococci, whereas Gram-negative species such as *Pseudomonas aeruginosa* and *Escherichia coli* are resistant (8). In addition to the physiological products and microbial metabolites that influence microbial growth, the vulvar area also contributes vaginal secretions and urine to the nutrient pool. Therefore, the overall microbial nutrition picture of the vulva that emerges is dynamic, and the resulting variability further contributes to the dynamic nature of the microbial ecosystem.

Microbial Interactions

The interactions among the members of microbial populations on skin are undoubtedly important, but poorly understood. Some may involve more or less direct interactions via competition for available nutrients. It is generally accepted that free fatty acids on the skin surface are products of microbial metabolism and that they are inhibitory to some organisms, particularly potential pathogens. Corynebacteria are among the most active lipase producers on skin (9), but micrococci have also been shown to be important contributors of lipolytic activity (10). It has been suggested that fatty acids are an important mechanism by which Gram-positive bacteria on skin exert an inhibitory effect over Gram-negative bacteria (11). Conversely, it has been shown that suppressing Gram-positive skin populations with antibiotics can be followed by the overgrowth of Gram-negative bacteria (12). Antagonism also can occur via excretion of bacteriocins, which are a chemically diverse group of substances produced by many microorganisms that inhibit the growth of other species. Bacteriocins produced by Gram-positive organisms tend to have activity against closely related strains or species, whereas those produced by Gram-negative bacteria have broader activity. Bacterial interference is likely to be an important natural phenomenon that is helpful in understanding the forces that shape microbial populations, but this concept has also been applied in a clinical setting for infection control. For example, artificial colonization of nasal mucosa and umbilical sites with a nonvirulent strain of *S. aureus* has been shown to result in a decreased incidence of infection at those sites (13). Not all microbial interactions are inhibitory in nature. *In vitro* studies of growth enhancement or satellitism have been reported between bacterial isolates from normal healthy skin (14). The mechanism of satellitism is not clearly understood, but could involve the production of growth factors by one organism that are stimulatory to another, or perhaps by the destruction of inhibitory materials. All of these interactions contribute to the composition of the skin microbiome, and it is apparent that the type and nature of the inhabitants, as well as the nature of the substrate, are important attributes that shape its composition.

Adherence

The ability of a microorganism to colonize a surface is generally proportional to the ability of the organism to adhere to that surface. This specific binding results from the interaction between the surface and specific cell receptors and provides an ecological advantage by ensuring that organisms can successfully colonize a surface that allows them to thrive. It has been suggested that fimbriae in Gram-positive bacteria and pili in Gram-negative bacteria may be involved in binding organisms to surfaces (15) and that teichoic acid is a major adhesin of *S. aureus* to epithelial cells (16). Human epithelial cells have been shown to bind specifically with *P. aeruginosa*, *Staphylococcus epidermidis*, *S. aureus*, *S. pyogenes*, and diphtheroids, but not with viridans streptococci and *Candida albicans* (4). Microbial adhesion to the vulva per se has not been studied satisfactorily, in part because this environment contains several cell types and is therefore ecologically complex. However, some microbial adherence properties of the labia majora and minora have been studied and the results demonstrate that labia majora cells generally are more amenable to microbial adherence than are labia minora cells (17).

Host Immune Mechanisms

Both innate and acquired host antimicrobial defense systems are operative on skin. Humoral and cell-mediated immune responses derive from Langerhans cells, keratinocytes, and endothelial cells that produce cytokines and lymphocytes. The skin-associated lymphoid tissue forms a protective barrier that can capture virtually any antigen that enters the skin. IgA and IgG antibodies produced locally can be secreted by the eccrine sweat glands and spread over the skin surface, where they exhibit antimicrobial effects and interfere with microbial adherence. The immunological factors important in the lower genital tract have been reviewed by Bulmer and Fox (18). Mucus is a highly viscous and elastic barrier that protects mucosal surfaces by selectively trapping and shedding pathogens, toxins, and ultrafine particles (19) while allowing the rapid flux of nutrients, antibodies, and cells of the mucosal immune system (20). Cervical mucus contains antibodies, particularly secretory IgA, which are bactericidal in the presence of lysozyme and complement and can agglutinate bacteria and opsonize them for phagocytosis. IgA_2 is usually the predominant isotype subclass in genital secretions (21). Interestingly, Kansal et al. (22) demonstrated that anti-TSST-1 IgA antibodies were absent from vaginal lavages in healthy women of reproductive age. Circulating antibodies to specific microorganisms can be demonstrated to result from many genital infections, but there is scant evidence of any resulting protective effect. For example, recurring episodes of chlamydial infection, genital herpes, trichomoniasis, and gonorrhea can take place in spite of high titers of circulating antibodies. Thus, a variety of immune mechanisms is operative on or in vulvar skin, but their role in shaping microbial populations is largely unknown.

Exogenous Microbiota

As a result of its anatomical proximity to the anal, vaginal, and urethral orifices, the vulva is easily subject to contamination by resident microorganisms from these sites. These exogenous sources have different microbiota from one another and the impact of these populations on the microbiota of the vulva is influenced not only by their diverse nature, but also by a number of other factors, including personal hygiene practices, the occlusive properties of clothing, and individual anatomy. A series of 13 randomized prospective trials of panty liners or ultrathin pads demonstrated no clinically significant adverse effects either on the skin or on isolation frequencies or cell densities of representative genital microbiota (23). These conclusions were corroborated by Giraldo et al. (24). Continuous seeding of diverse microorganisms contributes heavily to the dynamic diversity of vulva microbial populations.

MICROBIOTA OF THE VULVA

Few studies have been conducted into microbial populations on the vulva, and most of the results reported have been from traditional culture-based studies. Newer molecular methods may bring more clarity to issues such as resident versus transient microbiota and the prevalence of organisms that are difficult or impossible to isolate and identify by traditional culture/plating methods using artificial media.

Resident versus Transient Microbiota

It is generally accepted that resident microorganisms are those that multiply at a specific site, rather than simply survive. Transient organisms, on the other hand, arrive from an outside source and are unable to compete successfully for a permanent home. While simple to state in principle, this difference is not easy to demonstrate in practice. There is an extensive body of literature concerning the microbiota of the skin, but relatively little is known about the quantitative relationships among various microorganisms on various skin surfaces. Moreover, given the dichotomy between resident and transient microbiota, quantitative data become difficult to interpret vis-à-vis the "normal," healthy microbiota of a given site. Culturing a skin surface gives no indication of whether the isolate represents resident or transient microorganisms. It can be inferred from prevalence studies that an organism that is recovered repeatedly in large numbers is indeed a resident. However, minor residents are unlikely to be distinguishable from transients. Distinguishing resident from transient microbes on the vulva is likely to be even more difficult because of the large number of transient organisms that are contributed continuously by exogenous sources from the anus, urethra, and vagina. Thus, determining exactly what comprises the normal resident microbiota of the vulva will be difficult or impossible using traditional culture-based microbiological methods.

Culture-Based Studies

One of the first studies of vulvar microbiota attempted to understand the relationship between urinary tract infections and the microbes of the vestibule (25). The researchers found that women with recurrent infections were more likely to be colonized with Gram-negative bacteria and speculated that the vestibule could serve as a reservoir for these potential pathogens. Moreover, the vestibules of normal healthy women were generally free from Gram-negative bacilli and were also found to have an acidic pH more similar to the vagina than to that of other skin surfaces; the researchers suggested that this low pH might serve to inhibit the growth of Gram-negative enteric bacteria. Lactobacilli and corynebacteria were reported to constitute the predominant microbiota of the vestibule in this study. A more recent report (26) has shown a gradient in populations of enteric organisms from the perineum, through the vestibule, to the vagina. A pioneering study aimed at gaining an overall understanding of vulvar microbiota was reported in 1979 (27). Eighteen normal healthy women with a mean age of 39 years participated in this study, which compared vulvar skin with forearm skin using the cup-scrub sampling method (28). Microbial cell density was higher on the vulva (2.8×10^6 CFU/cm²) than on the forearm (6.4×10^2 CFU/cm²). Lipophilic diphtheroids, coagulase-negative staphylococci, micrococci, nonlipophilic diphtheroids, and lactobacilli were the dominant microbiota of the vulva, and streptococci, Gram-negative rods, and yeasts were also present. Most categories of bacteria found on the vulva were present at higher density and prevalence as compared with the forearm microbiota. Exceptions were noted for micrococci and *Bacillus* spp., which tended to occur more frequently on forearm skin. This may reflect the better adaptation of these organisms to the drier environment found on the forearm. This study also reported a surprisingly higher incidence of *S. aureus* on the vulva (67%) than on the forearm (11%). Quantitative results from this study are shown in Table 4.2.

A subsequent study (29) investigated the bacterial population of the epithelial surface of the labia majora during the menstrual cycle. Samples were obtained at days 2, 4, and 21 of the menstrual cycle, and the results essentially confirmed those

Table 4.2 Microbial Counts on Vulva and Forearm Skin (Mean of 18 Subjects)

Organisms	Vulva (CFU/cm²)	Forearm (CFU/cm²)
Staphylococcus aureus	4.1×10^4	1.4×10
Coagulase-negative staphylococci	5.7×10^5	1.8×10^2
Micrococci	5.1×10^5	2.9×10^2
Streptococci	3.7×10^2	0.48×10
Lipophilic diphtheroids	7.9×10^5	1.1×10^2
Nonlipophilic diphtheroids	4.6×10^5	1.1×10
Lactobacillus spp.	4.6×10^5	0.96×10
Bacillus spp.	Not detected	1.2×10
Gram-negative rods	1.8×10^3	0.12×10
Yeasts	8.2×10	0.8×10
Total count	2.8×10^6	6.4×10^2

Source: Adapted from Aly R, Britz MB, Maibach HI. *Br J Dermatol* 1979; 101: 445.

of the earlier study with regard to the incidence and densities of the microorganisms isolated and identified. While the authors expected vulvar counts of vaginally derived organisms (lactobacilli and *Gardnerella vaginalis*) to increase during menstruation, no significant changes in the microbiota occurred at any of the three time points (Table 4.3).

A larger study involving 224 participants compared the frequencies and semiquantitative densities of selected microbes from the posterior vaginal fornix and the inner labial groove of the vulva (30). This study focused on aerobic and facultative species that are potentially pathogenic or otherwise have a known association with vaginal, vulvar, or urinary tract infections. The results (Table 4.4) revealed that the same organisms were generally found at both sites, but frequencies were significantly higher in the labial groove for a number of species, including *S. aureus* and other staphylococci, coliforms, Gram-negative nonlactose fermenters, and Group D streptococci. *G. vaginalis*, in contrast, was more common in the vagina. The researchers also addressed the question of whether daily wear of panty liners would increase the prevalence and/or density of clinically important species. No changes were detected that would suggest any adverse clinical outcomes. Similarly, more recent studies (31,32) have also concluded that tight-fitting underwear and panty liners are unlikely to increase microbiological risk.

Table 4.3 Bacterial Populations on Vulvar Skin (CFU/cm²) during the Menstrual Cycle (Mean of 20 Subjects)

Organisms	Day 2	Day 4	Day 21
Staphylococcus aureus	5.6×10^3	4.0×10^3	6.1×10^3
Coagulase-negative staphylococci	2.2×10^5	1.2×10^5	6.9×10^5
Micrococci	5.7×10^4	2.0×10^4	6.5×10^3
Lipophilic diphtheroids	3.1×10^5	3.3×10^5	4.5×10^5
Nonlipophilic diphtheroids	8.9×10^5	1.5×10^5	9.0×10^3
Beta-hemolytic streptococci	1.0×10^2	N.D.	6.5×10
Alpha-hemolytic streptococci	7.1×10^2	6.9×10^2	3.6×10^3
Nonhemolytic streptococci	3.1×10^5	1.6×10^2	1.2×10^2
Gram-negative rods	1.9×10^2	N.D.	3.5×10^2
Gram-positive rods	1.0×10^4	5.5×10	8.5×10^3
Nonpathogenic *Neisseria*	N.D.	N.D.	1.9×10^3
Lactobacilli	1.8×10^5	2.9×10^3	3.4×10^5
Gardnerella vaginalis	5.7×10^2	2.2×10^5	8.0×10^4
Yeasts	N.D.	1.0×10	N.D.
Total count	2.0×10^6	8.9×10^5	1.6×10^6

Source: Adapted from Elsner P, Maibach HI. Microbiology of specialized skin: The vulva. *Semin Dermatol* 1990; 9: 300.
Abbreviation: N.D.: not detectable.

Nonculture-Based Studies

The microbiota of a particular anatomical niche can play many roles, such as resisting colonization by pathogens and nutritional interactions that shape and control the population (33). Adding to this complexity are the ecological pressures that the host brings to bear on the community, which vary from one individual to another and over time. Understanding the diversity and role of individual microbes in the various human niches has thus been hampered severely by existing culture-based microbiological methodologies. The advent of molecular methodologies has been a boon to understanding the complex nature of the oro-gastrointestinal microbiota (34,35). Over the last decade, metagenomics has had a major impact on the study of the microbiomes of environmental, clinical, and engineered habitats. Through shotgun sequencing of DNA extracted from microbial communities, metagenomics bypasses traditional culture-dependent biases and holds the promise of genome-based insights into the mostly uncharted microbial world (36). Future refinement and expansion of these metagenomic approaches will likely continue to unveiling intricate details of the various ecological niches of the human.

Although tremendous strides have been made in community analyses of microbial populations, knowledge of the ecology of the human microbiota is still largely in its infancy. Many studies of environmental microbial communities have clearly demonstrated the limitations of culture-dependent techniques for population analyses. Surprisingly, it has been estimated that more than 90% of microbial communities are not amenable to culture-based analyses and thus the composition (which species), species richness (number of species), and evenness (relative abundance of species) of microbial communities have been subjected to biased analyses resulting from the use of culture-based methods. Moreover, culture-based studies are fundamentally limited by their ability to grow and enumerate microorganisms on artificial culture media, where complex ecological and nutritional interactions found in natural habitats may be impossible to duplicate, even if such interactions were not so poorly understood.

Culture-independent technologies—in particular, those based on ribosomal RNA (rRNA) and their genes (rDNA)—are rapidly replacing conventional detection and enumeration methods and can provide insights into the phylogenetic diversity of communities. At present, the 16S rRNA molecule is the measure of diversity used most commonly because it is most amenable to DNA sequence analyses. By simply retrieving rDNA sequences from microbial samples (e.g., using 16S rRNA-specific oligonucleotide primers and the polymerase chain reaction), the biodiversity and population dynamics of the ecosystem can be investigated rapidly. Large-scale cloning and sequencing of 16S rRNA from feces has revealed that microbial diversity has been grossly underestimated (37). Fingerprinting techniques

Table 4.4 Comparison of the Frequencies and Densities of Selected Microorganisms Isolated from the Vagina and Vulva in 224 Women

	Vagina		Vulva	
Microorganisms	% culture positive	Density[a]	% culture positive	Density[a]
Candida albicans	12.1	1.3	8.5	1.3
Other yeasts	3.1	1.2	2.7	1.4
Gardnerella vaginalis	12.9	2.2	4.0[b]	1.5
Staphylococcus aureus	2.2	1.1	6.3[b]	1.8
Other *Staphylococcus* spp.	35.3	1.2	87.l[b]	1.9
Coliforms	17.0	1.7	37.9[b]	1.3
Gram-negative nonlactose fermenters	2.7	1.2	7.1[b]	1.0
Proteus spp.	1.3	1.0	3.1	1.2
Pseudomonas spp.	N.D.	–	N.D.	–
Streptococcus group A	0.9	1.0	1.3	1.5
Streptococcus group B	8.9	1.8	10.3	1.7
Streptococcus group D	19.6	1.5	30.8[b]	1.9
Streptococcus beta-hemolytic, non-A, -B, -D	N.D.	–	0.4	1.0
Viridans streptococci	15.2	1.8	19.6	1.7

Source: Adapted from Farage MA et al. *Infect Dis Obstet Gynecol* 1997; 5: 252.
[a] Semiquantitative 0–4 scale.
[b] Significantly different from vaginal site, $p < 0.05$.
Abbreviation: N.D.: not detectable.

for complex communities including denaturing/temperature-gradient gel electrophoresis have been applied to human intestinal samples. A study that analyzed 13,355 prokaryotic rRNA gene sequences from multiple intestinal sites revealed that each individual's microbiota is remarkably stable and unique (38). Designing of specific probes to the 16S rRNA sequences allows estimation of the microbiota diversity by dot-blot hybridization techniques (39). More accurate enumeration of the microbiota can be achieved by fluorescent *in situ* hybridization (40). Over the last 10–15 years, our understanding of the composition and functions of the human gut microbiota has increased exponentially. To a large extent, this has been due to new "omic" technologies that have facilitated large-scale analysis of the genetic and metabolic profiles of this microbial community (41).

Further improvements in sequencing methods and bioinformatics will involve the analysis of larger numbers of samples with greater speed and ease using high-throughput techniques.

Culture-Independent Analyses of Vaginal–Vulvar Communities

A variety of microbial communities and their genes (the microbiome) exist throughout the human body, playing fundamental roles in human health and disease. Our knowledge of these communities and their gene content, referred to collectively as the human microbiome, has to date been limited by a lack of population-scale data detailing their composition and function (42).

Characterization of the 16S rRNA via gene sequencing and reference genome approaches have been applied in order to analyze samples obtained from the urogenital tracts of healthy women. Results indicated that the diversity and kinds of organisms that comprise the vaginal microbial community varied among the women studied (43,44). Species of *Lactobacillus* dominated the communities in most of the vaginal samples analyzed. However, as an unexpected and surprising result, an *Atopobium* sp. was identified as a dominant member in one woman, and appreciable numbers of *Megasphaera* spp. and *Leptotrichia* spp. were identified in two women; none of these species have been shown previously to be common members of this ecosystem (44). The analysis revealed the dynamics of five major classes of bacterial communities and showed that some communities change markedly over short time periods, whereas others are relatively stable. Ravel et al. (45) have reviewed the ecological principles that govern the dynamics of the human microbiome (resilience, resistance, and persistence) and how a better understanding of these dynamic systems can be gained using descriptive microbial community compositional surveys (46), gene composition, and whole-community gene expression, or even metabolite analysis. Each of these analyses often reveals different intrinsic, dynamic patterns when applied to the same community. The review stressed the pitfalls that could result from *a priori* application of principles that might govern the microbial community at a given body site compared to another site (46). Thus, it is important to evaluate each human anatomical location as a unique ecological niche.

Progress has been made regarding the analysis of human vulvar microbial communities through the use of sequencing techniques (47–51). The results indicate that the microbial communities are more complex than previously thought and that the complexity of the microbial communities of the labia majora and minora varies among women. In some cases, the communities are comparatively simple and contain few numerically dominant populations, whereas others are more complex. Brown et al. (48) noted that the microbiota of the two regions of the vulva differed from each other, although the dominant phylotypes from the labia minora were generally dominant members of the labia majora communities of the same subject. Communities of the labia majora were more diverse than those of the labia minora, with 2–14 times as many phylotypes. A single study (49) that analyzed vaginal and labia minora samples from Japanese women both pre- and post-menstruation reported that the bacterial clones present on the labia minora were similar to those in the vaginal fluid, but that there were some shifts in populations during menstruation. In the first study of its kind of the adolescent urogenital tract, the vulvar microbiota of adolescents before menarche was found to closely resemble the vaginal microbiota, but often exhibited additional

taxa typically associated with skin microbiota (50). Jayaram and colleagues (51) published a study evaluating the microbial composition of the vagina and vestibule in healthy reproductive-aged women compared to those with vulvar vestibulitis syndrome. The bacterial genera identified in paired vaginal and vestibular samples from the healthy control women were similar to each other, and 20 genera were identified in the vestibule samples versus 13 in the vaginal samples. These results led the researchers to postulate that vaginal secretions are an important nutrient source for the bacteria present on the vestibule (51).

Further analyses of vulvar samples from larger populations over several time periods via nonculture-based techniques will undoubtedly provide more insight into these complex bacterial communities and lead to insights into their resilience, persistence, and resistance. Moreover, molecular techniques may open the door to the discovery of entirely new groups of microorganisms, independently of whether they can be cultured in the laboratory.

An unusual group of organisms identified as extremophiles was described in the late 1970s and was noted for its ability to grow at extreme temperatures (52). DNA sequence analyses showed that these organisms, which as a group exist typically in high temperatures and/or produce methane, clustered together well away from known bacteria (eubacteria) and eukaryotes. This observation led to the proposal that life should be divided into three domains: eukaryotes, eubacteria, and archaea. Not only have these organisms been isolated from extreme environments (such as icebergs or hot sulfur springs), they have also been identified in human clinical samples (53–55). The methanogenic archaea have been isolated from the human oral cavity (53), as well as from the human gut (54) and the vagina (55). Their potential presence on the vulva and their overall role in human microbial ecology are yet to be determined.

CONCLUSION

The vulva provides a complex microbiological environment. Its ecological characteristics range from zones of relative dryness to regions with high degrees of moisture and varying nutrient availability. Because of these variable characteristics, the vulva can be described as an anatomical structure with many diverse microbial habitats. Older culture-based studies have only hinted at the resulting microbial diversity. More recently, analyses of vulvovaginal samples using molecular techniques have indicated that microbial communities in this region are more complex than previously believed. As a result of using these improved tools, future research into the vulvar microbial ecology will likely yield a much more complete picture of the vulva's complex microbial communities.

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5

Vulvar ethnic differences
An overview

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INTRODUCTION

Are there differences in the vulva according to ethnicity? Reasonable evidence suggests that there are some differences in vulvar skin properties and function between ethnic (racial) groups. Previous studies have demonstrated equally thick stratum corneum in black and white skin, although black skin contains more cell layers (1). Black skin has higher transepidermal water loss (TEWL), variable blood vessel reactivity, decreased skin surface pH, and larger mast cell granules than white skin (2). Such differences in skin properties could account for racial disparities with regard to the diagnosis of vulvar dermatologic conditions.

We searched MD Consult, Science Citations Index, PubMed; Cochrane Database, the Melvyl Catalogue in the CDL-Hosted Database of University of California, San Francisco, Google, Yahoo, dermatology textbooks, and the University of California, San Francisco, Surge Building library files for relevant literature in this area published between 1967 and March 2016. The following keywords were searched: race, ethnicity, black, African, white, Caucasian, Hispanic, Asian, vulva, skin of vulva, and skin physiology.

We found that there were few studies of vulvar ethnic differences and that the few existing studies often had inconclusive results and findings that conflicted with other studies. This chapter presents a compilation of results of the studies of the vulvar ethnic differences with regard to TEWL, water content, corneocyte variability, blood vessel reactivity, skin elastic recovery, skin extensibility, pH gradient, lipid content, and skin surface microflora.

ASSESSMENTS OF VARIABLE CHARACTERISTICS OF ETHNICALLY/RACIALLY DIFFERENT SKIN

Transepidermal Water Loss

Table 5.1 (3–15) quantifies our knowledge of the ethnic differences in skin with regard to TEWL. Most studies assessed TEWL on the forearm, back, and inner thigh.

Two studies (16,17) reported that TEWL is higher in vulvar skin (labia majora) than in forearm skin. Elsner et al. (18) investigated the skin surface water loss (SSWL) dynamics of vulvar and forearm skin by measuring continuously for 30 minutes in order to clarify the possible effect of occlusion on TEWL of vulvar skin. Their results for SSWL after 30 minutes, which are assumed to be due to TEWL, were significantly higher in vulvar skin than in forearm skin. Warren et al. (19) also investigated SSWL dynamics between vulvar skin and that of the inner thigh in a larger number of subjects, and found the same relationship. Fujimura et al.'s investigation (15) of Thai women was consistent with previous reports, which indicates that TEWL is specifically higher in vulvar skin than in other sites, and the authors concluded that there is no ethnic difference.

Berardesca and Maibach (4) supported the findings that TEWL is higher in blacks in their 1988 study (Table 5.1). The investigators determined the difference in irritation between young black and white patients by applying the irritant 0.5% sodium lauryl sulfate (SLS) to untreated, pre-occluded back skin. They found a statistically significant difference in TEWL, with blacks having 2.7-times higher TEWL levels than whites ($p < 0.04$), suggesting that black skin in the pre-occluded state is more susceptible to irritation (Table 5.1). Hispanics were found to have higher TEWL values compared to whites, but this was not statistically significant (5). At baseline, Sugino et al. found TEWL levels to follow the sequence: blacks > Caucasians ≥ Hispanics ≥ Asians (8). After tape stripping, Berardesca and Maibach (4) found that TEWL is 1.2-times higher in black women than in Caucasian women on the midvolar forearm.

Most evidence supports the notion that blacks have higher TEWL than whites (Table 5.1); however, Berardesca et al. (6) and Fotoh et al. (13) found no significant difference between blacks and whites. In addition, Warrier et al. (10) found TEWL in blacks to be less than that in whites, and one recent study (14) also confirmed these results. TEWL measurements of Asian skin are inconclusive (Table 5.1) (7,8,12,14). Data from the studies in Table 5.1 are conflicting, possibly due to testing on different anatomic sites. In fact, data have often been difficult to compare due to other influencing factors such as internal factors (age, hormonal status, and psychological stress) and environmental conditions (temperature and other seasonal variations) (14). Future research should include more races and larger sample sizes.

Water Content

Various researchers studied ethnic differences in water content (hydration) of the skin at multiple body sites using various techniques (*in vivo* resistance, capacitance, conductance, and impedance) (Table 5.2) (4–6,8,10,13,15,20–23). The results for the stratum corneum water contents of the various studies are difficult to interpret, as other factors (e.g., sweat production and hair on the site of measurement) might impair the quality of electrode contact with the skin.

Fujimura et al. (15) found that the moisture was slightly lower in labial, mons pubis, and inner thigh skin than that of the inner forearm and groin. These authors believe that there are no clear, meaningful ethnic differences in the capacitance of vulva skin because the differences are relatively small.

Table 5.1 Transepidermal Water Loss

Reference	Technique	Subjects	Site	Results
(3)	*In vitro*	Blacks 10 (mean age 38.6); Caucasians 12 (mean age 41.1)	Inner thigh	TEWL blacks 1.1× > Caucasians (mean corrected log TEWL 2.79 and 2.61 μg/cm²/hour, respectively) ($p < 0.01$, for both values)
(4)	*In vivo* with topical application of SLS (irritant)	Black men 10 (age 29.9 ± 7.2); white men 9 (age 30.6 ± 8.8)	Back	• No significant difference in TEWL between blacks and whites at baseline *After SLS stress:* • TEWL blacks (untreated, pre-occluded, and pre-delipidized) > whites, but only statistically significant (2.7× greater) for 0.5% SLS applied in the pre-occluded area ($p < 0.04$)
(5)	*In vivo* with topical application of SLS (irritation)	Hispanic men 7 (age 27.8 ± 4.5); white men 9 (age 30.6 ± 8.8)	Upper back	• No significant differences in TEWL between Hispanics and whites at baseline *After SLS stress:* • TEWL Hispanics (untreated, pre-occluded, and pre-delipidized) > whites, but not statistically significant
(6)	*In vivo*	Blacks 15 (mean age 46.7 ± 2.4); whites 12 (mean age 49.8 ± 2); Hispanics 12 (mean age 48.8 ± 2)	Volar and dorsal forearm	• No significant difference in TEWL between sites or races at baseline
(7)	*In vivo* with topical application of MN vasodilator	Blacks 7; Caucasians 8; Asians 6 (ages 23–32)	Volar forearm	*Vasodilator given before tape stripping:* • TEWL blacks and Asians 1.3× > Caucasians ($p < 0.01$); no difference between blacks and Asians *Vasodilator given after 8 and 12 tape strips:* • TEWL Asians > blacks > Caucasians ($p < 0.05$) (Asians 1.7× > Caucasians)
(8)	*In vivo*	Blacks, Caucasians, Hispanics, Asians (number of subjects and ages not specified)	Not documented	• Baseline TEWL blacks > Caucasians ≥ Hispanics ≥ Asians
(9)	*In vivo*	*Skin type V/VI:* African–Americans 4; Filipinos 2; Hispanics 1 *Skin type II/III:* Asians 6; Caucasians 8 (ages 22–38)	Volar forearm	• Skin type V/VI required more tape strippings (66.7 ± 6.9) compared to skin type II/III (29.6 ± 2.4) to achieve the same TEWL (i.e., skin type V/VI had increased water barrier strength [integrity]) • Barrier function in skin type V/VI recovered more quickly
(10)	*In vivo*	Black women 30; Caucasian women 30 (ages 18–45)	Left and right medial cheeks, midvolar forearms, lateral mid-lower legs	• TEWL blacks < whites on cheeks (20% less) and legs (17% less) at baseline ($p < 0.05$); also lower on forearm, but not statistically significant
(11)	*In vivo*	Black women 8; Caucasian women 10 (mean age 42.3 ± 5 for both)	Midvolar forearm	*After tape stripping:* • TEWL blacks 1.2× > Caucasians after 3 ($p < 0.05$) and 6 tape strips ($p < 0.03$)
(12)	*In vivo* with topical application of SLS (irritation)	Asians 22 (mean age 25.8); Caucasians 22 (mean age 26.9)	Forearms	• TEWL Asians > Caucasians at baseline and after SLS (0.25% and 0.5%)
(13)	*In vivo*	Black women 25; African or Caribbean mixed-races 25; Caucasians 25 (age 20–32)	Forehead Volar forearm	• No significant differences in TEWL between the three ethnic groups
(14)	*In vivo*	African–Americans 73 Caucasians 119 East Asians 149	Left and right facial cheeks	• Baseline TEWL Caucasians > East Asians > African–Americans ($p < 0.001$)
(15)	*In vivo*	Thai women 99 (mean age 43.9 ± 10.9)	Labia majora, groin, mons pubis, inner thigh, and inner forearm	• TEWL vulvar skin > other sites • No ethnic and/or other differences

Source: Adapted from Wesley NO, Maibach HI. *Am J Clin Dermatol* 2003; 4: 843.
Note: Ages reported in years.
Abbreviation: TEWL: transepidermal water loss; SLS: sodium lauryl sulfate; MN: methyl nicotinate.

Table 5.2 Water Content

Reference	Technique	Subjects	Site	Results
(20)	*In vivo*—resistance (electrode paste and electrode placement, respectively)	St Louis (ages 83–92 months): black boys 22, black girls 32, white boys 65, white girls 55 San Diego (mean age 23): black men 16, black women 5, white men 16, white women 5	First and third fingers of right hand	• Skin resistance blacks > whites at baseline ($p < 0.01$) (i.e., blacks have lower water content)
(4)	*In vivo* with topical application of SLS (irritant)—capacitance (facial aqua-meter)	Black men 10 (age 29.9 ± 7.2); white men 9 (age 30.6 ± 8.8)	Back	• No significant differences between blacks and whites at baseline or after SLS stress
(5)	*In vivo* with topical application of SLS (irritant)—capacitance (facial aqua-meter)	Hispanic men 7 (age 27.8 ± 4.5); white men 9 (age 30.6 ± 8.8)	Upper back	• No significant differences between Hispanics and whites at baseline *After SLS stress:* • Hispanics > whites when negative visual score was given for irritation ($p < 0.01$) (large standard deviations)
(6)	*In vivo*—conductance (Dermodiag®)	Blacks 15 (mean age 46.7 ± 2.4); whites 12 (mean age 49.8 ± 2); Hispanics 12 (mean age 48.8 ± 2)	Volar and dorsal forearm	• Blocks (13% less) volar < dorsal forearm ($p < 0.02$) • Whites (22% less) dorsal < volar forearm ($p < 0.001$) • Hispanics (11% less) dorsal < volar forearm ($p < 0.05$) • Black and Hispanics > whites on dorsal forearm at baseline • Hispanics > blacks and whites on volar forearm at baseline
(8)	*In vivo*—impedance (not documented)	Blacks, Caucasians, Hispanics, Asians (number of subjects and ages not specified)	Not documented	• Asians > Caucasians, blacks and Hispanics
(10)	*In vivo*—capacitance (NOVA® dermal phase meter)	Black women 30; white women 30 (age 18–45)	Left and right medial cheeks, midvolar forearms, lateral mid-lower legs	• Blacks > whites on cheeks at baseline ($p < 0.05$) • No significant differences between races on the forearms and legs
(21)	*In vivo*—capacitance (Corneometer CM 820®)	Black women 7, white women 5 (mean age 25.8 ± 4.2 for both); black women 5, white women 5 (mean age 64.7 ± 3.8 for both)	Preauricle, post neck, dorsal upper arm, dorsal forearm, volar forearm, lower back, abdomen, thigh, lower leg	• No significant differences between blacks and whites at baseline
(22)	*In vivo*—capacitance (SkinChip®: dryness index)	African–Americans 114 Chinese 89 Caucasians 63 Mexicans 45 (age 18–87)	Dorsal and volar forearm	• No significant differences between races for the younger group (age 18–50) • Dryness index African–Americans > Mexicans and Chinese on volar forearm for the older group (age >51) • Dryness index African– Americans and Caucasians > Chinese on dorsal forearm for the older group (age >51)
(13)	*In vivo*—capacitance (Corneometer CM 825®)	Black women 25; African or Caribbean mixed-races 25; Caucasians 25 (age 20–32)	Forehead, volar forearm	• No significant differences between three ethnic groups
(15)	*In vivo*—capacitance (Corneometer CM 825®)	Thai women 99 (mean age 43.9 ± 10.9)	Labia majora, groin, mons pubis inner thigh, inner forearm	• Capacitance labia, mons pubis, and inner thigh < groin and inner forearm ($p < 0.05$)
(23)	*In vivo*—capacitance (MY-808S)	Japanese women 40 (mean age 31.5 ± 5.2)	Labia majora, groin, mons pubis, inner thigh	• Capacitance labia < mons pubis, groin, and inner thigh ($p < 0.001$)

Source: Adapted from Wesley NO, Maibach HI. *Am J Clin Dermatol* 2003; 4: 843.
Note: Ages reported in years unless specified otherwise.
Abbreviation: SLS: sodium lauryl sulfate.

Miyamoto et al. (23) assessed the skin moisture of these sites in Japanese woman and found that it is significantly lower in labial skin than in the skin at other sites. Overall, the studies indicate that racial differences in water content measured by resistance, capacitance, conductance, and impedance are inconclusive.

Corneocyte Variability

Three studies investigated corneocyte desquamation in black, white, and Asian subjects (Table 5.3) (10,21,24). All of the studies had statistically significant—yet conflicting—results. Corcuff et al. (24) reported that spontaneous desquamation measured on the upper outer arm was 2.5-times greater in blacks than in whites and Asians ($p < 0.001$); Warrier et al. (10) found desquamation to be less in blacks, and Manuskiatti et al. (21) detected a difference only at the preauricular measurement site. Again, variation in anatomic site may have caused these variable results, as well as the environmental conditions when the tests were conducted. Racial differences in corneocyte desquamation are inconclusive. The most clinically provocative observation is that of Corcuff et al. (24), who found a 2.5-times greater spontaneous desquamation rate in blacks compared to Caucasians and Asians.

Blood Vessel Reactivity

Several studies have investigated racial blood vessel reactivity as an assessment of skin physiology, irritation, evaluation of dermatologic pathology/treatments, effects and delivery of drugs, and wound healing. Earlier evaluation of cutaneous microcirculation depended on visual scoring in order to assess erythema or pallor (blanching), which has been proven to be unreliable. Two techniques, laser Doppler velocimetry (LDV) and photoplethysmography (PPG), can measure cutaneous blood flow. LDV has been utilized in skin physiology research, diagnostics, predictive testing of the irritancy of substances (cosmetics, cleansing agents, topical medications, etc.), and the cutaneous effects of drugs. PPG has been applied in skin physiology studies, dermatological disorders, and systemic diseases (25,26).

Table 5.4 summarizes the findings of six studies of blood vessel reactivity in blacks, whites, Hispanics, and Asians (4,5,7,26–29). Each study involved the administration of different vasodilating or vasoconstricting substances; thus, the results cannot be compared. However, each study, except for Berardesca et al. (5), found some variation in blood vessel reactivity when comparing Hispanics and whites. These findings are indicative of disparities in irritation, dermatotoxicology, and dermatopharmacology among different ethnic groups.

Surface skin temperature is the result of the equilibrium between the body's internal sources of heat supplied to the skin by vascular perfusion and heat loss to the external environment. Farage et al. (29) reported that the temperature of the skin at the labia minora and labia majora was lower in postmenopausal women, reflecting the underlying decrease in blood perfusion.

Skin Elastic Recovery and Extensibility

Racial differences in skin elastic recovery (Table 5.5) and extensibility (Table 5.6) were recorded by Berardesca et al. (6) and Warrier et al. (10). Extensibility is measured by applying torque parallel to the skin and measuring the amount of stretch; elastic recovery is the time that the skin takes to return to its original state after the torque is released.

Elsner et al. (30) found that the ratios between viscous deformation and elastic deformation and biological elasticity were both significantly lower in vulvar than in forearm skin. These data vary by anatomic site of testing and by race, and the age of study participants may affect the results as well. Therefore, conclusions cannot be drawn from these data, and further investigation, involving larger populations of participants and controlling for age differences, is necessary.

pH Gradient

Berardesca et al. (11) and Warrier et al. (10) (Table 5.7) also explored the differences in pH between the skins of Caucasian and black women. At baseline, no significant differences were found. After tape stripping, a lower pH in black skin compared to white skin was recorded in the superficial layers of the stratum corneum, but not in the deeper layers. Recently, Fotoh et al. (13) investigated the pH of the forehead skin of different races and found black women to have a cutaneous pH that is significantly higher than mixed-raced and Caucasian women.

Fujimura et al. (15) studied the pH of vulvar skin in Thai women, and their results showed that the skin pH around the vulvar area was significantly higher than that of control sites. However, no differences was found between these sites in Japanese women according to Miyamoto et al. (23).

Table 5.3 Corneocyte Variability

Reference[a]	Subjects[b]	Site	Results
(24)	Black (mean age 33.5 ± 7.5); Caucasian (mean age 31 ± 7); Asian (mean age 26.5 ± 7.5) (18–25 subjects per group)	Upper outer arm	• No difference in corneocyte surface area • Spontaneous desquamation (corneocyte count) blacks 2.5× > Caucasians and Asians ($p < 0.001$)
(10)	Black women 30; white women 30 (ages 18–45)	Left and right medial cheeks, midvolar forearms, lateral mid-lower legs	• Desquamation index blacks < whites on cheeks (18% less) and forearms (20% less) ($p < 0.05$), but no significant differences on the legs
(21)	Black women 7; white women 5 (mean age 25.8 ± 4.2 for both); black women 5; white women 5 (mean age 64.7 ± 3.8 for both)	Preauricle, post neck, dorsal upper arm, dorsal forearm, volar forearm, lower back, abdomen, thigh, lower leg	• No difference in desquamation index between blacks and whites except at preauricular area ($p = 0.02$) (which race was greater is not specified)

Source: Adapted from Wesley NO, Maibach HI. *Am J Clin Dermatol* 2003; 4: 843.

[a] No additional data available for vulva from *The Vulva: Physiology and Clinical Management*, First edition.

[b] Age reported in years.

Table 5.4 Blood Vessel Reactivity

Reference	Technique	Subjects	Site	Results
(26)	Topically administered MN (vasodilator); LDV and PPG	Blacks 6 (age 20–30); whites 6 (age 20–30); whites 6 (age 63–80)	Volar forearm	*Vasodilator given:* • No significant difference in time to peak response, area under response–time curve, or time for response to decay to 75% of its maximum value • PPG maximum response: young black (40% less) < young white ($p < 0.05$)
(4)	Topically administered SLS (irritant); LDV	Black men 10 (age 29.9 ± 7.2); white men (9) (age 30.6 ± 8.8)	Back	*SLS stress:* • No significant difference between blacks and whites • Blood vessel reactivity minimal in blacks from baseline to application of 0.5% SLS on untreated skin (see text for details)
(5)	Topically administered SLS (irritant); LDV	Hispanic men 7 (age 27.8 ± 4.5); white men 9 (age 30.6 ± 8.8);	Upper back	*SLS stress:* • Similar LDV response in Hispanics and whites
(27)	Topically administered corticoid[a] (vasoconstrictor); LDV	Black men 6; Caucasian men 8 (mean age 27 ± 3, both)	Forearm	*After vasoconstrictor given:* • 40% decreased area under the curve response in blacks compared to whites ($p< 0.04$) • 50% decreased peak response in blacks compared to whites ($p < 0.01$) • Decreased decay slope after peak blood flow in blacks compared to Caucasians; in blacks, • $y = 3.3672 – 0.0737x$ before treatment compared to • $y = 2.5347–0.0367x$ after treatment ($p < 0.04$) (i.e., less blood vessel reactivity in blacks)
(28)	Topically administered MN (vasodilator); LDV	Blacks 5; Caucasians 5; Asians 5 (ages 20–35)	Upper third of volar forearm	*Vasodilator given:* • Area under the curve for LDV response versus time in blacks > Caucasians for all MN concentrations ($p < 0.05$) • Area under the curve for LDV response versus time in Asians > Caucasians for higher dose levels of MN ($p < 0.05$)
(7)	Topically administered MN (vasodilator); LDV	Blacks 7; Caucasians 8; Asians 6 (ages 23–32)	Volar forearm	*Vasodilator given:* • Before tape stripping: no difference between the groups in basal perfusion flow, but lag time before vasodilatation was blacks > Caucasians > Asians ($p < 0.05$) • After 8 and 12 tape strips: lag time before vasodilatation decreased in all three groups, but significantly decreased in Asians > Caucasians > blacks ($p < 0.05$)
(29)	Skin temperature (Exergen Derma Temp)	45 women Pre-M, Post-M HRT, and Post-M non-HRT 15 each (ages 21–70)	–	• Differences in values of skin temperature at all the sites were small but significantly different *Surface skin temperature:* Labia minora: the Post-M non-HRT < Pre-M and Post-M HRT ($p = 0.0087$ and 0.0388, respectively) Labia majora: Pre-M > Post-M HRT and Post-M non-HRT ($p = 0.0035$ and 0.0025, respectively)

Source: Adapted from Wesley NO, Maibach HI. *Am J Clin Dermatol* 2003; 4: 843.
Note: Ages reported in years.
[a] Corticoid, clobetasol propionate 0.05% ointment.
Abbreviation: MN: methyl nicotinate; LDV: laser Doppler velocimetry; PPG: photoplethysmography; SLS: sodium lauryl sulfate; Post-M: postmenopausal; Pre-M: premenopausal; HRT: hormone-replacement therapy.

Table 5.5 Skin Elastic Recovery

Reference	Technique	Subjects	Site	Results
(6)	*In vivo*	Blacks 15 (mean age 46.7 ± 2.4); whites 12 (mean age 49.8 ± 2); Hispanics 12 (mean age 48.8 ± 2)	Volar and dorsal forearm	• No significant difference between races on dorsal forearm • Elastic recovery: blacks (26% less) < whites on volar forearm ($p < 0.001$)
(10)	*In vivo*	Black women 30; white women 30 (ages 18–45)	Left and right medial cheeks, midvolar forearms, lateral mid-lower legs	• No significant difference between races on the legs • Elastic recovery of blacks 1.5× > whites on cheeks ($p < 0.05$)

Source: Adapted from Wesley NO, Maibach HI. *Am J Clin Dermatol* 2003; 4: 843.
Note: Ages reported in years.

Table 5.6 Skin Extensibility

Reference	Technique	Subjects	Site	Results
(6)	*In vivo* (Twistometer®)	Blacks 15 (mean age 46.7 ± 2.4); whites 12 (mean age 49.8 ± 2); Hispanics 12 (mean age 48.8 ± 2)	Volar and dorsal forearm	• Significant dorsal < volar extensibility within whites and Hispanics ($p < 0.001$ and $p < 0.002$, respectively) • Black > white extensibility in dorsal forearm ($p < 0.01$) • Black < white extensibility in volar forearm ($p < 0.01$)

Source: Adapted from Wesley NO, Maibach HI. *Am J Clin Dermatol* 2003; 4: 843.
Note: Ages reported in years.

Table 5.7 pH Gradient

Reference	Subjects	Site	Results
(11)	Black women 8; Caucasian women 10 (mean age 42.3 ± 5 for both)	Midvolar forearm	• No significant difference in pH at baseline *After tape stripping*: • pH significantly decreased in blacks after three tape strips (i.e., superficial SC layers) • No differences between races after 9, 12, and 15 tape strips (i.e., deeper SC layers)
(10)	Black women 30; white women 30 (ages 18–45)	Left and right medial cheeks, midvolar forearms, lateral mid-lower legs	• pH blacks (pH = 5.15) < whites (pH = 5.52) on cheeks at baseline ($p < 0.05$) • No significant difference in pH on the legs at baseline
(13)	Black women 25; African or Caribbean mixed-races 25; Caucasians 25 (age 20–32)	Forehead	• pH blacks (pH = 5.9) > mixed-race and Caucasians (pH = 5.4 for both) ($p < 0.001$)
(15)	Thai women 99 (mean age 43.9 ± 10.9)	Labia majora, groin, mons pubis, inner thigh, inner forearm	• pH labia and mons pubis > inner thigh and forearm ($p < 0.05$)
(23)	Japanese women 40 (mean age 31.5 ± 5.2)	Labia majora, groin, mons pubis, inner thigh	• No significant difference in pH between these sites
(31)	45 women Pre-M, Post-M HRT and Post-M non-HRT 15 each	Vaginal, introitus, labia minora, labia majora	• Higher pH at vagina and introitus of self-declared sensitive skin subjects in all groups (no statistical significance, $p > 0.05$)

Source: Adapted from Wesley NO, Maibach HI. *Am J Clin Dermatol* 2003; 4: 843.
Note: Ages reported in years.
Abbreviation: SC: stratum corneum; Pre-M: premenopausal; HRT: hormone-replacement therapy.

Farage et al. (31) identified a potential association between self-declared sensitive skin in the genital area and the level of pH in premenopausal, postmenopausal women on hormone-replacement therapy, and post-menopausal non-hormone-replacement therapy women. The differences in pH were small; however, the sensitive group had a higher pH at the vagina and introitus. There was no consistent pattern at the labia minora or labia majora (Table 5.7).

However, these studies differed in anatomic testing sites. Although the results suggest that there may be some difference in the pH of the stratum corneum between these races, the factors responsible for this remain unknown.

LIPID CONTENT

Five studies evaluated lipid content (Table 5.8) (8,13,14,32,33). Again, the studies were variable in the anatomic sites tested, and one early study also evaluated the skin of black male cadavers. Sugino et al. (8) and Muizzuddin et al. (14) found lower ceramide level in blacks as compared to other races. Reinertson and Wheatley (32) found higher lipid levels in blacks; however, Harding et al. (33) and Fotoh et al. (13) found no difference between participants from different races.

Surface Microflora

The vaginal ecosystem changes continually over a lifetime, as both intrinsic and extrinsic factors assail the fragile balance between competing organisms (34). Few studies have been conducted in order to understand the microbial population on the vulva (35), and the microbiota of the aged population has not been completely characterized (36). A strong influence on the vaginal microbiota is hormonal changes. According to Farage et al. (37), *Lactobacillus* and other lactic acid-producing microbes form the foundation of a healthy vaginal microbiota during the reproductive years. Vaginal lactobacilli depend on the presence of estrogen, which decreased after menopause. Hormone-replacement therapy during menopause seems to restore vaginal pH and to re-establish the normal vaginal microbiota in postmenopausal women. Jakobsson and Forsum (38) verified that *Lactobacillus iners* is a dominant part of the vaginal flora when the flora is at a transitional stage between abnormal and normal.

There are no studies on racial differences of vulvar skin. Researchers inoculated the forearm skin of 10 black and 10 white men with *Candida albicans* and visually scored the severity of dermatitis by the severity of pustules (Table 5.9) (10,39). They also assessed microflora populations after aerobic incubation.

Table 5.8 Lipid Content

Reference[a]	Subjects	Site	Results
(32)	*Cadavers*: Black man 1; white men 3 *Living*: Black man 1; white man 1 (ages 49–68)	*Cadavers:* abdomen *Living:* back and thigh	• Lipid and sterol content in total epidermis blacks > whites
(8)	Blacks, Caucasians, Hispanics, Asians (number of subjects and ages not specified)	Not documented	• Ceramide levels: blacks (50% less) < whites and Hispanics ($p < 0.05$)
(33)	UK 41; Thai (dry season) 31; Thai (humid season) 31 (ages 20–40)	Scalp	• UK and Thai subjects demonstrated similar levels of total lipids
(13)	Black women 25; African or Caribbean mixed-races 25; Caucasians 25 (age 20–32)	Forehead Volar forearm	• No significant differences in lipid index between three ethnic groups
(14)	African–Americans 73 Caucasians 119 East Asians 149	Left and right facial cheeks	• Ceramide levels of Caucasians and East Asians > African–Americans ($p < 0.001$)

Source: Adapted from Wesley NO, Maibach HI. *Am J Clin Dermatol* 2003; 4: 843.
Note: Ages reported in years.
[a] No additional data available for vulva from *The Vulva: Physiology and Clinical Management*, First edition.

Another study evaluated facial skin microflora in black and white women. Both studies found that blacks had more skin microflora than whites, but the results differed with regard to the density of aerobes. Thus, further investigation will be necessary before conclusions can be drawn.

Mast Cell Granules

Sueki et al. (40) used electron microscopy in order to study punch biopsies of normal skin from black and white men. The study revealed statistically significant structural differences between the mast cells of the medial–lateral buttock skin of blacks versus whites (Table 5.10); black skin had larger mast cell granules, increased parallel–linear striations, and increased tryptase localized in parallel–linear striations. A clinical study evaluated several biomolecules and physical measures in the genital skin of premenopausal and postmenopausal women (29). The concentration of interleukin-1α was lower in the premenopausal group than in postmenopausal women, demonstrating less inflammation at the site. The levels of histamine and histidine were higher for the premenopausal group compared to both postmenopausal groups. The histidine/histamine ratio was much lower for the premenopausal group at the tested anatomic sites, probably due to the higher levels of histamine. Further research should focus on investigating additional proinflammatory mediators and involve a larger participant pool.

CLINICAL OBSERVATIONS

Clinically, acute contact dermatitis generally occurs more commonly in whites than in blacks (1). Blacks, however, develop disorders of pigmentation and lichenification more often than whites. Hyperpigmentation is thought to occur more readily in black patients after contact with mild irritants. Blacks show the dermatological signs of aging at a more advanced age compared with whites. Skin wrinkling and sagging is a predominant problem of whites, whereas mottled hyperpigmentation and uneven skin tone is associated with black skin (41). These data suggest that there are ethnic/racial predispositions to certain skin conditions.

Qualitatively, it has been noted that vulvar appearance in dark-skinned blacks and Hispanics is somewhat different from that of fair-skinned patients with atopic dermatitis and neurodermatitis (7). The erythema is masked by the dark skin color, leading examiners to underestimate the severity of the inflammatory process. Lichenification is often exaggerated and postinflammatory hyperpigmentation is always present (42). Wesley and Maibach (2) concluded that differences exist, but that much remains to be done in order to clarify their extent, mechanisms, and clinical relevance.

Racial (ethnic) differences in the skin of the vulva are likely to exist, considering that there are such differences in other areas of the body. Given the reasonable evidence of objective studies supporting differences in the skin function and physiology between ethnicities/races in general, it is likely that such difference also exists with regard to the skin of vulva. Racial hair differences are dramatic and unquestioned (43).

CONCLUSION

Differences of skin characteristics have been linked with ethnic background. However, racial differences of the skin have not been thoroughly investigated. To this day, the available research indicates variation of the skin's properties between all racial groups. However, the data are often contradictory, such as that of TEWL, water content, corneocyte desquamation, and skin surface pH. The literature regarding some skin parameters are limited (i.e., blood vessel reactivity, mast cell granules, elasticity, lipid content, and skin microflora), making the drawing of conclusions difficult. Further evaluation of different ethnic skin types is needed in order to obtain a better understanding and less conflicting results.

It is known that the vulva is more permeable than the exposed skin due to its structure, hydration, occlusion, and susceptibility to friction. Future studies in dermatology should address such differences by studying vulvar skin directly. The morphology and physiology of the vulva undergo characteristic

Table 5.9 Skin Surface Microflora

Reference	Subjects	Site	Results
(39)	Black men 10; white men 10 (ages 21–59)	Forearm	• *Candida albicans* infection: blacks (150% greater) > whites ($p < 0.025$) • Aerobes infection: blacks (650% greater) > whites ($p < 0.025$)
(10)	Black women 30; white women 30 (ages 18–45)	Left and right medial cheeks, midvolar forearms, lateral mid-lower legs	• Density of *Propionibacterium acnes* in blacks > whites, but not statistically significant • No significant difference in aerobes

Source: Adapted from Wesley NO, Maibach HI. *Am J Clin Dermatol* 2003; 4: 843.
Note: Ages reported in years.

Table 5.10 Mast Cell Granules

Reference	Technique	Subjects	Site	Results
(40)	EM of biopsy specimen	Black men 4 (mean age 29.2 ± 3); Caucasian men 4 (mean age 29.4 ± 1.2)	Medial–lateral buttock	• Mast cells contain 1.5× larger granules in black skin compared to white skin ($p < 0.0001$) • Mast cells contain 15% more PLSs in blacks compared to whites ($p < 0.05$) • Mast cells contain 30% fewer curved lamellae in blacks compared to whites ($p < 0.05$) • Tryptase immunoreactivity localized to PLS regions in black skin compared to curved lamellae regions in white skin ($p < 0.0001$) • Cathepsin G localized to electron-dense amorphous subregions in both black and white skin

Source: Adapted from Wesley NO, Maibach HI. Racial (ethnic) differences in skin properties: The objective data. *Am J Clin Dermatol* 2003; 4: 843.
Note: Ages reported in years.
Abbreviation: EM: electron microscopy; PLS: parallel–linear striation.

Table 5.11 Considerations for Future Research of Racial Skin Differences

- Definition of ethnicity/race
- Larger sample sizes
- Ethnic groups in the same versus varying geographies
- Comparable anatomic site assessments
- Age-related study of racial skin
- Comparable measurement methods
- Comparable environmental conditions
- Comparable psychological stress
- Comparable diets (e.g., controlled diets)
- Skin care habits relationship
- Body mass relationship
- Prior dermatologic disease
- Socioeconomic factors
- Correlation of skin parameters with pigmentation

Source: Adapted from Wesley NO, Maibach HI. *Am J Clin Dermatol* 2003; 4: 843.

age-related changes over a lifetime (44,45). Thus, it is necessary to consider age when investigating ethnic differences in vulvar skin (Table 5.11). In order to better understand the properties of vulvar skin among ethnic groups, more large-scale studies are needed, which will involve subjects representing different ages and racial groups. Classic and also new, noninvasive techniques are recommended for use during practice (46). Such studies will be more challenging to perform given the potential difficulty of accessing the vulva and collecting objective data, as well as the potential difficulty of recruiting sufficient numbers of participants to achieve statistical power. A greater understanding of these ethnic/racial differences should lead clinicians to a more effective path toward management.

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Vulvar and extragenital clinical sensory perception*

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INTRODUCTION

Research on sensory perception of the vulva has focused largely on the sexual response (1) and on the sensation of pain in pathological conditions such as provoked vestibulodynia (vulvar vestibulitis syndrome [VVS]) and idiopathic vulvodynia. Our interest is in better characterizing vulvar sensory perception in healthy women, the factors that affect it, and any insights that might apply in clinical settings or even to products research. This article reviews two sources of information on vulvar sensation: (i) quantitative sensory testing (QST), which measures the perception thresholds of quantifiable stimuli such as temperature, touch, pressure, and vibration; and (ii) subjective sensory effects (wetness, dryness, itch, burning, and stinging) reported by women who used external feminine hygiene products under controlled conditions. For perspective, trends in the sensory perception of extragenital skin in comparison to vulvovaginal tissue are also summarized. Although the research on vulvar sensation is very limited, objective QST and surveys of subjective sensation experienced in product trials provide complementary information about sensory perception on the vulva and the effects of variables such as age, the menstrual cycle, and menopause.

NEURAL SENSATION OF PHYSICAL STIMULI

It is helpful to briefly review how the perception of sensation is mediated by the nervous system. In glabrous and semiglabrous skin, the sensation of mechanical stimuli (touch, pressure, and vibration) and the sensations of temperature and pain are mediated by different parts of the nervous system. Touch, pressure, and vibration are detected by specialized mechanoreceptors: rapidly adapting receptors, such as Meissner corpuscles and Pacinian corpuscles, detect transient light touch and transient deep pressure, respectively; slowly adapting receptors, such as Merkel cells and Ruffini receptors, respond to more sustained touch, such as sensing texture or shape. The sensory input from these mechanoreceptors is conducted by large myelinated fibers in the peripheral nerves and by the dorsal column of the spinal cord.

Temperature and pain are detected by free nerve endings in the skin; the sensory input is conducted by the small fiber system and its central connections in the spinothalamic tracts. Moreover, within the small fiber system, different fibers convey sensory impulses in response to temperature and pain: thinly myelinated fibers convey impulses from heat and cold receptors and unmyelinated fibers convey impulses from nociceptors that respond to painful or noxious stimuli. Sensory information transmitted along the spinal cord is ultimately processed via the thalamus to be interpreted by the cerebral cortex and cerebellum.

Various sensory nerves innervate the vulva and perineum (Figure 6.1): the posterior femoral nerve innervates the latter aspect of the perineum posteriorly and the lateral margin of the vulva superiorly along the leg crease; the genitofemoral and ilioinguinal nerves (originating from L1–L2) innervate the mons pubis and upper labia majora, approximately to the level of the urethra; and the perineal branch of the pudendal nerve (from sacral roots S2–S4) is viewed by most clinicians as the primary source of vulvar innervation (lobes of the labia majora through the vestibule). A network of nerves over the dorsal aspect of the glans clitoris arises from the deeper pudendal nerve. Coverage of the vulva can also include the inferior cluneal nerve, which originates from S1–S3. The correlation between these anatomical details and the characteristics of vulvar sensation and pain is not well characterized, and mapping these relationships is an area of active research in our laboratories (2).

QUANTITATIVE SENSORY TESTING

QST is used to quantify sensory function in healthy people and in patients at risk for neurological impairment (3). It is also employed to assess factors that affect pain perception (4–6). In QST, a measurable stimulus is applied to the skin and the subject or patient reports his or her perception of it. The method employs calibrated instruments in order to deliver known intensities of physical stimuli; for example, mild electric current (by means of surface electrodes), temperature (via electric thermodes with controlled surface temperatures), touch (using filaments whose bending force depends on diameter and length), pressure (exerted by spring-loaded devices), and vibration (using tuning forks or vibrators that deliver sinusoidal stimuli at a given frequency). A stimulus of a given intensity is applied, and the subject reports whether or not the stimulus is perceived (or, in pain studies, whether or not the stimulus elicits pain). The lowest intensity that is perceptible (or, if pertinent, painful) is the detection threshold.

Two general methods are employed to determine these thresholds: (i) the method of limits; and (ii) the method of levels. With the method of limits, the stimulus is progressively increased and the subject declares when it first becomes perceptible. With the method of levels, a stimulus of a defined intensity is applied, then increased or decreased by specific

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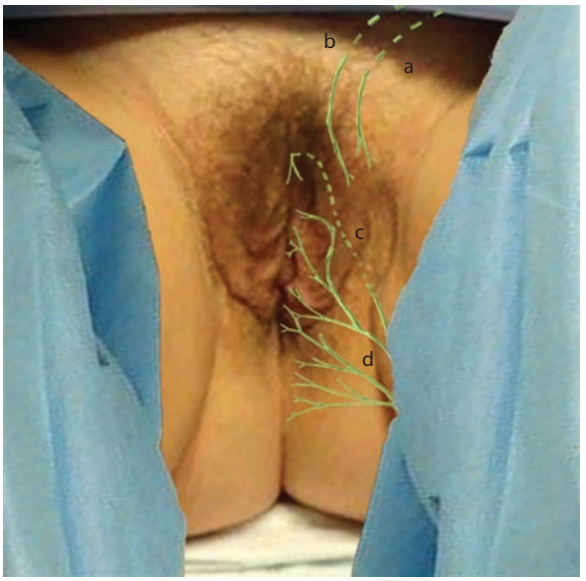

Figure 6.1. Schematic of the innervation of the vulva. (a) Anterior labial branches of ilioinguinal nerve. (b) Genitofemoral nerve. (c) Dorsal nerve of the clitoris (continuation of pudendal nerve shown deeper [as dashed lines] in muscles of urogenital diaphragm). (d) Branches of pudendal nerve.

increments depending on whether or not the subject perceives it. (Protocols may differ in terms of the number of consistent responses required to progress upward or downward in stimulus intensity.)

With the method of limits, sensory information is processed neurologically at the same time as the stimulus intensity is being changed. The inherent response lag leads to a small error in threshold measurement; consequently, thresholds measured with the level of limits skew higher than those measured with the method of levels (7,8). Moreover, the rate of change of the stimulus affects the thresholds obtained by the method of limits

The method of levels is known as "forced choice," as the subject must declare or "choose" whether or not the stimulus is perceived. Because this method takes longer and is more repetitive, errors can result if the subjects become fatigued or distracted as the test proceeds.

Experimental variables such as the application site, the surface area of contact, the frequency of the stimulus (in the case of vibration), and the rate of change of stimulus intensity affect the absolute values of the thresholds measured. Consequently, the absolute values measured are functions of the experimental conditions employed, and the lack of standardization complicates comparisons between experiments. This review will focus on the relative thresholds assessed within experiments (e.g., thresholds measured at different anatomical sites or in people of different ages) to draw conclusions about the variables that affect sensory perception.

SENSORY THRESHOLDS ON EXTRAGENITAL SITES

Before discussing sensory perception on the vulva, it is helpful to review what is known about responses at extragenital sites. Table 6.1 (5,7,9–14) summarizes some representative QST studies. The research shows that sensitivity to touch, vibration, and thermal stimuli varies by site. For example, the hands appear to be more sensitive to touch, and especially to vibration, than the feet (3,11).

Of the various demographic (age, gender, and ethnicity) and anthropometric variables (height, weight, and side of the body) that have been studied, advancing age appears to have the most significant effect on sensory perception. QST of the hand and foot shows that sensitivity to mechanical stimuli (touch and vibration) declines with age. The decline becomes apparent by the fifth decade and progresses exponentially after 65 or 70 years of age (9,10). The rate of decline differs by site. For example, thresholds of perception of touch and vibration remain approximately constant on the face, but the sensitivity to touch on the hands declines rapidly with advancing age (3). Moreover, age-related losses in sensitivity to vibration or skin indentation are more severe for the lower extremities (7,9,12), perhaps reflecting the longer distance of the neural pathway that the sensory input must travel.

Some evidence exists that thermal thresholds also decline with age, but the effect may be weaker or less consistent at various sites (7,10,11,13), as several studies show no change. Interestingly, a British study of people aged 20–39 and 55–65 years detected an age-related decrease in sensitivity to warm and cold stimuli on the finger and forearm, but only with a probe having a surface area of 2.8 cm^2, not with a probe of 1 cm^2. Moreover, the absolute heat perception thresholds were lower and cold perception thresholds higher overall when the larger probe was used (13). This indicates that contact area affects the absolute values of experimentally determined perception thresholds.

Gender differences in sensory perception have been found, but not consistently. The degree of difference in sensitivity between men and women may depend on the age range studied, the anatomical sites assessed, and the sample size. With regard to mechanical stimuli, several studies found no gender differences in perception thresholds on the forehead (3), on the hand, distal phalanx of the middle finger, or dorsal surface of the forearm, regardless of age (13), or on the thenar eminence of the hand or plantar surface of the foot (12). However, some studies have detected gender-related differences in the perception of mechanical stimuli. A U.S. study of 350 people found that, among those aged over 50 years, women were more sensitive to vibration on the dorsum of the hands and feet than men (9); similarly, vibratory thresholds among 484 Taiwanese were lower in women than in men on the dorsum of foot, but no different on the thenar eminence of the hand (7). A study of 44 Belgian and Japanese subjects found that, in both ethnic groups, women were more sensitive than men to filament touch on the cheek and to filament prick pain and pressure pain on the cheek, gingiva, and thenar skin (14).

With respect to the effect of gender on thermal sensitivity, some but not all studies found women to be more sensitive than men. The ethnicity and age range of the subjects as well as the anatomical sites examined varied among studies. A Dutch study found women to be more sensitive to thermal stimuli on the foot than men (11). A Taiwanese study of 484 people found women to be more sensitive to warm thresholds on the both the thenar eminence of the hands and the dorsal surface of the feet than men (7). A British study similarly found women to be more sensitive to heat and cold stimuli on the thenar eminence of the hand, the distal phalanx of the middle finger, and the dorsal

Table 6.1 Factors Affecting Sensory Thresholds at Extragenital Sites

Population	N	Type of stimulus	Method used	Anatomical location	Key results	Comments	References
USA Children to adults aged 3–79 years	350	Vibration	*Method of limits* Stimuli: • 128 Hz Rydel–Seiffer tuning fork applied perpendicularly to skin surface • 120 Hz hand-held electromagnetic Vibrameter™	Dorsum of hands Dorsum of feet	***Location*** Hands more sensitive than feet ***Gender*** Perception threshold higher in men than in women over 50 years of age ***Age*** Perception threshold unaffected by age up to 17.9 years of age Threshold increased slightly in adults >40 years of age Perception threshold increased substantially in adults aged 70–79 years compared to those aged 18–29 years (30% increase on hands and 41% increase on feet in by Vibrameter™)	Absolute levels depend on method used The two methods were correlated (r = 0.954) Retest reliability was high Results not affected by skin temperature, body side, weight, or height	(9)
Age groups / Group size 3–4.9 / 19 5–6.9 / 54 7–11 / 110 12–17 / 113 18–29 / 82 30–39 / 41 40–49 / 42 50–59 / 31 60–69 / 24 70–79 / 14							
Canada Healthy adults aged 20–86 years	148	Temperature Vibration	*Method of levels* Medoc™ thermal sensory analyzer (computer-driven thermode) Vibratron II™ 200-μm max amplitude	Thenar eminence of right hand Dorsum of foot Index finger and big toe on opposite sides	***Height and age effects*** Thermal thresholds on hand and foot increased with height and age Thresholds on the hand but not on the foot increased with height Vibratory thresholds on the foot increased with height and with age Thresholds were exponentially higher after age 65 Vibratory thresholds on the hand unaffected by height	Height correlates to gender, men being generally taller than women Height is related to the distance that impulses from the foot must travel	(10)
Age groups / Group size 20–29 / 29 30–39 / 27 40–49 / 29 50–59 / 24 60–69 / 17 70+ / 22							

(*Continued*)

Table 6.1 (Continued) Factors Affecting Sensory Thresholds at Extragenital Sites

Population	N	Type of stimulus	Method used	Anatomical location	Key results	Comments	References
The Netherlands Healthy volunteers aged 21–92 years	71	Temperature (heat/cold)	*Method of levels* Peltier thermostimulator 3 × 4 cm double probe surface. One probe 5°C below body temperature; second varied higher or lower	Foot (dorsum)	***Age*** Significant increase in warm and cold thresholds with age ***Gender*** Women had lower thresholds than men	Similar decline with age for both warm and cold thresholds	(11)
USA Healthy adults	48		*Method of levels*	Hand (thenar eminence)	***Gender*** Young men more sensitive than young women to warm stimuli on the feet Sexes combined for remaining analyses	Losses in sensitivity to mechanical stimuli in older adults was apparent by fifth decade and was more severe at lower extremities	(12)
Age groups 19–31 55–84	Group size 27 21	Temperature increase/ decrease Tactile skin indentation Vibration	Peltier™ thermal transducer, probe surface 7.1 cm² Skin clamp, 1 mm/ second; indentation range 3–170 μm or 63–1640 μm, 2.9 cm² area 40 and 250 Hz transducer	Foot (plantar surface)	***Site*** In young adults, hands more sensitive than feet to temperature changes and high-frequency (250 Hz) vibration ***Age*** Older individuals less sensitive to warm stimuli on the feet Older hands, and especially older feet, less sensitive to skin indentation Older hands and feet less sensitive to vibration		
England Healthy volunteers Age groups 20–39 55–65	80 Group size 40 40	Vibration Temperature	Vibrometer at 31.5 and 125 Hz Thermal anesthesiometer, either 1 cm or 2.8 cm in diameter	*Hand*: Thenar eminence Distal phalanx of the middle finger *Forearm*: Dorsal surface	***Surface area of application*** Hot threshold lower and cold threshold higher with larger surface area of application regardless of age ***Age*** No difference in vibratory thresholds of hand and forearm with age, regardless of gender Significant increase in warm and cold thresholds with age at finger and forearm with 2.8 cm area of application ***Gender*** No difference in vibratory thresholds between genders, regardless of age Women had lower hot thresholds and higher cold thresholds than men	Sensitivity to temperature changes increased with larger surface area of application Changes in vibratory sensitivity with age were more apparent in studies that tested distal anatomic sites (foot) and older subjects (≥65 years)	(13)

(*Continued*)

Table 6.1 (Continued) Factors Affecting Sensory Thresholds at Extragenital Sites

Population	N	Type of stimulus	Method used	Anatomical location	Key results	Comments	References
Taiwan Healthy volunteers aged 20–86 years Age groups 20–39 40–59 ≥60	484 Group size 122 251 111	Vibratory Temperature	*Methods of levels and method of limits* Vibratory sensory analyzer Thermal sensory analyzer	Hand (thenar eminence) Foot (dorsum)	***Age*** Significant increase in vibratory, warm, and cold thresholds with age Rate of change with age greater on the foot than on the hand ***Site*** For each subject, thresholds on the foot always higher than on the hand ***Gender*** Women had lower warm thresholds on the hand and lower warm and vibratory thresholds on the foot than men ***Method*** Methods highly correlated, but thresholds by method of limits higher than by method of levels	For each modality, age had a more significant effect on thresholds than gender or anthropometric measurements	(7)
USA Healthy adults Age groups 19–31 55–84	48 Group size 27 21	Heat pain threshold	*Method of limits* (increasing temperature ramp)	Hand (thenar eminence) Foot (plantar surface)	***Site*** Hands more sensitive than feet ***Gender*** No difference in heat pain threshold ***Age*** No difference in heat pain threshold	Heat pain thresholds increased when repetitive temperature reversals were made, suggesting either receptor adaptation or subjects' increasing tolerance	(12)
Australia	20	Heat/cold pain threshold Measured over 3 weeks with two protocols	*Method of limits* (increasing or decreasing temperature ramp) Standard protocol Pre-exposure to non-noxious temperatures for familiarity, followed by standard protocol Peltier thermode 3 × 3 cm	Hand (dorsum)	***Pre-exposure*** Previous experience did not influence pain thresholds ***Test session*** Minimal variation between sessions ***Pain ratings*** Pain ratings higher at hot thresholds than cold thresholds Pain ratings at hot threshold were higher in women than in men	Wide interindividual variations were observed in pain thresholds	(5)

(*Continued*)

Table 6.1 (Continued) Factors Affecting Sensory Thresholds at Extragenital Sites

Population	N	Type of stimulus	Method used	Anatomical location	Key results	Comments	References
Belgium Caucasian adults Japan Japanese adults	Belgium 44 22 male 22 female Japan 44 22 male 22 female	Tactile detection threshold (TDT) Filament prick pain threshold (FPT) Pressure pain detection threshold (PPT) Pressure pain tolerance (PTOL) Numeric pain ratings	Pressure esthesiometer: Semmes–Weinstein monofilaments (TDT and FPT) *Method of levels* (stepwise raising and lowering of filament pressure based on positive or negative subject response) Pressure algorimeter (PPT and PTOL)	For TDT and FPT ***Orofacial*** • Cheek skin • Maxillary gingiva • Tip of tongue ***Hand*** • Thenar skin For PPT and PTOL ***Orofacial*** • Masseter muscle ***Hand*** • Thenar muscle	***Gender*** TDT on cheek lower in women than in men FPT on cheek, gingiva, and thenar skin lower in women than in men; women rated the pain lower than men at all sites except the cheek PPT and PTOL lower in women at both sites ***Ethnicity*** TDT on cheek and thenar skin lower in Japanese overall TDT on thenar skin lower in Japanese women than in Caucasian women FPT on cheek, tongue tip, and thenar skin lower in Japanese; FPT on cheek skin lower in Japanese men than in Caucasian men FPT pain ratings at gingiva and thenar skin lower in Japanese PPT pain rating at masseter and thenar muscles lower in Japanese PTOL ratings lower in Japanese	Overall, women more sensitive at detecting pain than men Japanese more sensitive at detecting pain than Caucasians However, despite being more sensitive at detecting pain, women rated pain intensity lower than men and Japanese rated pain intensity lower than Caucasians	(14)

surface of the forearm (13). However, a North American study of 48 people found men aged 19–31 years to be more sensitive to warm stimuli on the plantar surface of the feet compared to women in the same age group, but not on the thenar eminence of the hand (12).

One fairly consistent finding is that perception thresholds of mechanical and thermal stimuli and heat pain differ between distal and proximal limbs. In a group of 48 healthy American adults, the hands were more sensitive to heat pain than the feet, although no age- or gender-dependent differences were found (12). In this study, heat pain thresholds increased when repetitive temperature reversals were made, suggesting either a sensory or affective adaptation to pain. However, in an Australian study of 20 subjects, prior exposure to the experimental conditions did not affect pain detection thresholds (5). Adaptation may depend on the experimental conditions employed.

Ethnic differences in sensory perception have also been reported. For example, Japanese subjects were more sensitive to touch on the cheek and the thenar eminence of the hand than Caucasians. This group was also quantitatively more sensitive to pain elicited by a filament prick to the cheek, tongue, or thenar skin or to pressure on the masseter muscle of the jaw and thenar muscle of the hand (14). However, the Japanese subjects rated the pain as less severe on a subjective scale than Caucasians, despite being more sensitive at perceiving it. In the study just cited, cultural stoicism may have contributed to a higher tolerance to pain in the Japanese, although their perception thresholds were measurably lower. In the USA, quantitative studies comparing Hispanic, African–American, and Caucasian ethnic groups have found that Hispanics (15) and African–Americans (4,15–17) have comparable pain perception thresholds to Caucasians, but exhibit a lower pain tolerance. Studies suggest that among African–Americans, both social factors (such as high levels of stress) and physiological changes in endogenous mechanisms of pain regulation may contribute to lower pain tolerance in this group (18,19). The interpretation of ethnic differences in pain perception is controversial and no consensus exists on whether such differences result from physiological or cultural influences. A recent study demonstrated age and ethnic differences in pain sensitivity, with the greatest decline in lower extremities (20).

A comprehensive discussion of the causes and implications of ethnic differences in pain perception is beyond the scope of this chapter.

VULVOVAGINAL SENSORY THRESHOLDS

Published quantitative testing on vulvovaginal sensory thresholds is summarized in Table 6.2 (11,21–26). Studies that compared vulvovaginal sensory perception to sensory perception at other anatomical sites suggest that the vulva and vagina are relatively less sensitive to sensory stimuli. For example, among 58 premenopausal women in The Netherlands, the labia majora, labia minora, and clitoris were less sensitive to mild electric current than the lower abdomen or the dorsum of the hand; the vaginal wall was the least sensitive site studied (25). A Canadian study of 40 premenopausal women found the labium minus and the mucosa of the vulvar vestibule to be less sensitive than the forearm to filament touch and pressure, although the labium minus was more sensitive to pain than the forearm (26). Similarly, a Canadian study of 13 premenopausal women found the vulvar vestibule to be less sensitive to filament touch and pressure than the deltoid muscle, the forearm, or the thigh (27).

When vibratory thresholds were considered, a Swedish study found the clitoris to be less sensitive to the perception of vibration than the dorsum of the hand, but more sensitive than the dorsum of the feet (24). A study of vibratory thresholds performed in Turkey found that vulvar sites (labia majora and minora, clitoris, and vaginal introitus) were comparable in sensitivity to the first and second fingers and to the nipples; in this study, the ears and lips were the least sensitive to vibratory stimuli (22). A study showed that light touch sensation in the neck, forearm, and vaginal margin was greater than in the areola (28).

A few studies have compared sensory perception among various sites on the vulva. A U.S. study of 17 premenopausal women found slightly lower sensitivity to touch on the perineum, comparable sensitivity on the labia majora, labia minora, and clitoris, and slightly higher sensitivity on the anal verge (29). A Canadian study of 13 premenopausal women found the 1 o'clock position of the vulvar vestibule to be more sensitive to touch than the 6 or 9 o'clock positions or the inner aspect of the labium minus (27). Another study of 20 premenopausal women found the 9 o'clock position of the vestibule to more sensitive to touch than the labium minus (26). As noted earlier, a Dutch study reported that the vaginal wall was less sensitive to mild electric current than the labia majora, labia minora, or clitoris (25).

As is the case at extragenital sites, vulvar sensitivity to mechanical stimuli deteriorates with age. A U.S. study of 58 women aged 20–78 years found that age affected both genital and peripheral sensation: vibratory thresholds increased progressively with age at the vulva, clitoris, external urethral meatus, perineum, and ankle (22); on the vulva, the age effect first became apparent in the 30–39 years of age group. A study performed in Israel of 89 women aged 18–78 years found that sensitivity to vibration decreased with age on the clitoris and on the anterior vagina, but that the effect of age on clitoral sensitivity was smaller (23). In the latter experiment, the effect of age on vulvovaginal sensitivity to thermal stimuli was less straightforward: sensitivity to warmth decreased with age on the clitoris, but remained constant on the anterior vagina; however, sensitivity to cold decreased with age on the anterior vagina, but remained constant on the clitoris (23). One small study examined the impact of the menstrual cycle on vulvar sensitivity to vibration and found no effects at the clitoris, the hands, or the feet (24).

Along with age, the menopausal transition and the associated decline in estrogen levels appear to be critical determinants of the perception of touch on the vulva. The impact of estrogen status on vulvar and perineal sensitivity to punctate touch was demonstrated in a study of 38 women divided into five comparison groups: (i) premenopausal and postmenopausal women; (ii) normoestrogenic women (premenopausal women and postmenopausal women on estrogen-replacement therapy) and hypoestrogenic women (postmenopausal women not on estrogen-replacement therapy); (iii) women with or without clinical signs of vulvar atrophy; (iv) neurologically impaired women and healthy controls matched by age, parity, and estrogen status; and (v) women reporting sexual dysfunction and controls. Semmes–Weinstein monofilaments were used to apply different intensities of punctate pressure to the glans clitoris, bilateral sites on the labium minus and perineum, and the anal verge.

A clear effect of estrogen on vulvar sensitivity to punctate touch was demonstrated, with menopause, non-use of

Table 6.2 Factors Affecting Vulvovaginal Sensory Thresholds

Population	N	Type of stimulus	Method used	Anatomical location	Key results	Comments	References
USA Healthy and neurologically impaired women	38 32 healthy 5 impaired *Premenopausal* 17 *Postmenopausal* 15 6 with ERT 9 without ERT *Normoestrogenic* (premenopausal and postmenopausal women on ERT) 23 *Hypoestrogenic* (postmenopausal women not on ERT) 9 Neurologically impaired women compared to controls matched by age, parity, and estrogen status *Impaired sexual function* (by questionnaire)	Pressure/ touch	Pressure esthesiometer: Semmes–Weinstein monofilaments *Method of limits* Sequential application of pressure filaments to point of detection	Vulva/perineum • Clitoral glans • Labium minus (right and left) • Perineum (right and left) • Anal verge • Average vulvar score (all sites)	Significant loss of sensitivity to pressure/touch in postmenopausal women, hypoestrogenic women, women with vulvar atrophy, neurologically impaired women, and women with impaired sexual function	A clear effect of estrogen on vulvar sensitivity was demonstrated: menopause, non-use of ERT, and vulvovaginal atrophy were associated with decreased sensitivity to pressure/touch Although vulva has lower density of estrogen receptors than vagina, effect of estrogen on touch sensitivity appears profound	(11)
USA Postmenopausal hypoestrogenic women with lower genitourinary tract complaints (e.g., urinary incontinence, frequency, urgency, nocturia, and vaginal atrophy)	39 (30 completed study)	Pressure/ touch	*Protocol* RCT: topical application of estradiol cream to vulvar vestibule and vagina, nightly for 2 weeks, then 3× weekly for 2 weeks and 2× weekly for 2 more weeks, with or without pelvic muscle biofeedback *Intervention groups* 1. Active cream with biofeedback 2. Active cream with sham biofeedback 3. Placebo cream with biofeedback 4. Placebo cream with sham biofeedback *Outcome measure* Method of limits 1. Von Frey monofilament thresholds (mN) at vulvar vestibule 2. Maximum intravaginal pressure	Vulvar vestibule Vaginal wall	Estradiol treatment significantly increased sensitivity of vestibule to pressure/touch relative to placebo at 4 and 6 weeks Greatest improvements occurred in women aged 70–79 years	Mechanism of estrogen action on sensory function of vestibule not known Potential sensorineural targets may be C fibers or Merkel cells	(21)

(*Continued*)

Table 6.2 (Continued) Factors Affecting Vulvovaginal Sensory Thresholds

Population	N	Type of stimulus	Method used	Anatomical location	Key results	Comments	References
USA Women aged 20–78 years Examined variables of age, menopause, prior vaginal delivery, and history of neurological disorder	58 10 age 20–29 13 age 30–39 17 age 40–49 8 age 50–59 10 age 60–79	Vibration	*Method of limits* Commercially available 120 Hz biothesiometer	Vulva Clitoris External urethral meatus Right and left perineum Medial right ankle	*Age* Vibratory sensation thresholds progressively increased with age at vulva, clitoris, external urethral meatus, and ankle *Menopause* Sensitivity to vibration decreased on genital sites but not ankle	Age affected both genital and peripheral sensation Menopause affected genital sensation only	(22)
Israel Healthy women aged 18–78 years	89	Thermal (warm and cold) Vibratory	*Method of limits* *Thermal* Cylindrical clitoral thermal probe, 25-mm diameter, with contact element on end; vaginal thermal probe with thermal contact on outer cylindrical surface (28-mm diameter) *Vibratory* Vibrameter, 100 Hz, amplitude 0–130 μm Method of limits (linear change): 1°C/second for thermal, 1 μm/second for vibratory	Clitoris Vagina	*Thermal thresholds with age* Sensitivity to warmth decreased with age at clitoris, but was constant on anterior vagina Sensitivity to cold decreased with age at anterior vagina but remained constant on clitoris *Vibratory thresholds with age* Sensitivity to ascending vibration decreased with age on both vagina and clitoris	A smaller age effect on vibratory threshold was seen on clitoris compared to vagina	(23)
Sweden Healthy women aged 27–44 years	Age 35–45 N = 95 examined once Age 27–44 N = 8 examined over the menstrual cycle	Vibration	*Method of limits* Commercially available 100 Hz Vibrameter™	Clitoris Hands (dorsum) Feet (dorsum)	*Vibratory thresholds by site* Clitoris less sensitive than the hands, but more sensitive than the feet	No change in sensitivity with menstrual cycle	(24)

(*Continued*)

Table 6.2 (Continued) Factors Affecting Vulvovaginal Sensory Thresholds

Population	N	Type of stimulus	Method used	Anatomical location	Key results	Comments	References
Turkey Women with diabetes (age 39–50 years) and without diabetes (age 35–42 years) Sexual function (questionnaire) and genital and extragenital sensory function assessed	30 with diabetes 20 without diabetes	Vibration	*Method of limits* Commercially available 120 Hz biothesiometer, 300 mm^2 surface area 500 ms stimulus duration	*9 genital sites* Right and left labia majora, right and left labia minora, left and right side of clitoris, glans clitoris, and superior and inferior vaginal introitus *14 extragenital sites* Right and left nipple, upper and lower lip, right and left ear lobe, first and second fingers of right and left hand, first and second toes of right and left feet	Genital sites, nipples, and fingers did not differ in sensitivity; ears and lips were the least sensitive extragenital sites Women with diabetes were less sensitive to vibration at all anatomical sites tested In women with diabetes, the genital sites with greatest deficit in sensitivity to vibration were the vaginal introitus, followed by labia minora and clitoris	Absolute threshold values are highly dependent on type of equipment used	(22)
The Netherlands Healthy women aged 18–60 years All but 2 were premenopausal	60	Electric current	*Method of limits* Electrode Range 0–30 mA 100 Hz 5 ms duration Threshold of perception of prickly sensation	*Genital sites* Vaginal wall (2–4 cm from introitus) Left and right labia majora Left and right labia minora Clitoris *Extragenital sites* Hand (dorsum) Left and right lower abdomen	Genital sites less sensitive (~1 mA) than extragenital sites Vaginal wall least sensitive site The 12-hour position (upper vaginal wall) slightly more sensitive than other positions on vaginal tract circumference Dorsum of the hand more sensitive than abdomen	Absolute values depend on specific experimental conditions	(25)
Canada Nulliparous premenopausal women with or without VVS	26 13 VVS 13 controls	Pressure/ touch	Modified von Frey filaments of suture material monofilaments calibrated to Semmes–Weinstein, plus three lower pressures *Tactile thresholds* Method of levels (2-down, 1-up staircase method: 2 positive responses to same stimulus needed to move to next lower, one negative needed to move to next higher) *Pain thresholds* Method of limits (sequential pressure increase from tactile threshold)	Vulvar vestibule (1–3, 6, and 9 o'clock) and inner aspect of labium minus	*Controls* Thresholds higher at 1 o'clock position of vestibule than at 6 and 9 o'clock positions, or on labium minus *VVS* At all vestibular positions, tactile thresholds dramatically lower in VVS group: 6 o'clock most sensitive Pain thresholds significantly lower in VVS patients	In controls, vulvar vestibule was less sensitive to punctate tactile stimuli than glabrous skin of arm and leg Labium minus most sensitive to touch. Pain thresholds similar at all body sites tested	(21)

(*Continued*)

Table 6.2 (Continued) Factors Affecting Vulvovaginal Sensory Thresholds

Population	N	Type of stimulus	Method used	Anatomical location	Key results	Comments	References
					Genital vs. extragenital sites In controls, vestibule at 1 o'clock less sensitive to touch than deltoid, forearm, and thigh; similar pain thresholds at all sites In VVS group, vestibule more sensitive than deltoid, and pain thresholds lower at all sites	In women with VVS, tactile and pain thresholds in vestibule dramatically lower: tactile sensation levels in controls caused pain in some women with VVS, and they perceived vestibular touch at levels imperceptible to controls	
Canada Premenopausal women aged 18–45 years with or without VVS	40 20 VVS 20 controls	Touch and pressure under erotic and neutral conditions (erotic film or travel film viewing)	*Tactile thresholds* Method of limits, using modified von Frey filaments *Pain thresholds* Method of limits using vulvalgesiometer (spring-based pressure device with cotton swab tip) *Sexual arousal* Labial thermistor clip on labium minus	Vulvar vestibule (9 o'clock) Inner aspect of labium minus Volar surface of forearm	*Genital vs. extragenital sites* Forearm more sensitive to touch than genital sites Vestibule more sensitive to touch than labium minus Labium minus more sensitive to pain than forearm *Controls vs. VVS* VVS subjects more sensitive to touch and pain than healthy controls under both erotic and non-erotic conditions	Sexual arousal had no effect on extragenital sensation (forearm) Forearm, though more sensitive to touch, was less sensitive to pain than the labia Data suggest dyspareunia in VVS patients not due to lack of arousal	(26)

Abbreviation: RCT = randomized controlled trial; ERT = estrogen replacement therapy.

estrogen-replacement therapy, and vulvar atrophy all associated with decreased clitoral, labial, and overall vulvar sensitivity (29). For perspective, thresholds to touch averaged over all vulvar sites (clitoris, labium minus, perineum, and anal verge) were 4.6-fold lower in normoestrogenic compared to hypoestrogenic women. Sexual dysfunction and neurological impairment were also correlated with loss of vulvar sensitivity to touch.

Clinical trials of topical estrogen therapy support the conclusion that estrogen stimulation helps maintain vulvar sensory perception to touch. A prospective controlled trial examined the impact of topical estradiol cream applied to the vulvar vestibule and vaginal wall (either with or without biofeedback) in women with urogenital complaints aged 60 years or older (21). Topical estradiol cream was associated with a significant increase in vulvovaginal sensitivity to touch that improved as the duration of therapy progressed (specifically, after 4 and 6 weeks of treatment). The greatest improvements occurred in women aged 70–79 years.

Lastly, a U.S. study of women aged 20–78 years found that whereas age affected both genital and extragenital vibratory sensation, menopausal status affected genital sensation only (22). Taken together, these data indicate that the perception of punctate touch and vibration on the vulva and vagina is critically and uniquely dependent on estrogen status.

The perception of provoked vulvar pain is an issue of clinical importance. Some women with no identifiable pathology experience localized pain when pressure is applied to the vulvar vestibule. This idiopathic pain condition is known as provoked vestibulodynia or VVS (see Chapter 23 and (30) for reference). It is worth noting that QST has revealed objective, quantifiable differences in pain perception in women with this condition. Two Canadian studies examined vestibular perception of filament touch and touch-induced vestibular pain in premenopausal VVS patients and controls (26,27). A study with 13 nulliparous patients and 13 controls found tactile and pain thresholds on the vestibule to be dramatically lower in VVS patients than in controls. Specifically, tactile thresholds were approximately four-fold lower and pain thresholds approximately seven-fold lower in VVS patients; moreover, levels of pressure that were perceived as touch by healthy controls caused pain in some VVS patients, and thresholds to touch in VVS patients were imperceptible to the controls (27). A separate study examined the sensitivity of the vulvar vestibule to touch and pressure under neutral (travel film viewing) and erotic (erotic film viewing) conditions (26). A labial thermistor applied to the labium minus registered the level of arousal. Results showed the forearm to be more sensitive to touch than genital sites (vestibule or labium minus), but less sensitive to pain. On the vulva, the vestibule was more sensitive to touch than the labium minus. As in the previously cited study, VVS patients were more sensitive to vestibular touch than controls; sexual arousal increased vestibular sensitivity to touch in both patients and controls. However, in VVS patients, arousal also increased vestibular sensitivity to pain, whereas in healthy women, the pain sensitivity of the vestibule was unaffected. Sexual arousal had no impact on the sensation threshold to touch at an extragenital site (forearm). These data indicate that VVS patients have measurably heightened sensitivity to both vestibular touch and pain; moreover, dyspareunia in these patients is not necessarily due to a lack of sexual arousal, but in fact may be exacerbated by it.

In summary, QST indicates that the vulva is less sensitive to mechanical stimuli (touch and pressure) than some peripheral sites (e.g., the hand, forearm, deltoid muscle, thigh, and abdomen), vulvar sensitivity to punctate touch and vibration decreases with age, and the perception of these stimuli deteriorates profoundly with the decline in physiological estrogen levels after menopause, but can be restored with topical estrogen supplementation. QST also demonstrated that young women with VVS have a measurable, heightened sensitivity to vestibular touch and pain and that stimulus intensities perceived as touch by healthy women elicit pain in VVS patients.

SUBJECTIVE VULVAR SENSATION IN CONTROLLED TRIALS OF EXTERNAL HYGIENE PRODUCTS

Further perspective on vulvar sensation is gained from prospective, randomized trials of external feminine hygiene products (menstrual pads, panty liners, and feminine wet wipes) in which participants reported sensory experiences of a more subjective quality. Over the past 26 years, dozens of randomized trials in various parts of the world have assessed observable vulvar irritation and the subjective sensory effects associated the use of such products (reviewed in (31,32)).

Women who use feminine hygiene products report a low frequency of vulvar sensory effects (such as rubbing, chaffing, burning, itching, or a moist, wet, sticky, or sweaty feeling). Data from a prospective randomized trial conducted in Greece are representative (33). This trial in 115 menstruating women aged 18–45 years assessed the skin effects of two thin menstrual pads that differed solely in the surface covering. Participants wore the assigned pads for menstrual protection over two consecutive cycles, and all participants wore the same panty liner design between menstrual periods. Objective visual scoring after each menstrual period or intermenstrually (close to midcycle) revealed few instances of visually perceptible vulvar irritation in either product group. A low frequency of sensory effects, specifically rubbing, itching, and burning, was reported. Approximately 1%–2% of participants in each group reported any such effects after the first cycle; the frequency of reports dropped to between 0.4% and 1% after the second cycle.

Subjective sensory effects are less quantifiable and more complex that the simple perception of a single physical stimulus: rubbing is the perception of a mechanical stimulus (touch) combined with friction; the sensation of wetness may be a combination of the perception of fluid contact combined with a sensation of cooling through heat transfer and evaporation; itching and burning are subjective pathological sensations. Nevertheless, the frequencies of such effects in different groups of women also yield useful information on vulvar sensation.

A prospective trial of feminine wet wipes and dry toilet tissue conducted in France among groups of pre- and postmenopausal women is instructive. The trial examined both clinically observable skin irritation and wetness and subjective sensory responses to the two types of products in 120 premenopausal women aged 18–45 years and in 60 postmenopausal women aged 55–80 years who were not on hormone-replacement therapy (34). Participants used either the wet wipes or dry tissue for menstrual or post-urination cleansing for 28 consecutive days (beginning 2–4 days before the onset of menstrual flow in premenopausal women). Premenopausal women

were assessed on days 2–4 of the cycle and 2–4 days prior to the onset of the menstrual period. Postmenopausal women were assessed on study days 14 ± 2 and 28 ± 2.

In this study, objective vulvar erythema was either not observed, barely discernible, or slight in both product groups, with no statistical difference in frequencies between them. Reported sensory effects included slight burning, itching, or stinging (in both product groups) and a wet or sticky sensation (reported in the wet wipe product group only).

The frequencies of vulvar burning and itching in this study did not differ by menopausal status. A slight burning sensation was reported by 14% and 12.9% of premenopausal and postmenopausal wet wipe users, and by 1.8% and 3.4% of pre- and post-menopausal tissue users, respectively. Slight itch was reported by 1.6% and 3.2% of premenopausal and postmenopausal wet wipe users, compared to 7% and 0% of premenopausal and postmenopausal of tissue users, respectively.

Interestingly, the frequency of reports of vulvar wetness was not significantly different between premenopausal and postmenopausal wet wipe users (frequencies of 8% and 10%, respectively), despite a clinically observable and statistically significant increase in skin moisture on the labia majora and perineum of postmenopausal women upon clinical examination. This observation is notable because it suggests that the perception of heightened vulvar wetness may have been attenuated in postmenopausal women. Postmenopausal women significantly preferred wet wipes to dry tissue for comfort (84% of postmenopausal compared to 54% of premenopausal women rated the wet wipes excellent to very good for comfort.) An improvement in skin hydration may have contributed to their experience of greater comfort with the wet wipe product compared to dry tissue if the postmenopausal vulvar tissue was atrophic. The experience of "comfort" could reflect a summation of several sensory effects.

Stinging was the only sensory reaction for which reported frequencies differed by menopausal status. Stinging is not an end-point typically associated with dry articles; 2% of premenopausal and 3% of postmenopausal women in the toilet tissue group reported slight stinging. Wet wipe users were more likely to report stinging, and premenopausal users reported a slight stinging sensation significantly more frequently than postmenopausal users (17% vs. 9.6%). This observation suggests that the sensory perception of sting on the vulva may be somewhat muted after menopause. The sensation of sting is of interest because dermatologists use the sting response to topically applied lactic acid as a surrogate marker for skin that is hyper-reactive to wind, temperature, and chemical stimuli (35).

In summary, in a study of potential skin irritation and the vulvar sensory effects of wet wipes, the sting response was less frequent in postmenopausal women; moreover, these women did not perceive vulvar skin to be wet with any higher frequency following use of the wet wipes, even though this product led to a clinically discernible rise in vulvar wetness among these women when compared to premenopausal wet wipe users. Consequently, sensations of sting and wetness appear to have been attenuated in postmenopausal women. However, perceptions of burning and itching were unaffected by menopausal status. We speculate that the perceptions of burning and itching on the vulva may be conserved to a greater degree with age because these sensations play a role in signaling pathology (e.g., vulvovaginal infection, contact dermatitis, and systemic vulvar dermatoses). Indeed, some pathological conditions that are accompanied by itch (e.g., lichen sclerosus) are more prevalent in older women.

EPIDEMIOLOGIC STUDIES OF GENITAL SENSATION

A large percentage of people in industrialized countries consider their skin to be "sensitive" (36–38), although this is a self-declared condition lacking objective diagnostic criteria. Few systematic studies have been performed on ethnic differences in genital sensory perception. Limited evidence comes from a large epidemiological study of the perception of sensitive skin in the USA by age, gender, and ethnicity based on responses to a questionnaire given to 1039 people (36). The perception of having slight, moderate, or very sensitive skin on the face or the body did not depend on ethnicity, but a higher percentage of African–Americans (66.4%) than whites (54.2%) perceived their genital skin to be sensitive. This was true of both genders: 65% of African–American men and 37.3% of white men reported genital skin sensitivity; 66.7% of African–American women compared with 57% of white women considered their genital skin to be sensitive. Interestingly, older people were also more likely to claim sensitivity on the genitalia but not on the face and body. The characteristics of the sensations leading to these perceptions of sensitivity were not reported.

CONCLUSIONS

QST has been used to assess the perception of mechanical, thermal, and electrical stimuli on various parts of the anatomy, including the external female genitalia. QST studies indicate that in healthy women, the vulva is less sensitive to mechanical stimuli (touch and pressure) than some peripheral sites (e.g., the hand, forearm, deltoid muscle, thigh, and abdomen). Perhaps the relatively low sensitivity of the labia minora, vestibule, and vagina to mechanical stimuli in healthy women represents an adaptation to the mechanical forces endured during sexual intercourse and childbirth. Interestingly, evidence also exists that the vulva is relatively insensitive to skin irritation induced by either menses or blood when compared to extragenital sites such as the skin of the upper arm. This could be a necessary adaptation to menstruation (39).

Sensitivity to punctate mechanical stimuli on the vulva in healthy women decreases with age, although limited data suggest that clitoral sensitivity to mechanical stimuli does not deteriorate as rapidly with age as does the perception of such stimuli at other vulvar sites. Although the sensitivity to mechanical stimuli declines with age both on the vulva and at extragenital sites, the decline in vulvar sensitivity to punctate touch is linked to the level of estrogen stimulation of the vulva: perception declines after menopause, but is restored by systemic or topical estrogen supplementation. Estrogen was not shown to affect perceptions of these stimuli at extragenital sites.

One caveat is that conclusions about the postmenopausal decline in vulvar sensitivity to touch are based on applying fine punctate pressure to defined locations. Perceptions of other types of stimuli may not be affected in the same way. For example, the mechanical properties of vulvar tissue, skin barrier function, and vaginal lubrication are altered after menopause, and postmenopausal women report higher levels of subjective sensations, such as irritation and discomfort, associated with these atrophic vulvar changes (40,41). The subjective sensory

effects reported in clinical trials provide further evidence that estrogen status does not affect all forms of vulvar sensory perception in the same way. In clinical trials of external hygiene products, the frequency of slight vulvar burning and itching in response to physical contact with wet wipes or dry tissue was unaffected by menopausal status, but the stinging response (which, when measured on the face, is often associated with hyper-reactive or "sensitive" skin) appeared to be muted in postmenopausal women. Different sensory pathways in the vulva may be differentially affected by age or estrogen status.

Lastly, in contrast to healthy women, women with a pain dysfunction known as provoked vestibulodynia (i.e., VVS) have a measurably heightened sensitivity to vestibular touch and pain; mechanical stimulus intensities perceived as touch by healthy women elicit pain in VVS patients. QST studies have been helpful in quantifying and validating these differences.

Although the techniques reviewed herein provide some insights, systematic inquiry into vulvar sensory perception is hindered by the lack of standardized assessment methodologies for this morphologically complex tissue. Foundational work is needed in order to validate the experimental conditions used and to enable comparisons between experiments. Moreover, in the vulva, glabrous and semiglabrous keratinized skin are juxtaposed with areas of nonkeratinized mucosa, tissues that differ in their embryonic derivation and structure (42). Factors such as labial shape and thickness may affect the way the stimuli are applied, and stimulus of the labia may affect sensation at other sites, such as the clitoris or vulvar vestibule. For example, in our laboratories, we (DZ) have found that a non-painful increase in physical traction on the labia majora increases the pain sensitivity of the vulvar mucosa (vestibule) by an average of 30% (unpublished data). Furthermore, the direction of pressure applied to the vestibular mucosa (tangential vs. perpendicular) significantly affects sensory perception at this site, but has only a marginal effect on glabrous skin (unpublished data). The challenge of assessing sensation on closely juxtaposed skin and mucosal sites that vary both anatomically and functionally is not unique to the vulva: orofacial researchers address similar challenges (43), and some of their approaches may be useful to the study of vulvar sensation. Future research will seek to standardize and validate conditions for applying stimuli and measuring responses and to investigate the various anatomical, neurological, and dermatological factors that affect vulvar sensory perception.

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7

The menstrual cycle, the composition of menses, and the effect of menses on the skin

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INTRODUCTION

A discussion of vulvar physiology in the reproductive years is incomplete without reference to the menstrual cycle. This chapter describes hormonal and endometrial cycling leading to menstruation, the physical properties and composition of menses fluid, and investigations of the effects of menses and blood on vulvar skin.

THE MENSTRUAL CYCLE

The hypothalamic–pituitary–ovarian axis is central to female reproductive function. It involves the cyclic secretion and feedback mechanisms of a hierarchy of hormones from the pituitary gland and the ovary that: (i) result in the cyclic production of the steroid hormones, estrogen, and progesterone; and (ii) promote endometrial growth in preparation for conception, with resulting menstrual cyclicity and endometrial shedding in the absence of conception. The cyclic production of these hormones ensures that a mature ovum is released from the ovaries approximately once a month and that the endometrium is concurrently receptive to the implantation of a fertilized ovum (embryo) should fertilization occur. If fertilization does not occur, the endometrium is shed in an orderly fashion, menstruation ensues, and the cycle proceeds anew. In adult women, the average cycle lasts 28 days, but ranges from 21 to 35 days; shorter or longer cycles are statistically uncommon (1,2).

The hierarchy of hormones that governs the menstrual cycle is produced by the hypothalamus, the pituitary gland, and the ovary, as follows:

1. Gonadotrophin-releasing hormone (GnRH), secreted by the hypothalamus, stimulates production of the gonadotrophic hormones follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the anterior pituitary gland.
2. FSH and LH modulate ovarian function to promote follicular growth, follicular maturation, and release of the ovum (ovulation).
3. Estrogen (secreted by the ovaries in response to the gonadotrophic hormones) and progesterone (produced by the corpus luteum that develops at the site of a ruptured ovarian follicle) stimulate the proliferation and secretory development of the endometrium. Along with non-steroidal factors such as inhibin, estrogen and progesterone also modulate pituitary production of the gonadotrophic hormones through feedback inhibition.

Concentrations of these gonadotrophic and ovarian hormones vary cyclically in a characteristic pattern over the course of the menstrual cycle (Figures 7.1a and 7.1b). Convention dictates that the first day of menstruation is considered day 1. Modulation of ovarian function by FSH and LH, leading to follicular maturation and ovulation, is known as the ovarian cycle. The concurrent phases of endometrial development to sustain an embryo, induced by estrogen and progesterone, are known as the endometrial cycle (Figure 7.1c).

The Ovarian Cycle

The ovarian cycle describes hormonally induced changes in ovarian function that follow the onset of menstrual flow. The first half of the cycle, referred to as the follicular phase, is marked by a rise in FSH and LH concentrations stimulated by the pulsatile release of GnRH. During the follicular phase, a pattern of low-amplitude, high-frequency GnRH pulses is thought to preferentially stimulate the secretion of FSH relative to LH. The rise of FSH and LH causes the follicles within the ovaries to grow. After a week or more of follicular growth—but before ovulation occurs—usually a single follicle outgrows the others, begins to secrete high concentrations of estrogens (notably estradiol), and then matures. Heightened estrogen production by this dominant follicle creates feedback inhibition of the pituitary secretion of FSH and LH, which in turn causes the remaining ovarian follicles to involute (a process known as atresia).

In an idealized 28-day cycle, ovulation occurs at midcycle, 14 days after the onset of menstruation. An elevated concentration of LH is necessary for final follicular growth and ovulation. High-amplitude, low-frequency GnRH pulses mediate the preferential stimulation of LH. In response, approximately 2 days before ovulation, the rate of secretion of LH increases markedly (6–10-fold), peaking about 18 hours prior to ovulation (the LH surge) (Figure 7.1a). Concurrently, FSH increases by approximately two-fold. FSH and LH act synergistically to induce ovulation; that is, the rupture of the mature follicle and release of the mature ovum.

The LH surge is a marker of ovulation. Mild unilateral abdominal pain experienced around the time of ovulation by some women, known as *Mittleschmerz* (German for "mid-pain"), may be related to the leakage of blood and fluid from the ruptured follicle.

The second half of the ovarian cycle is known as the luteal phase. Most of the variation in menstrual cycle length (21–35 days) is due to variation in the follicular phase; the luteal phase is relatively constant at 14 days from ovulation to menses (3).

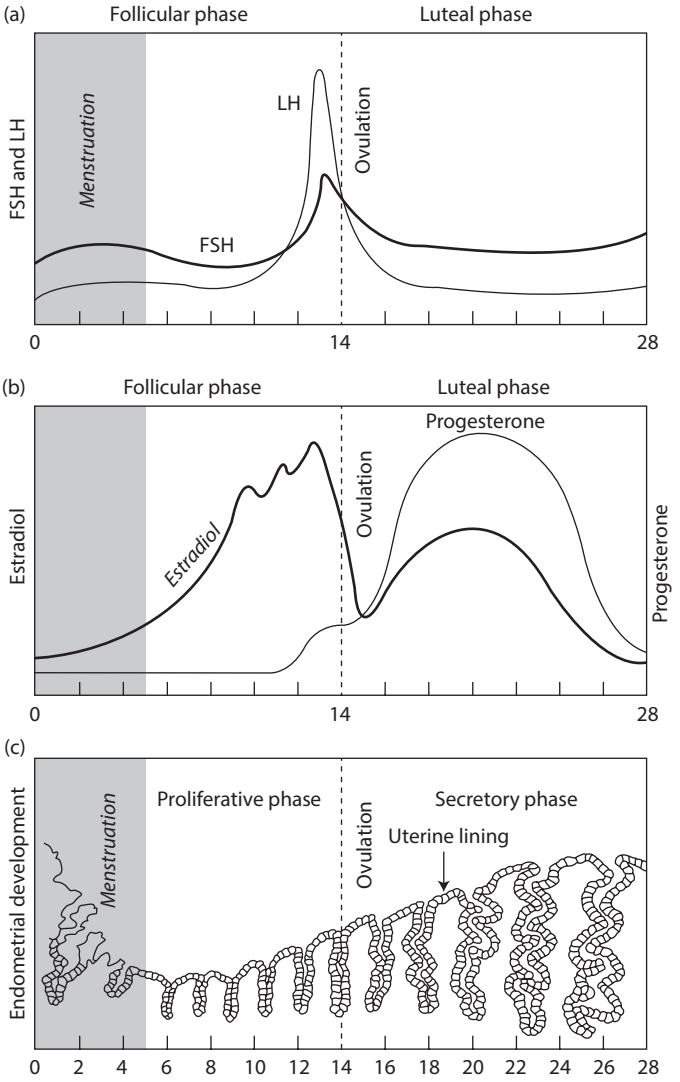


Figure 7.1 An idealized menstrual cycle of 28 days. (a) The pituitary hormone cycle: cycling of gonadotrophins (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]). (b) The ovarian hormone cycle: cycling of ovarian hormones (estradiol and progesterone). (c) The endometrial cycle: corresponding cyclical development of the endometrium.

Under the influence of LH during the last few days prior to ovulation, and continuing for a day or so after ovulation, the granulosa cells of the follicle undergo a physical and biochemical change called luteinization. The mass of cells remaining at the site of the ruptured follicle becomes the corpus luteum and begins secreting large quantities of the hormones progesterone and estrogen (Figure 7.1b). A small increase in body temperature occurs due to heightened progesterone secretion. Feedback inhibition by these hormones, and by other non-steroidal factors such as inhibin, reduces the secretion of FSH and LH, thereby preventing the growth of new ovarian follicles.

At about day 26 of the idealized cycle, the corpus luteum degenerates. The resulting drop in progesterone and estrogen is followed by menstruation. The loss of progesterone acts as a trigger for endometrial desquamation and the onset of menstrual flow. Concurrently, feedback suppression of the gonadotrophic hormones is lost. As a result, the anterior pituitary once again secretes high levels of FSH and moderate levels of LH in response to the GnRH stimulus, re-initiating the ovarian cycle.

The Endometrial Cycle

The cyclic production of estrogen and progesterone during the ovarian cycle induces a corresponding cycle of endometrial proliferation and development (Figure 7.1c). This endometrial cycle includes a proliferative phase lasting about 11 days, a secretory phase lasting about 12 days, and a desquamative or menstrual phase of about 5 days, during which menstruation ensues.

During the follicular phase of the ovarian cycle, the endometrium proliferates and increases in thickness under the influence of estradiol. This marks the proliferative phase of the endometrial cycle. During the luteal phase of the ovarian cycle, progesterone stimulates further endometrial cell proliferation, differentiation, and secretory development to support implantation and to nourish the developing conceptus. This is the secretory phase of the endometrial cycle. Progesterone also promotes secretory changes in the lining of the fallopian tubes that will support the fertilized egg as it travels down the fallopian tube prior to implantation.

If fertilization occurs, human chorionic gonadotropin produced by the developing placenta maintains the corpus luteum, thereby sustaining progesterone secretion. If fertilization does not occur, the corpus luteum is lost, causing a sudden drop in progesterone. This triggers endometrial desquamation in an orderly fashion, resulting in menstruation.

Menstrual Flow Volumes and Menstrual Blood Loss

Menses is a suspension of blood and tissue matter in fluid derived from the sloughed endometrium and cervicovaginal secretions. The composition of menses is discussed in detail in the "Composition and properties of menses" section. Historically, the focus of clinical research has been on characterizing the volume of menstrual blood loss (specifically, the volume of the blood component of menses fluid from a single period) (4), the regularity of menstrual cycle length (2,5), and other aspects of bleeding patterns in order to define normal and abnormal uterine bleeding (6). Depending on the population studied, total menstrual flow and the corresponding volume of menstrual blood loss may vary from cycle to cycle, among individual women, and at different stages of reproductive life.

The gold standard for measuring menstrual blood loss volumes is the alkaline hematin technique, a colorimetric assessment of blood-based iron extracted from sanitary products (7,8). In brief, this technique requires scrupulous quantitative capture of menses fluid from pads and tampons, followed by extraction with 5% sodium hydroxide and the determination of heme (7). The volume of menstrual blood is calculated by comparison to reference standards prepared by sodium hydroxide extraction of known volumes of whole blood applied to sanitary pads and tampons.

The blood content of menses fluid depends on the study population. One study, performed over two consecutive menstrual cycles, evaluated 53 women who were not using any

Table 7.1 Menstrual Blood Loss Volumes for a Range of Total Volumes of Menstrual Fluid in a Single Menstrual Cycle

	Menstrual blood loss[a] for different levels of total menstrual flow[b] in a single period				
	Regardless of type of sanitary product used			By product type	
Total fluid lost during one menstrual period[a] (mL)	Corresponding menstrual blood loss volume (mL)	Menstrual blood loss volumes, 95% CI[c]	Blood content of menses fluid (%)	Tampon users' menstrual blood loss (mL)	Pad-only users' menstrual blood loss (mL)
100	47.6	44–52	47.6	42.9	53.9
120	57.9	54–62	48.2	52.4	65.9
130	63.1	59–67	48.5	57.2	71.9
140	68.3	64–73	48.8	62.1	78
150	73.5	69–79	49.0	66.9	84.1
180	89.4	83–96	49.7	81.7	102.7
200	100.2	92–108	50.1	91.8	115.3
300	154.7	138–174	51.6	143.1	179.7
350	182.5	160–208	52.1	169.4	212.8

Source: Adapted from Fraser IS, Warner P, Marantos PA. Estimating menstrual blood loss in women with normal and excessive menstrual fluid volume. *Obstet Gynecol* 2001; 98(5 Pt 1): 806–14.

[a] By alkaline hematin method (colorimetric assay of heme extracted from sanitary products) (7).

[b] Total menstrual flow (menses fluid loss) determined by weighing sanitary products before and after use.

[c] 95% confidence interval (CI) for mean blood loss volumes at the given total menstrual fluid volume.

form of hormonal or intrauterine contraception (34 with subjectively normal periods, 14 with subjectively heavy periods, and 5 who had previously but not currently experienced subjectively heavy periods) (9). Menstrual fluid loss per period was assessed by weighing sanitary products from each period before and after use; the corresponding volume of blood lost was assessed by the alkaline hematin technique. A significant correlation existed between total menstrual fluid volume and menstrual blood loss volume ($r = 93$, $p < 0.001$) (9). Blood comprised 48%–49% of total flow for women with menstrual blood loss levels were between 60 and 100 mL per period and 50%–52% of total flow for menstrual blood loss levels of >100 mL or more (Table 7.1).

A similar study was performed during a single cycle among 28 women using different forms of contraception (10). In this population, the blood content of menses fluid varied greatly, ranging from 1.6% to 81.7%, with a mean of 36.1 ± 3.6%. No significant difference in the proportion of blood in menses fluid was found between women using no contraception (35.5 ± 4.5%, N = 13) and women who had undergone tubal ligation (36.2 ± 8.8%, N = 5). Those on oral contraceptives had lower menstrual blood losses overall and a lower proportion of blood in menstrual fluid than those not using contraception (17.3 ± 5.1%, N = 5, $p < 0.05$). In those using the intrauterine device (IUD), blood made up a significantly greater proportion of menstrual fluid loss (56.5 ± 6.9%, N = 5, $p < 0.025$). The proportion of blood in menses fluid over the course of a single menstrual period remained about the same for different cycle days and volumes of flow.

The clinical definition of abnormal menstrual blood loss derives from a study of Swedish women from the early 1960s that aimed to study blood loss variations and define normality (4). The study was performed in 476 women in six age groups judged likely to represent certain criteria: age 15 years (postmenarche); 23 years (50% likelihood of being married); 30 years (age with highest frequency of parturition); 40 years (not yet likely to experience climacteric symptoms), 45 years (perimenopausal), and 50 years (on the cusp of menopause). Medical and dietary histories were obtained and blood chemistry analysis performed to assess iron deficiency and its relationship to menstrual blood loss. (Contraceptive use was not reported, likely because oral contraceptives were not introduced in Europe until the mid-1960s.) Women were instructed to use tampons with backup sanitary pads and to have tampons in place when toileting to minimize loss of fluid to analysis. Mean menstrual blood loss for the study population was 43.4 ± 2.3 mL, ranging from a mean of 33.8 ± 2.4 mL for age 15 years to 62.4 ± 13.2 mL for age 50 years (Table 7.1). (The investigators speculated that the values obtained for 15-year-olds may have underestimated blood loss due to less stringent collection among these participants.) The distribution was highly skewed at the upper end of blood loss volumes. The population median was 30 mL, the 10th percentile was 10.4 mL, and the 90th percentile was 83.9 mL (Table 7.1).

This study established the clinical definition of excessive menstrual blood loss in one cycle as >80 mL. However, signs of iron deficiency in the study population (defined as blood hemoglobin concentrations of <12 g/100 mL and plasma iron concentrations of <80 µg/100 mL) significantly increased when menstrual blood loss values exceeded 60 mL ($p < 0.05$) (Table 7.2). Reductions in hemoglobin and plasma iron concentrations were even more frequent and more pronounced at >80 mL menstrual blood loss (Table 7.3). Nevertheless, the proposed upper limit of normal menstrual blood loss was based on the 95th percentile value in a subgroup of women with subjectively defined "normal" periods who also showed no evidence of iron deficiency. This 95th percentile value of 76.4 mL was consistent with the 80 mL blood loss level at which the frequency of iron deficiency became highly significant in the study population as a whole. The latter value was adopted as the upper limit of normal menstrual blood loss.

Further perspective on abnormal levels of menstrual blood loss can be gained from more recent studies. A group of British investigators found median menstrual blood loss levels of 35.5 mL in women who perceived their flow to be normal (N = 47) and 78.9 mL in women who perceived their flow to be abnormally heavy (N = 207) (11). Notably, 66% of the latter group lost 60 mL or more. In the Australian study of 53 hospital clinic

Table 7.2 Menstrual Blood Loss Volume in a Single Menstrual Cycle in Different Age Groups (Mean, Median, and 10th and 90th Percentiles)

	Population characteristics						
Age (years)	All subjects	15	23	30	40	45	50
Number of subjects	476	95	77	89	92	86	37
	Menstrual blood loss volumes (mL)						
Mean ± SE	43.4 ± 2.3	33.8 ± 2.4	49.0 ± 7.0	49.0 ± 7.0	44.5 ± 5.7	42.7 ± 4.5	62.4 ± 13.2
10th percentile	10.4	10.4	8.7	10.0	12.0	7.9	13.1
Median	30.0	28.4	30.6	30.9	30.8	29.5	36.4
90th percentile	83.9	65.1	77.8	86.3	87.1	88.1	133.1

Source: Adapted from Hallberg L, Hogdahl AM, Nilsson L, Rybo G. *Acta Obstet Gynecol Scand* 1966; 45(3): 320–51.

Table 7.3 Iron Status in Menstruating Women as a Function of Menstrual Blood Loss[a]

Range of menstrual blood loss per cycle (mL)	N	Blood hemoglobin concentration (mean ± SE g/100 mL)	Proportion of subjects with blood hemoglobin concentrations <12 g/100 mL (%)	N	Plasma iron concentration (mean ± SE, µg/100 mL)	Proportion of subjects with plasma iron concentrations <80 µg/100 mL (%)
All subjects	474	12.2 ± 0.03	29	458	100 ± 1.8	26
1–20	134	12.4 ± 0.08	25	128	108 ± 3.3	16
21–40	165	12.5 ± 0.07	21	159	101 ± 2.7	25
41–60	83	12.4 ± 0.09	24	81	109 ± 5.0	25
61–80	38	12.1 ± 0.20	**30**[b]	36	96 ± 5.8	**36**[b]
>80	54	**11.4 ± 0.17**[c]	**67**[c]	54	**87 ± 5.7**[d]	**44**[c]

Source: Adapted from Hallberg L, Hogdahl AM, Nilsson L, Rybo G. *Acta Obstet Gynecol Scand* 1966; 45(3): 320–51.

[a] Menstrual blood loss during one menstrual period in Swedish menstruating women with regular cycles from six age strata (15, 23, 30, 40, 45, and 50 years). A total of 125 subjects were enrolled per group. Menstrual blood loss was measured by the alkaline hematin method. Data are shown for those who completed the study measurements.

[b] Significantly different from the 1–60 mL range at the 5% confidence level.

[c] Significantly different from the 1–60 mL range at the 0.1% confidence level.

[d] Significantly different from the 1–60 mL range at the 1% confidence level.

patients discussed earlier (9), menstrual fluid volumes and the corresponding menstrual blood loss volumes were examined in three groups: women who subjectively considered their periods to be normal (N = 34); those who complained of excessively heavy periods (N = 14); and those who had previously attended the clinic because of excessively heavy periods but who currently did not experience problems (N = 5). Menstrual fluid volumes ranged from <20 mL to >390 mL, with corresponding menstrual blood loss volumes of <5 mL to 242 mL. The distributions displayed a marked positive skew: the majority of the study population had menstrual blood loss volumes of <45 mL; a cluster of groups of two to four women exhibited blood loss values between 60 and 100 mL; finally, individual instances of menstrual blood losses between 100 and 242 mL were observed. Based on these observations, the investigators classified menstrual blood loss <60 mL as "normal," 60–100 mL as "moderately heavy," and >100 mL as "excessive," irrespective of the patients' subjective assessment.

These studies, as well as the earlier Swedish study, suggest that blood loss values of >60 mL skew higher than the bulk of the population (4,9), that a significant majority of women who complain of heavy menstrual periods have blood losses of >60 mL (9,11), and that blood losses of >60 mL are associated with a higher frequency of iron deficiency (4). However, the International Federation of Gynecology and Obstetrics (FIGO) Menstrual Disorders Working Group, which recommends adopting new definitions for disturbances of regularity, frequency, and volume of menstrual flow, so far has retained the historical definition of >80 mL as heavier than normal menstrual blood loss (6).

The clinical definition of excessive blood loss is not meaningful to patients in a practical sense. Women cannot accurately judge their quantitative level of flow. Moreover, not all women presenting with complaints of excessively heavy periods meet the clinical definition of excessive menstrual blood loss. For example, in a study of 226 Scottish women with subjective complaints of abnormally heavy flow, median menstrual blood loss was 53 mL (interquartile range, 27–101 mL) (12). A British study examined both subjective and objective assessments of menstrual blood loss over two consecutive cycles in 92 women complaining of heavy periods (13). In this population, 34% of periods described as light involved blood losses of >80 mL (median, 63 mL; range 1–283 mL); 55% of periods described as "medium" involved blood losses of >80 mL (median, 99 mL; range, 8–493 mL); and 47% of periods described as "heavy" met the >80 mL clinical definition of excessive blood loss (median, 97 mL; range, 27–758 mL).

Rather, the evidence suggests that other characteristics of flow influence women's perceptions. For example, women who complain of heavy periods have more variable blood loss volumes, with changes of >25 mL from one period to the next (9); hence, the experience of intermittent periods with flow that is substantially heavier than usual may contribute to the perception of abnormality. Qualitative surveys indicate that concerns

about abnormally heavy bleeding stem from multiple factors, such as perceived changes in flow characteristics (as described above), sensations of prolonged gushing on the heaviest flow days, the presence of large clots, the frequency of product saturation or soiling, and difficulties maintaining hygiene during the day or at night (14).

Because analytical measurements of total blood loss are cumbersome and impractical in everyday clinical practice, focus has shifted to estimating monthly menstrual blood loss from diary data. Menstrual pictograms of pad and tampon fluid loadings, which estimated blood loss volumes by product type and absorbency level, exhibited a high level of agreement with values obtained by the alkaline hematin method (15). However, this was not consistently reproduced by other investigators (16). The volumes depicted by the fluid loading pictograms must be tailored to specific products and absorbencies, which can vary by brand and change with product innovation. Another approach, which involved statistical modeling of multiple variables from diary studies of women who complained of heavy flow (including number of days with spotting, light, normal or heavy bleeding in consecutive cycles), have also produced menstrual blood flow estimates that correlated well with alkaline hematin analyses (17). Such techniques, if validated and updated to reflect technology innovations, may be useful in clinical research.

COMPOSITION AND PROPERTIES OF MENSES

Menses principally consists of blood, desquamated endometrial tissue, sloughed vaginal epithelial cells, cervicovaginal secretions, and endogenous vaginal microbes. Consequently, menses differs from venous blood both in its composition (Table 7.4) (18–25) and in its physical properties. The composition and physical properties of menses vary among individuals and over the course of menstrual flow. Hence, the mean values for menses reported in Table 7.4 represent values obtained from sample populations and may not broadly reflect population norms.

Menses may be considered a suspension of blood- and tissue-derived solids within a mixture of serum and cervicovaginal fluid. Agglomerates of tissue debris, red blood cells, and mucins are scattered throughout a serum-like phase. Figure 7.2 shows microscopic images obtained from two locations within the same sample of menses. The images show intact and ruptured red blood cells, finer particulate matter, and predominantly fluid regions, demonstrating the non-homogenous nature of menses (Flood JA. The Procter & Gamble Company, unpublished data).

The blood content of menses depends on the extent of endometrial breakdown and dilution of blood- and tissue-derived constituents with cervicovaginal fluid. Vaginal fluid in menses contributes principally water, common electrolytes, organic moieties, and at least 14 proteins (26), including glycoproteins with molecular weights up to 82 kDa (27).

Consequently, the concentrations of many elements in menses are lower than their respective concentrations in venous blood. For example, solid matter in venous blood after evaporation of water is typically 20% of the mass, but the solid matter in menses ranges from 7% to 23% of the total mass; hence, menstrual fluid often has a higher water content than venous blood (Hood WH. The Procter & Gamble Company, unpublished data). Likewise, the hemoglobin and iron contents of menses depend on the extent of endometrial breakdown and display far broader ranges than those of venous blood (Table 7.1). As other investigators have reported (9), we have found that the blood content of menses averaged over all days of menstrual flow is close to 50%. The average hemoglobin content of venous blood is about 14 g/dL, but the hemoglobin content of menses samples obtained at the time of peak flow was closer to 10 g/L, with a range of 1.5–19.9 g/dL (Ventura AM. The Procter & Gamble Company, unpublished data). White blood cell and platelet counts in menses are as much as 100-fold lower than those of venous blood (Table 7.1).

The pH of menses is similar to that of venous blood, reflecting the serum content of its fluid phase. The median pH measured in a range of menses samples was 7.2 with a skewed distribution tailing into the range of pH 5–6 (measured at 25°C using a small-diameter glass electrode) (21).

The concentrations of certain serum-derived constituents, such as serum proteins, total cholesterol, and bilirubin, fall within the range found in venous blood (Table 7.1). The absence of clotting is the most notable biochemical difference between menses and venous blood. What appear to be menstrual blood clots actually represent large samples of the aforementioned blood–tissue agglomerates.

In venous blood, clotting involves three broadly defined steps:

1. Prothrombin activator complex is formed in response to vessel or blood damage.
2. Prothrombin activator complex catalyzes the activation of prothrombin into the proteolytic enzyme, thrombin.
3. Thrombin cleaves fibrinogen into peptides, which polymerize into fibrin threads that enmesh platelets, blood cells, and plasma to form the clot itself.

Other coagulation factors participate in the process. Clot lysis requires the activation of plasminogen to plasmin, a proteolytic enzyme that digests fibrin threads in the blood clot.

Unlike venous blood, menses is depleted of key clotting factors, has lower platelet counts, and has reduced platelet activity, but is high in fibrinolytic activity (Table 7.1). Prothrombin, free thrombin, fibrinogen, and fibrin are absent from menstrual blood (21,22,28). Instead, high levels of tissue plasminogen activator and fibrin degradation products are found (21,23,28). The plasmin present in menses, though comparable in concentration to that of venous blood, is no longer fibrinolytically active. Moreover, platelets in menses differ from platelets in venous blood in that they fail to aggregate in response to stimuli or to produce chemical messengers involved in the clotting response (20). These data suggest that clots initially formed in endometrial blood are degraded during menstruation.

Besides these differences in coagulation components, menses but not venous blood contains matrix metalloproteinases (MMPs), enzymes that catalyze endometrial breakdown through proteolysis of the stromal extracellular matrix (29–32). Examples include MMP-1 (interstitial collagenase), MMP-2 (gelatinase-A), MMP-3 (stromelysin 1), MMP-9 (gelatinase-B), and MMP-10 (stromelysin-2). MMPs are secreted as inactive proenzymes. In the endometrium, they are expressed and activated during the late secretory and menstrual phases of the cycle in response to progesterone withdrawal, the hormonal trigger for menstruation (33,34).

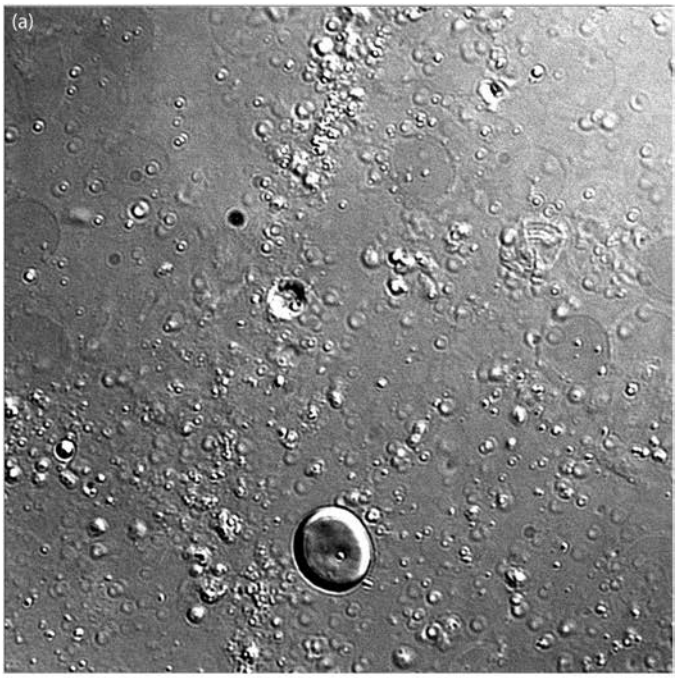
Table 7.4 Composition of Venous Blood and Menses[a]

Component	Venous blood		Menses		Reference[b]
	Mean	Range[c]	Mean	Range	
Hematological components					
Red blood cells (cells per mm^3)	N/A	$4.2–5.0 \times 10^6$	N/A	$2.4–3.9 \times 10^6$	(18,19)
White blood cells (cells per mm^3)	N/A	$2.4–2.8 \times 10^6$	N/A	$2.1–3.6 \times 10^4$	(18,19)
Platelets (cells per mm^3)	N/A	$1.4–3.5 \times 10^5$	3.0×10^4	$3.1–3.3 \times 10^4$	(19,20)
Hemoglobin (g/dL)	14	12–18	10	2–20	Ventura AM. The Procter & Gamble Company, unpublished data
Albumin (g/L)	44 ± 8.8	N/A	43.6 ± 11.8	N/A	(21)
Hematological components (coagulation factors)					
Prothrombin	Present in 24/24 subjects studied	N/A	Not detectable	Not detectable	(22)
Plasminogen activator (CTA units/mL)	0.15	0–0.2[d]	1.04	0–3.5	(21)
Plasmin(ogen) protein (g/L)	0.15 ± 0.03	N/A	0.17 ± 0.05	N/A	(21)
Plasmin activity (μmol/L)	0	0	0.83 ± 0.97	N/A	(21)
α_2-antiplasmin activity	Present in 24/24 subjects studied	N/A	Not detected	N/A	(21)
Fibrinogen (mg/100 mL)	N/A	200–400	Not detected	Not detected	(23)
Fibrinogen degradation products (μg/mL)	10.5 ± 0.8	N/A	>1280	N/A	(23)
Inorganic materials					
Sodium (ppm)	3300	N/A	2600	2300–3100	(24)
Calcium (ppm)	105	85–105	100	90–110	(24)
Iron (ppm)[e]	455	390–585	320	60–650	Ventura AM. The Procter & Gamble Company, unpublished data
Phosphate (ppm)	270	N/A	360	320–450	(24)
Chloride (ppm)	3600	N/A	3500	3200–3900	(24)
Organic materials					
Serum protein (g/100 mL)	7	6.0–8.0	6.5	5.9–7.5	(24)
Amino acids (ppm)	100	N/A	250	160–350	(24)
Nitrogen (ppm)	350	N/A	800	600–1000	(24)
Urea (ppm)	400	N/A	150	100–200	(24)
Bilirubin (ppm)	7	2–9	4	3–7	(24)
Fatty acids (ppm)	3500	N/A	3000	2200–3300	(24)
Total cholesterol (ppm)	1750	1400–3100[f]	1500	1350–1700	(24)
Blood sugar (ppm)	900	700–1100[g]	500	300–500	(24)
Glycogen (ppm)	350	N/A	500	400–600	(24)
Lactic acid (ppm)	110	60–160	300	240–370	(24)

[a] Cited values for venous blood and menses are based on sample populations and do not necessarily represent population norms.
[b] References for menses values only.
[c] Normal clinical ranges according to Wallach (25), unless otherwise referenced.
[d] From (21).
[e] Calculated from hemoglobin content.
[f] For ages 30–49 years, as observed clinically (25). Values skew higher with age.
[g] Fasting glucose.
Abbreviation: CTA: committee on thrombolytic agents; N/A: not available.

The physical properties of menses are highly dependent on its composition. Because the proportions of proteins, lipids, mucins, blood, and tissue-derived constituents vary temporally over the course of menstrual flow, it is not meaningful to cite average values for physical properties such as viscosity and elasticity. Rather, the following discussion highlights the tremendous range in these properties.

For example, menses viscosity (measured at a given shear rate) varies dramatically, by as much as an order of magnitude in a single set of samples (data not shown). The viscosity of menstrual fluid samples was measured at the Procter & Gamble Company in order to formulate a realistic menstrual fluid simulant to use in laboratory testing and in the design of absorbent articles. These artificial menstrual fluid formulations were patented by Procter & Gamble in 2010 (35). Menstrual fluid samples were measured at a shear rates ranging from 0.01 to 100 s^{-1} using an AR-2000 rotational viscometer from TA Instruments (Newcastle, Delaware), with the fluid between parallel plates at spaces 500–1000 μm apart. Freshly collected menstrual fluid samples measured in this manner



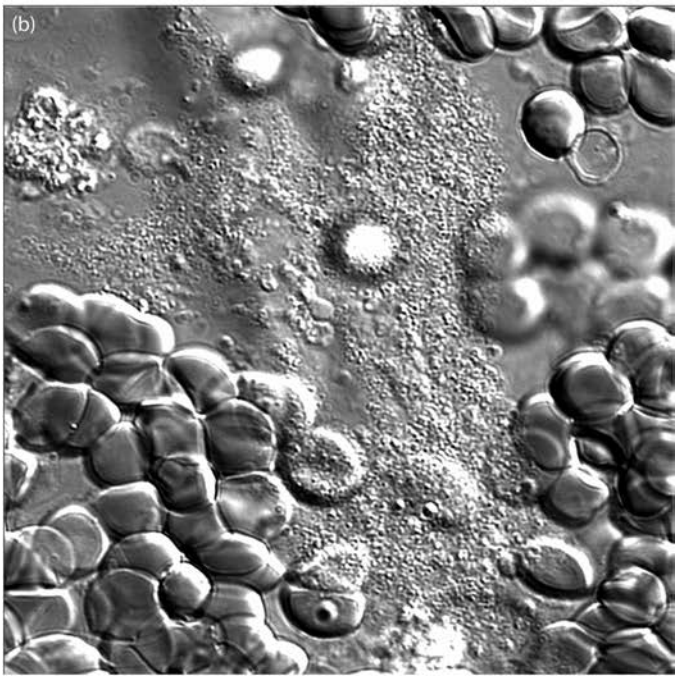


Figure 7.2 (a & b) Images of menses obtained by differential interference contrast microscopy (approximately 1000× magnification), demonstrating cellular agglomerates and a predominantly fluid phase within the same menses sample.

were found to have a viscosity ranging from several centipoise (cP) to several hundred cP. The viscosity of menstrual fluid was found to be highly dependent on shear rate and temperature with viscosity. Menstrual fluid viscosity was found to decrease with higher temperatures and higher shear rates (35). The thinnest samples, collected when menstrual flow was greatest, had a viscosity similar to that of venous blood.

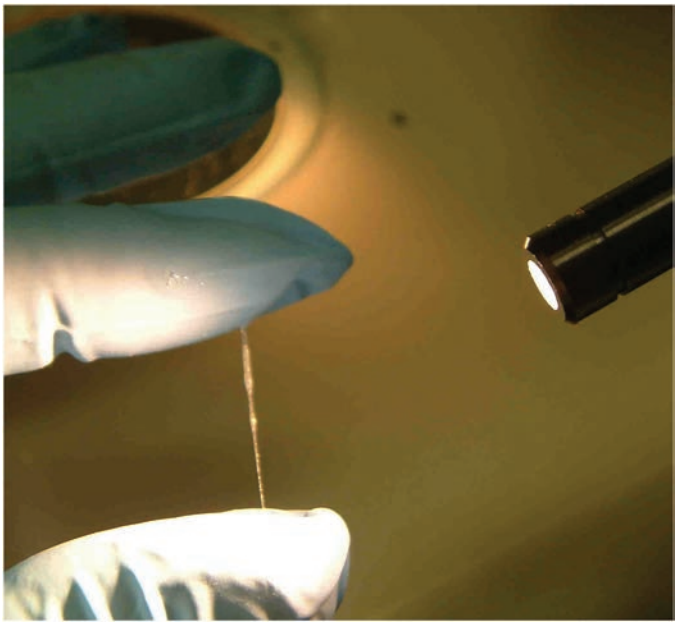


Figure 7.3 *Spinnbarkeit* test for menses elasticity.

Samples collected during times of low menstrual flow were more viscous; indeed, some could be described as more gelatinous than liquid in nature. It is fair to say that a large proportion of menses samples are considerably more viscous than blood or water—about four-times more viscous than venous blood and 35-times more viscous than water (Hartt WH. The Procter & Gamble Company, unpublished data).

The elasticity of menses also varies considerably. *Spinnbarkeit*, a clinical term applied to the elasticity of cervical mucous, can be used to describe the elasticity of menses. As background, cervical mucous responds to estrogen with a decrease in viscosity, which results in a clinically important observation that the elasticity of cervical mucous (i.e., the length of a strand formed when cervical mucous is extended is greatest at the time of ovulation). (This observation can be helpful in either avoiding or planning conception.) *Spinnbarkeit*, or the ability to form a strand, can also be used to measure the elasticity of menses (Figure 7.3). The length of a "strand" formed when menses fluid is rapidly extended often reaches 30 mm before it breaks; however, strand length can range from 0 mm (no elasticity) to 70 mm (more elastic than maple syrup) (Minoguchi R. The Procter & Gamble Company, unpublished data).

In short, menses differs in important respects from venous blood because its constituents are derived from endometrial breakdown and passage through the vaginal tract. Besides red blood cells and serum constituents, menses contains tissue agglomerates, endometrial proteases, and cervicovaginal secretions not found in venous blood. Menses is also depleted of certain clotting factors. Consequently, it exhibits a broader range in physical characteristics and chemical composition than does venous blood. Recent reliable heptaplex methods are helping discriminate between menstrual and peripheral blood samples, which is critical in forensic and criminal casework (36).

EFFECTS OF MENSES AND VENOUS BLOOD ON THE SKIN

Some women report vulvar irritation during the menstrual period. To assess whether menses contributes to vulvar irritation, we performed a 4-day skin patch test of menses and venous blood on the labia majora and on the upper arm in 20 women volunteers (37). Compositional differences between blood and menses (e.g., proteinase content) (36,38) and anatomical differences in irritant susceptibility (38,39) could affect the erythema response.

In brief, physiologic saline (non-irritant control), aqueous sodium lauryl sulfate (SLS; 0.6% w/v, irritant control), and each volunteer's own venous blood and menses (collected overnight with an intravaginal cup; 0.3 mL each) were applied for two consecutive 24-hour periods to the lateral labia majora (randomized across two clipped sites on each labium) and to the upper arm (randomized across five sites per arm, see below). Occlusive patches were applied to the labia and to one upper arm; semi-occlusive patches were applied to the other arm. The fifth site on each arm was pretreated with a proprietary, petrolatum-based emollient prior to menses application. A standard four-point erythema scale was used to score skin irritation (40,41).

Effect of Anatomical Site

The labia majora were less responsive than the upper arm to all applied materials (Figures 7.4a and 7.4b). On the labia majora, menses and venous blood elicited no significant erythema at either time point; SLS, the irritant control, elicited significant, mild erythema (0.6 ± 0.08 and 1.2 ± 0.15 at 24 and 48 hours, respectively).

On the upper arm, menses and venous blood elicited mild erythema at the 48-hour time point only (0.7 ± 0.14 and 1.1 ± 0.14, respectively) (Figure 7.5b). SLS elicited moderate to severe erythema at both the 24- and 48-hour time points (2.3 ± 0.09 and 3.4 ± 0.14, respectively) (Figures 7.5a and 7.5b). Mean scores to SLS on the arm were three-to four-fold higher than those observed on the labia; this is consistent with prior reports that the arm is more susceptible to SLS-induced skin irritation than the labia (42,43).

Effect of Occlusion

Semi-occlusive conditions attenuated the erythematous response to all materials (upper arm, 48 hours) (Figure 7.5). Notably, SLS-induced erythema was reduced almost six-fold (mean scores of 0.6 ± 0.1 vs. 3.4 ± 0.14 for semi- and full-occlusion, respectively). Pretreatment of the upper arm with emollient prevented menses-induced skin irritation, regardless of the degree of occlusion.

Taken together, these observations suggest that the vulva (labia majora) is adapted to be less sensitive to menses-induced skin irritation and that pretreatment with a petrolatum-based emollient attenuates potential skin irritation from menses.

The findings noted above suggest that vulvar skin may have unique properties relative to skin at other sites. This investigative approach may have clinical utility in addressing women's complaints about vulvar irritation. For example, similar methods may be used to assess the responsiveness of prepubertal and postmenopausal skin to vaginal bleeding, or to investigate the response of vulvar skin to menses in the presence or absence of pathological conditions such as candidal vulvitis, lichen sclerosus, or vulvar ulcers associated with herpes simplex infection. The pursuit of such questions will add to our knowledge of vulvar reactions in health and disease.

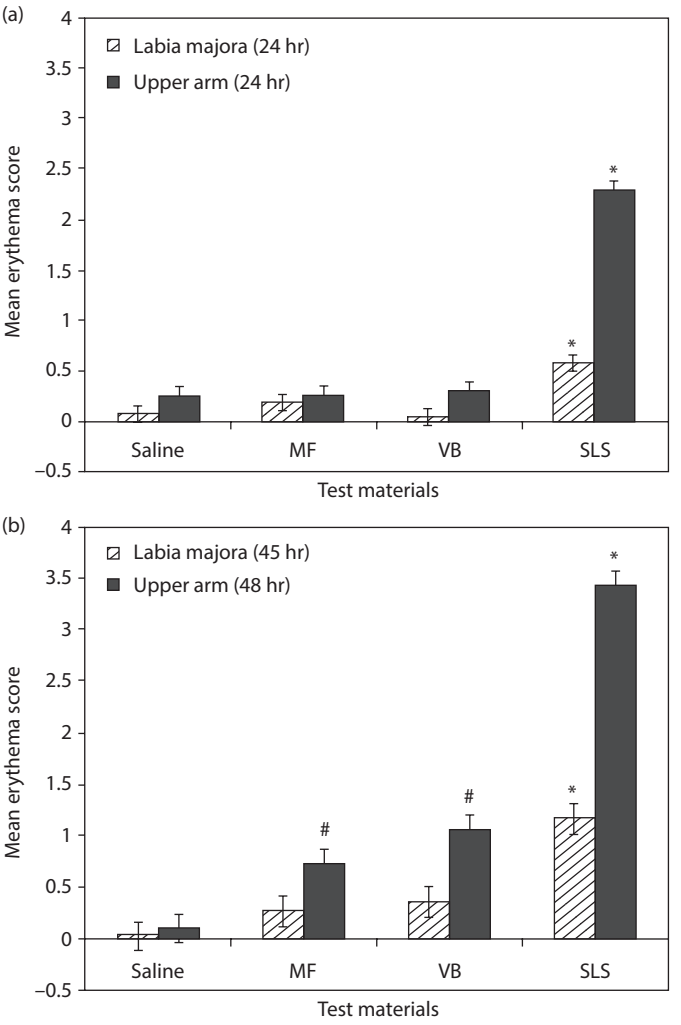


Figure 7.4 Skin erythema of the labia majora and upper arm following test material application under an occlusive patch for 24 and 48 hours. Test materials: saline (non-irritant control); MF = menses fluid; VB = venous blood; SLS = 0.6% aqueous sodium lauryl sulfate (irritant control). (a) 24-hour exposure. (*Significantly different from other test materials applied to that anatomical site.) (b) 48-hour exposure. (#Significantly different from the non-irritant control [saline] applied to that anatomical site. *Significantly different from other test materials applied to that anatomical site.) (From Farage M, Warren R, Wang-Weigand S. *Cutan Ocul Toxicol* 2005; 24(4): 243–6. With permission.)

CONCLUSIONS

The menstrual cycle is central to female reproductive function. In an idealized cycle, cyclical variations in the production and concentrations of hypothalamic, pituitary, and ovarian hormones over a 28-day period lead to the release of a mature ovum at approximately midcycle and to the concurrent development of the endometrium in anticipation of fertilization.

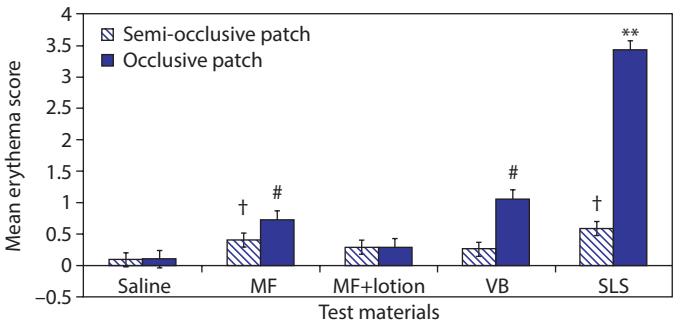


Figure 7.5 Skin erythema of the upper arm induced by test materials applied for 48 cumulative hours under a semi-occlusive or occlusive patch. Test materials: saline (non-irritant control); MF = menses fluid; MF + lotion = menses fluid applied to prelotioned skin; VB = venous blood; SLS = 0.6% aqueous sodium lauryl sulfate (irritant control). (†Significantly different from the non-irritant control [saline] under semi-occlusive conditions. #Significantly different from the non-irritant control [saline] under occlusive conditions. *Significantly different from other test materials under occlusive conditions.) (From Farage M, Warren R, Wang-Weigand S. *Cutan Ocul Toxicol* 2005; 24(4): 243–6. With permission.)

When fertilization does not occur, the endometrium is shed, menstruation ensues, and the cycle begins anew. Menses is composed of blood that is depleted of clotting factors as well as desquamated endometrial tissue, sloughed vaginal cells, and cervicovaginal secretions. The composition and physical properties of menses vary both temporally and among individuals because the concentration of menses constituents changes as flow progresses. Menses and blood might be expected to differ in their potential effects on vulvar skin because menses is more complex and contains endometrial metalloproteinases not present in blood. However, vulvar patch testing of blood and menses revealed minimal vulvar irritation in response to these substances when compared to patch testing on the upper arm. These findings suggest that vulvar skin may be uniquely adapted to be less sensitive to the cyclical exposure to menses that occurs during women's reproductive years.

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8

Characterization and treatment of lochia
A review

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INTRODUCTION

Lochia or puerperal loss refers to the vaginal discharge that occurs during the postpartum period. The term "lochia" originates from a Greek word that means "relating to childbirth." The placental implantation site in the uterus does not scar, otherwise the region would not be able to hold any future pregnancies. After the placenta comes out, the uterus undergoes a process called "involution," or shrinking. Involution is required to reduce the surface area of the uterus that can otherwise bleed since it becomes rich in blood vessels during pregnancy. During involution, the bed of the uterus is separated and falls away as part of the lochia. The tissue underneath heals and gets pushed away, similar to a scab falling off. In this way, the number of babies a woman can have is not limited by the previous placental implantations. The average duration of lochia, from the available published studies, is expected to be 24–36 days. However, lochial flow beyond 6 weeks is not unusual. The reason for this inconsistency could be that most of the studies terminated observation before the actual cessation of bleeding.

COMPOSITION OF LOCHIA

The composition of lochia is complex, reflecting the nature of the biochemical and immunologic mechanisms that are active during the early stages of labor at the maternal–fetal interface. Lochia consists of blood, sloughed-off tissue from the lining of the uterus, mucus, fetal hair, and bacteria. The sequential three stages of lochia—lochia rubra → lochia serosa → lochia alba—correspond to the color of the discharge (red, brown–pink, and yellow–white, respectively; see Table 8.1). For an initial period of days to weeks, the discharge contains a high proportion of blood and fetal membrane, thereby giving the color red or red–brown (1,2). Lochia rubra gradually transitions to brown–pink lochia serosa, which contains more leukocytes and mucus (2). The last stage of lochia is yellow–white lochia alba, which contains decidual cells, leukocytes, mucus, cholesterin crystals, fatty and granular epithelial cells, and microorganisms (1,2). In some cases, uterine infection can result in secondary postpartum hemorrhage (PPH) that extends the duration of lochia rubra phase for weeks or months (3).

The normal level of hemoglobin in circulatory plasma is usually below 0.005 g/dL (4). The lowest mean concentration of free hemoglobin measured in uterine excretion of pregnant women in the last stage of gestation, but without labor evidences, was estimated at 0.05251 g/dL (4), and the concentration of free hemoglobin in lochia samples from advanced labor increased to 0.1194 g/dL (4). Thus, the level of free hemoglobin in lochia correlates with cervix dilation and increases as labor advances. Similar patterns of increase in peptide concentrations, including hemocidins, with progression of labor have also been demonstrated (4). Hemocidins—antibacterial peptides generated from hemoglobin—are abundant in normal menstrual discharge and serve as unspecific immune factors that help maintain vaginal homeostasis during physiologic menstrual bleeding (5,6). Surgical procedures and other factors such as the placental removal method and its separation time, bleeding intensity, and cervical dilation stage during the surgical procedure may affect the molecular mechanisms involved in the production of hemocidins and, in effect, may be responsible for the higher frequency of secondary infections or puerperal morbidity after cesarean delivery as compared to normal vaginal labor. To date, nothing is known about the changes in the levels of hemocidins and other peptides during the various stages of lochia.

AMOUNT OF LOCHIA

No standardized or validated measures of scales exist to measure the quantity of lochial blood loss. While some of the reported studies used an objective method such as the weight of perineal pads, the majority of studies relied on subjective descriptions (7). A woman's own description of lochial loss has limited clinical value. Studies suggest that visual evaluations of menstrual and lochial loss are often underestimates (8–10). Several studies used the following scale: light or small bleeding was defined as less than a 4-inch stain on a perineal pad (11), similar to menstrual bleeding (12), or less than a 2-inch stain on a sanitary pad (2); while heavy bleeding was operationalized as requiring more than four pads per day for up to 10 days (12) or a saturated perineal pad within 1 hour (11). A recent study by Chi et al. used a pictorial blood assessment chart (PBAC)—a semi-objective method—to quantify the amount of lochia (13). This method involves the usage of standardized predetermined sanitary pads and completing a booklet consisting of weekly modified PBACs to assess the amount of lochia loss until complete cessation (14–16). The average blood loss ranged from 171 to 548 mL in eight studies, as reported by Sloan et al. (8). These studies measured blood loss by either: (i) placing a bedpan underneath the parturient woman immediately after the cord was clamped and cut after delivery; or (ii) using the blood collection sheet or delivery drape, sometimes tied around the woman's waist, with a funnel portion hanging between her legs. Most studies measured blood loss until active bleeding stopped, regardless of a pre-specified duration for

Table 8.1 Three Stages of Lochia

Stage	Color	Composition	Typical duration
1: lochia rubra (or curenta)	Red	Large amount of blood	3–5 days
2: lochia serosa	Brownish or pink	Serous exudate, erythrocytes, leukocytes, cervical mucus	Until 10th day post-delivery
3: lochia alba (or purulenta)	Whitish or yellowish–white	Fewer red blood cells; mainly leukocytes, epithelial cells cholesterol, fat, mucus	Second through third to sixth week post-delivery

Source: Data from Sherman D et al. *Am J Perinatol* 1999; 16: 399–402.

blood measurement. The median lochial blood loss estimated by the PBAC method was about 428 mL (range, 112–1330 mL) in women with no inherited bleeding disorders (13). Thus, there is a critical need for the establishment of valid, reliable, and feasible methods to quantify postpartum blood loss for patients, medical providers, and researchers. More randomized studies using standard sanitary pads in which saturation levels have been predetermined and standard amounts of loss per PBAC category have been validated are necessary in order to establish the use of PBACs as a standard method.

DURATION OF LOCHIA

Postpartum bleeding is a normal part of recovery from childbirth. Yet the duration of postpartum bleeding is not well characterized (2,17). The old textbook description of duration of lochia ranges from 18 days (18) to 6 weeks (19). Several other studies have reported a mean or median duration of postpartum bleeding or lochia of 21–35 days (1,2,11,17,20). The World Health Organization (WHO) conducted a study in 3955 breastfeeding women at seven different WHO study centers (21). The overall median of postpartum bleeding was 27 days, with significant variability across the globe. The shortest duration was a median of 22 days (2–56 days) and the longest duration was a median of 34 days and the range was from 2 to 90 days (see Table 8.2). A recent study conducted in the United Kingdom reported that the median duration of lochia in women without a bleeding disorder was 31 days (range, 10–62 days), whereas in women with an inherited bleeding disorder, it was 39 days (range, 21–58 days) (13). About a third of the women participating in this study had lochia lasting longer than 6 weeks post-delivery. The same study reported that the duration of lochia was not influenced by covariates such as maternal age, booking weight, parity, gestational age at delivery, birth weight, estimated blood loss at delivery, perineal tear/episiotomy, or the method of feeding (13).

Table 8.2 Median and Range of Postpartum Bleeding in Multinational Study[a]

	Duration of lochia (days)	
	Median	Range
Overall	27	2–90
WHO Study Center		
Chengdu, China	22	2–56
Sagamu, Nigeria	23	6–80
Guatemala City, Guatemala	24	22–26
Santiago, Chile	25	2–57
New Delhi, India	26	3–75
Melbourne and Sydney, Australia	31	5–90
Uppsala, Sweden	34	12–87

Source: Data from World Health Organization Task Force on Methods for the Natural Regulation of Fertility. The World Health Organization multinational study of breast-feeding and lactational amenorrhea. IV. Postpartum bleeding and lochia in breast-feeding women. *Fertil Steril* 1999; 72: 441–7.

[a] Subjects were 3955 breastfeeding women.

A study conducted in 39 healthy women who had normal vaginal delivery described three types of lochia patterns based on the assessment of the color of lochia (11). Three different types of lochia color patterns were identified: type 1, rubra–serosa–alba sequence; type 2, rubra–serosa–alba sequence with prolonged rubra phase and short serosa and alba phases; and type 3, two rubra phases (rubra–serosa/alba–rubra–serosa/alba sequence with near-equal duration of each phase). The overall duration of lochia was 36.0 ± 7.5 days (range, 17–51 days; see Table 8.3). Type 1 was the most prevalent and can be considered as the classic type. Type 2 was associated with short or no breastfeeding and type 3 may be a variant of type 2.

Various studies have also examined the effect of different factors on the duration of postpartum bleeding. For example, Oppenheimer et al. have reported that mothers that delivered heavier infants had a longer duration of lochia (1). In the WHO study, the duration of lochia was positively associated with infant weight taken within 1 week of delivery only in two of the seven study sites—Guatemala and Australia (21). In another study in Filipinas, no association with birth weight was observed (17). No studies have found an association between maternal weight or maternal age and the duration of lochia. However, Oppenheimer et al. reported that women of higher parity had a shorter duration of lochia (1). Other studies have not found any such effect of parity (11,17,21). Also, the sex of an infant showed no association with the duration of postpartum bleeding (1,17,21).

There is evidence that breastfeeding can potentially affect the quantity and/or duration of lochia. Bernstine and Bernstine reported that breastfeeding women showed more lochial discharge (22). Another study reported an association of lochial color-change pattern with breastfeeding, but not that of the overall duration of lochia (11). Other studies did not find any link between the duration/quantity of lochia and breastfeeding intensity (1,17,21) or the level of supplemental feeding (17). One proposed mechanism to explain the effect of breastfeeding is that breastfeeding releases oxytocin into the circulation (23), which can cause uterine contractions. Uterine contractions, in turn, can help to expel the placenta and reduce maternal blood loss (24,25).

The lactational amenorrhea method (LAM) during breastfeeding is also promoted as an alternative family planning method. The end of the sixth weeks after delivery (42 days) is usually considered the end of the postpartum period. By this time, the reproductive organs usually return to their pre-pregnant state, and the menses begin in non-breastfeeding

Table 8.3 Lochia Patterns Based on Color of Lochia

Type	Sequence	N	Description	Duration of rubra phase (days)
1	Rubra–serosa–alba	20	–	12.1 ± 6.7
2	Rubra–serosa–alba	11	Prolonged rubra with short serosa and alba	24.8 ± 5.0
3	Rubra–serosa/alba–rubra–serosa/alba	8	Near equal duration of each phase	5.5 ± 2.5 (first rubra)
Overall		39		36.0 ± 7.5

Source: Data from Sherman D et al. *Am J Perinatol* 1999; 16: 399–402.

women (26). However, during breastfeeding, menses do not return until much later. In breastfeeding women, a bleeding episode beyond 6 weeks is assumed to be postpartum bleeding. Therefore, LAM is widely used as a safe contraceptive method. As discussed above, a bleeding episode beyond 6 weeks is beyond the average duration of lochia even in breastfeeding women. Hence, the assumption of infertility at up to 6 months during breastfeeding is questionable (17,27). A clear understanding of the duration of lochia can help provide sound training to women who use the LAM method of birth control and can help them make more informed decisions on the best time to initiate the use of contraceptives (28).

TROPHOBLASTIC INVASION

During early pregnancy. trophoblasts derived from the placenta invade the maternal uterine tissues in order to regulate adequate blood flow and nutrient supply to the growing fetus (29). The trophoblast invasion continues until the 20th week of gestation (30). Trophoblasts produce various hormones and cytokines that have profound effects on maternal physiology (31,32). Factors secreted from endometrial glands such as epidermal growth factor, vascular endothelial growth factor, and various cytokines are critical in early trophoblast differentiation processes (31,33). Once the placenta switches from histiotrophic to hemotrophic nutrition, trophoblast plugs dissolve and remodeling of the decidual and myometrial spiral arteries by endovascular and interstitial trophoblasts occurs (34). The transformation involves interactions between vascular smooth muscle cells, uterine natural killer (uNK) cells, and invasive trophoblasts (35). The invading trophoblasts control plugging and remodeling of maternal vessels and pressure and rate of blood flow into the intervillous space, thereby supporting a constant delivery of oxygen and nutrients to the developing fetus (29,36). Early placental development takes place under low-oxygen conditions and hypoxia-induced factor 1α is required for proliferation in placental villi in the first trimester (29,30). Hypoxia and re-oxygenation of placental tissue can induce stress-mediated secretion of harmful cytokines into the maternal circulation, which may result in endothelial dysfunction and the clinical symptoms of pre-eclampsia (36,37). Interstitial trophoblasts also interact with uNK cells and modulate maternal immune responses (30). Invasive trophoblasts also secrete human chorionic gonadotrophin, which provides signals to uterine leukocytes, affecting decidual angiogenesis (35). Failure in trophoblast-mediated plugging of maternal arteries may lead to non-physiological oxygen-mediated placental apoptosis, endangering proper development of the fetus (36). Incomplete plugging of spiral arteries may lead to miscarriage (29). Towards the end of the first trimester, trophoblast plugs disappear from the spiral arteries and blood flow increases in order to meet the increasing need of the fetus for nutrients (30). Once the child is born, the spiral arteries are regenerated (38). Due to the regenerative process of endometrium arteries and capillaries, and unavoidable injury to the uterus as the attached placental tissue is removed, the first flow after delivery is heavy (31,39). At term, mother stroke volume increases 35% (39) and, furthermore in the delivery process the immune system is activated to prevent infections and hemorrhage postpartum (31,40).

COMPLICATIONS AND THE IMPORTANCE OF GYNECOLOGICAL HEALTH

Postpartum bleeding is a normal part of recovery from childbirth. However, abnormal conditions such as secondary postpartum bleeding, PPH, or uterine infections can be life threatening. One study showed that uterine infection affects about 20% of women, with 2% requiring hospitalization (41).

The review of postpartum maternal deaths by Li et al. showed that the occurrence rates of postpartum deaths in developing countries and in the USA are remarkably similar, in spite of the different systems of maternity care (42). About 80% of maternal deaths are due to obstetric causes such as PPH, obstetric infection, and pregnancy-induced hypertension. Amongst the studies mentioned in the review, 45% of postpartum deaths occurred in first day after delivery, 68%–73% of deaths occurred within the first week after delivery, and 82%–88% of deaths occurred within 2 weeks after delivery (42). Thus, the first 24 hours postpartum is the highest-risk period for maternal deaths, and the risk remains significantly high until the second week after delivery (see Figure 8.1).

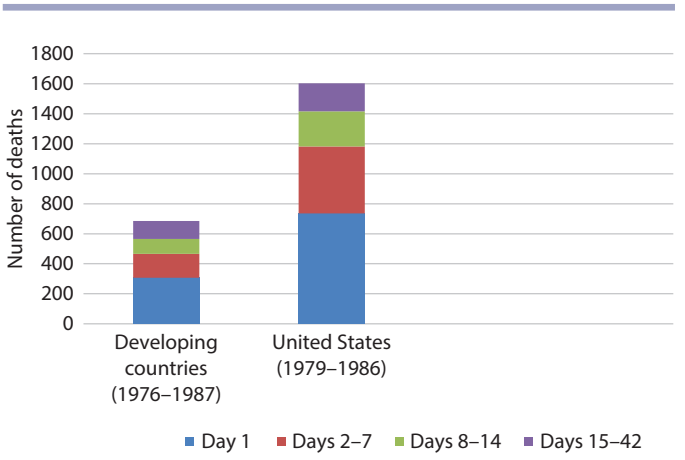

Figure 8.1 Postpartum maternal deaths. (Based on data derived from Li XF et al. *Int J Gynaecol Obstet* 1996; 54: 1–10.)

Postpartum Hemorrhage

PPH is a leading cause of maternal mortality and morbidity and accounts for about a quarter of deaths that occur as a consequence of complicated pregnancy (43). PPH is generally defined as blood loss from the genital tract in the third stage of labor, and PPH within the first 24 hours following delivery of the placenta (so-called immediate PPH or primary PPH) forms the majority of postpartum complications (44). The blood loss can range from 500 mL for vaginal delivery (1000 mL for cesarean) to 2500 mL or more (see Table 8.4). PPH or severe postpartum hemorrhage (SPPH) may also sometimes develop in the postpartum period between 24 hours and 12 weeks and is also sometimes referred to as delayed/late PPH or secondary PPH. Delayed PPH has been defined as "any abnormal or excessive bleeding from the birth canal occurring between 24 hours and 12 weeks postnatally" by Marchant et al. (41), whereas Bang et al. defined delayed PPH as "after 5 days post delivery, the use of more than five pads a day" or "increased bleeding after bleeding had decreased or stopped" or "any increase in use of pads by two or more after it was less or none" (45). The definition used by Fronczak et al. was passing fresh or clotted blood more than 3 days postpartum (46).

Primary PPH is mainly caused by uterine atony, whereas secondary PPH may be caused by subinvolution of the placental site, retained products of conception, infection, or inherited coagulation defects (47). Clinically problematic PPH, which develops within 1–2 weeks in 1% of women, is predominantly associated with abnormal involution of the placental site (44).

von Willebrand Disease

Women with von Willebrand disease (vWD), an inherited autosomal bleeding disorder caused by defects of von Willebrand factor (a platelet-binding protein), are at a higher risk of bleeding because of menorrhagia and delivery (48). In a recent case-controlled study of 4067 deliveries in women in USA, women with vWD had higher occurrence rates of PPH (49).

Puerperal Sepsis

Puerperal sepsis is the third leading cause of maternal mortality. Puerperal sepsis is defined as "the infection of the genital tract occurring any time between the rupture of membranes or labor and the 42nd day postpartum" (50). The risk of death from the sepsis is disproportionately higher in low- and middle-income areas such as Africa (2.7-fold higher), Asia (1.9-fold higher), and Latin America (2.1-fold higher) than in developed countries (51). Most puerperal sepsis occurs as either intrapartum uterine infection preceding or during labor (clinical chorioamnionitis), or early postpartum infection following birth, as well as postpartum endometritis (PPE). These infections are usually caused by ascending infections from the lower genital tract or exogenous, sexually transmitted microorganisms, including *Neisseria gonorrhoeae*/*Chlamydia trachomatis* (52), and may be associated with neonatal infectious sequelae. PPE occurs in 5% of vaginal births and 10% of cesarean deliveries, even in high-income countries (53). Intrauterine infection is a leading risk factor for PPE (54). There is still a lack of reliable population-based incidence rates and accurate microbiological data in this area, which in turn hinders the development of efficacious treatments and preventions of these serious infections (54).

Table 8.4 Postpartum Hemorrhage

Category	Blood loss after vaginal delivery
Postpartum hemorrhage	>500 mL
Severe postpartum hemorrhage	>1000 mL
Very severe postpartum hemorrhage	>2500 mL

Asherman Syndrome

Asherman syndrome or intrauterine adhesions (IUAs) is the partial or complete obliteration of the uterine cavity by adherence of the uterine walls, leading to menstrual abnormalities (amenorrhea or hypomenorrhea), infertility, and habitual abortion (55). Any event that damages the endometrium can lead to the development of IUAs. The major cause is damage to the basilar layer of the endometrium after curettage. In a review of 1856 women with IUAs, pregnancy was a predisposing factor in 91% (55,56). Of these, 67% had undergone curettage because of induced or spontaneous abortion, and 22% because of PPH. Symptoms of IUAs vary according to the extent of the disease and are usually one of the following: infertility, including sterility; repeated and habitual abortion; complications of late pregnancy such as premature labor, placenta previa, or placenta accrete; or menstrual disorders such as amenorrhea, hypomenorrhea, dysmenorrhea, or menometrorrhagia (55).

The treatment of Asherman syndrome includes dilatation and curettage, hysteroscopy, and hysterotomy. In order to prevent reoccurrence, intrauterine devices (e.g., uterine balloon stents, Foley catheters, and anti-adhesion barriers) may be used. Hormonal treatment may also be added in order to restore normal endometrium (56).

PROPHYLACTIC INTERVENTIONS

As mentioned above, the postpartum period between 24 hours and 12 weeks can be a potentially hazardous period during childbirth. Atonic PPH, caused due to failure of the uterus to contract adequately after birth, is the most prevalent of all of the various conditions described. Administration of oxytocin soon after delivery is a routine management therapy used to prevent uterine atony and associated bleeding (47). The WHO, along with the International Confederation of Midwives (ICM) and the International Federation of Gynecology and Obstetrics (FIGO), have issues a joint policy statement that recommends active management of the third stage of labor by administration of oxytocin or another uterotonic drug within 1 minute of the birth of the child, early umbilical cord clamping and cutting, controlled cord traction, and uterine massage after delivery of the placenta (57–59).

However, use of uterotonic drugs for the prevention of PPH after delivery of the placenta has not been recommended in this joint statement. Several studies report the use of ergot alkaloids, with varying dosing regimens (60–62). Several studies on oral ergometrine or methylergometrine report them as not satisfactory alternatives to parenteral prophylactic oxytocin drugs, mainly due to the less effective, unstable, and pharmacokinetically unreliable oral dosage form (63,64). Numerous other prophylactic interventions in the form of herbal therapies, homeopathic remedies, and other oxytocic drugs also exist (65). However, the safety and effectiveness of these interventions are not well investigated.

CONCLUSION

The reduction of pregnancy-related maternal deaths is a priority for the international community. However, in order to provide better prophylactic options and counseling to women in order to avoid morbidity and mortality related to postpartum bleeding disorders, it is crucial to understand lochia in every aspect discussed in this paper. Methodological studies are needed in order to obtain more epidemiological information from around the world so as to increase the robustness of estimates of the duration of lochia, as well as the complications related to it. In addition, programs related to the prevention, management, and treatment of postpartum bleeding disorders need more attention.

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Biomolecular markers and physical measures in the urogenital area

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INTRODUCTION

The skin, comprising a full one-sixth of body weight, is a sophisticated and dynamic organ that protects the sensitive internal tissues of the body from the external environment. However, skin is not a mere barrier. It is essential to the maintenance of body temperature and internal hydration, sensory functions, and immunological surveillance (1). Skin is a highly active metabolic tissue, and there is growing interest in the relationship between the presence and concentrations of certain biomolecules and the existence of certain dermatologic conditions. Lee and colleagues (2) examined and compared the potential roles of interleukin-1α (IL-1α) and tumor necrosis factor-α in the activation and release of secondary cytokines/chemokines in irritant contact dermatitis. Gerber and colleagues (3) reviewed the roles of cytokines and chemokines in rosacea. Distinct patterns of cytokine secretion from the skin surface have been demonstrated in patients with psoriasis compared to patients with atopic dermatitis (4). Psoriasis is associated with the differential expression of a wide variety of inflammatory and immune-related mediators. Those markers most easily accessible in the skin are those associated with abnormal keratinocyte differentiation and proliferation (5). Tanghetti (6) reported on recent data indicating that acne vulgaris is a primary inflammatory disease, and IL-1 and IL-8 expression and secretion are dramatically increased during the development of acne lesions. In addition to dermatologic conditions, a variety of systemic and internal pathological conditions may be reflected in the skin (4), including diabetes mellitus, atherosclerosis, inflammatory bowel diseases, AIDS, mental stress, and aging.

A wide variety of compounds can be extracted from the skin using minimally invasive or noninvasive methods such as scraping, tape stripping, or skin surface washing (4). With this capability, there is growing interest in quantifying biomolecules in the skin as a means of monitoring skin disorders or other clinical conditions. As a manufacturer of feminine protection products, we were interested in evaluating cytokines and other biomarkers from genital tissue in order to better understand and distinguish between the urogenital skin environment of premenopausal and postmenopausal women (estrogenized and non-estrogenized). In addition, these measures have the potential to provide additional information for traditional safety and efficacy testing, thereby increasing the ability of these tests to discriminate between very similar product and material options. This is the first report of non-invasive measures of temperature, pH, cytokines, and other biomarker measures of vulvar tissue in post- and pre-menopausal women.

OVERVIEW OF METHODOLOGY

This study was designed to evaluate and compare multiple parameters, including subjective genital symptoms, physical measurements (pH and temperature), cytokines, and other biomarkers collected via tape stripping. Specific details of the study methodology have been reported previously (7). Potential subjects, aged 21–70 years, were recruited by an independent test facility (Radiant Research, Cincinnati, OH). Information was collected on menopausal status, and a urogenital examination was performed in order to grade the degree of urogenital atrophy. The groups consisted of 15 premenopausal females (Pre-M), 15 postmenopausal females who were not receiving any type of hormone-replacement therapy and who showed signs of urogenital atrophy based on a urogenital examination (Post-M Non-HRT), and 15 postmenopausal females receiving HRT for at least 12 consecutive months (via oral, vaginal, or transdermal patch) and showing no signs of urogenital atrophy (Post-M HRT). Test group demographics and the mean scores for vaginal atrophy are presented in Table 9.1. Among the Post-M HRT group, the average time on HRT was 5 years. Approximately half of the subjects (7 out of 15) were on oral HRT.

Self-assessed, subject-reported symptoms were recorded. Panelists were asked to rate specific urogenital symptoms, including genital skin dryness and itch, vaginal dryness and itch, and perceived difficulty having intercourse. Skin temperature and pH were obtained from three different body sites: labia majora, labia minora, and introitus. The upper thigh was used as a control site for the skin temperature measurement. A hand-held infrared thermographic scanner (Exergen DermaTemp®, Exergen Corporation, Watertown, MA) was used to record skin temperature, and skin pH measurements were taken using a portable meter (Skincheck™ HI98109, Hanna Instruments, Woonsocket, RI) fitted with a specialized electrode. In addition, vaginal pH was measured using a strip of pH paper (3.0–7.0 range).

Sequential tape strips (22 mm D-Squame® skin sampling discs, CuDerm Corporation, Catalog # D100, Dallas, TX) were collected from each of the three sites (labia majora, labia minora [outer surface], and introitus [6 o'clock position]). For each panelist, if the tape stripping procedure caused any discomfort, it was discontinued immediately. The first and second tape strips were extracted and evaluated for soluble protein content (BCA™ Protein Assay Kit, Thermo Scientific, Rockford, IL), and cytokines IL-1α, IL-1ra, IL-6, and IL-10 (Human Cytokine Multiplex Immunoassay Kit, Bio-Plex Pro™, Bio-Rad Laboratories, Hercules, CA). The third tape strip was used for

Table 9.1 Summary of Demographics and Baseline Vaginal Atrophy Scores

	Premenopausal group (Pre-M) (N = 15)	Postmenopausal, non-HRT group (Post-M Non-HRT) (N = 15)	Postmenopausal with HRT group (Post-M HRT) (N = 15)
Parameter	Mean ± SD	Mean ± SD	Mean ± SD
Age (years)	33.0 ± 6.4	60.7 ± 3.6	60.5 ± 3.6
Height (inches)	64.7 ± 3.7	63.5 ± 2.8	63.9 ± 2.5
Weight (lb)	156.0 ± 22.8	149.2 ± 27.0	147.8 ± 23.7
BMI (%)	26.2 ± 3.3	25.9 ± 3.6	25.5 ± 4.3
Years since last period	NA	15.8 ± 9.3	14.2 ± 8.2
Average time on HRT	NA	NA	5 years, 2 months
	Number %	Number %	Number %
Ethnicity			
African–American	6 40%	2 13%	0 0%
Caucasian	8 53%	13 87%	15 100%
Other	1 7%	0 0%	0 0%
	Mean ± SE	Mean ± SE	Mean ± SE
Vaginal atrophy scores	0.29 ± 0.12	6.98 ± 0.44[a]	0.71 ± 0.22
Vaginal pH	4.72 ± 0.12	6.77 ± 0.25[a]	4.36 ± 0.20
Types of HRT (Post-M HRT group only)	Method	Number (%)	Average length of time used
	Oral	7 (46.7%)	7 years, 6 months
	Genital	4 (26.7%)	3 years, 5 months
	Patch/dermal	2 (13.3%)	5 years, 10 months
	Oral + dermal	1 (6.7%)	4 years
	Oral + dermal + genital	1 (6.7%)	1 year

Source: Farage MA et al. *J Clin Gynecol Obstet* 2015; 4(3): 237–50. Reprinted with the kind permission of Elmer Press.

[a] Post-M HRT group significantly different from Pre-M and Post-M Non-HRT groups ($p < 0.0001$).

Abbreviation: BMI: body mass index; HRT: hormone-replacement therapy; NA: not applicable.

natural moisturizing factor (NMF) analysis, which included the measurement of histamine, histidine, 2-pyrrolidone-5-carboxylic acid, proline, *trans*-urocanic acid, *cis*-urocanic acid, and protein. For histamine analysis, tape strips were placed into individual polypropylene vials, each vial was spiked with stable isotope-labeled histamine (D_4-histamine) internal standard, and extracted with acidified water. An aliquot of each sample was evaluated against a set of histamine standards. For analysis of histidine, 2-pyrrolidone-5-carboxylic acid, proline, *trans*-urocanic acid, *cis*-urocanic acid, and tape strips were spiked with stable isotope internal standards (D_3-proline, D_5-pyrrolidone-5-carboxylic acid, and $^{13}C_3$-*cis*-urocanic acid). A set of combined standards (histidine, 2-pyrrolidone-5-carboxylic acid, proline, *cis*-urocanic acid, and *trans*-urocanic acid) was prepared over an appropriate calibration range in acidified water. The standards and extracts of the tape strips were analyzed using gradient reversed-phase high-performance liquid chromatography/tandem mass spectrometry. The initial results (in nanograms of material per tape strip) were normalized for the amount of total protein on the tape strip (in micrograms). The net results were ultimately expressed as ng/µg protein. Tape strips number 4 and 5 were used for SkinMAP (Skin Multiple Analyte Profile) analysis. One aliquot was analyzed for soluble protein content (BCA™ Protein Assay Kit). The second was analyzed for multiple human skin analytes (human serum albumin, keratin-1,10, and involucrin) using a MILLIPLEX™ MAP Human Skin Magnetic Bead Panel (EMD Millipore Darmstadt, Germany).

Stratum corneum protein content was estimated using a bench-top infrared densitometer (Squame Scan™ 850A, Heiland Electronic GmbH, Wetzlar, Germany) in order to measure the optical absorption of the skin sampling discs at a wavelength of 850 nm. Readings with this instrument are linearly proportional to stratum corneum protein content, and were used to indirectly measure the amount of protein present on each skin sampling disc (8,9).

A separate linear mixed model was used to analyze each measurement at three different sites (introitus, labia minora, and labia majora), with body mass index and age used as covariates. Data were transformed to the natural log scale before analysis and then back-transformed to the original scale for the adjusted means. All statistical analyses were conducted using SAS 9.3.

RESULTS AND DISCUSSION

Subjective Symptoms

Menopause is accompanied by a number of physical and psychological changes that can lead to vasomotor symptoms (hot flushes), sleep disorders, decreased sexual response, genitourinary factors, and mood changes. HRT is known to relieve many of these symptoms and to have a positive impact on overall quality of life (10). Our study was focused on specific genital sensations that may also be associated with menopause, such as genital dryness and itch and difficulties with intercourse in order to determine whether there was an indication that HRT relieved these symptoms.

The prevalence rates of specific urogenital symptoms as reported by the panelists are shown in Figure 9.1. Compared

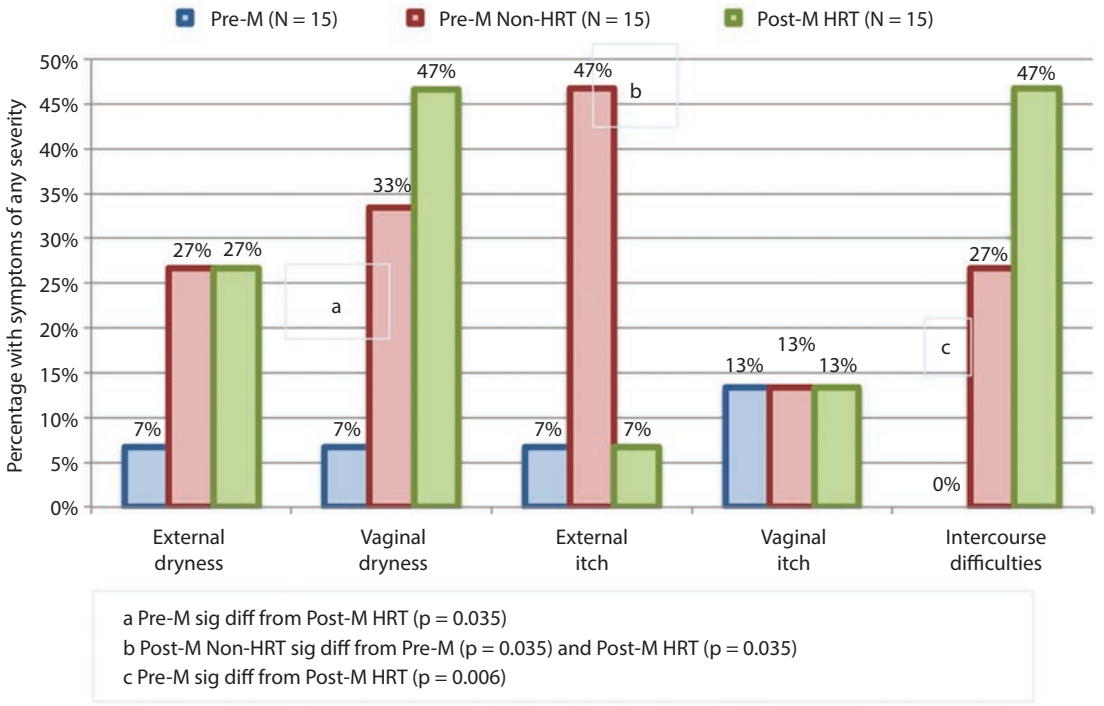


Figure 9.1 Incidence of subjective urogenital symptoms among test groups. Panelists were asked to rate specific urogenital symptoms, including genital skin dryness and itch, vaginal dryness and itch, and perceived difficulty having intercourse. The proportions of individuals in each test group claiming some degree of symptoms are plotted. Pairwise comparisons were conducted using Fisher's exact test. Significant differences between groups are indicated on the graph. (From Farage MA et al. *J Clin Gynecol Obstet* 2015; 4(3): 237–50. Reprinted with the kind permission of Elmer Press.)

to the premenopausal group, a higher proportion of postmenopausal women in both the Non-HRT and the HRT groups reported external dryness, although the differences were not statistically significance. When asked about vaginal dryness, only 7% of the Pre-M group reported this symptom. A higher incidence was reported by the postmenopausal groups, with 33% of the Post-M Non-HRT subjects and 47% of the Post-M HRT subjects responding in the affirmative. The difference was significant ($p = 0.035$) when the Pre-M group was compared to the Post-M HRT group. External itch was experienced by a significantly higher proportion of the Post-M Non-HRT group (i.e., 47%) compared to the other two groups (each with 7% responding in the affirmative; $p = 0.035$). Difficulties with intercourse were reported by a higher proportion of postmenopausal women in both groups (Non-HRT and HRT) compared to premenopausal women; however, the difference was significant only for the comparison of the Pre-M with the Post-M HRT group ($p = 0.006$). In the Post-M HRT group, no significant differences were found between reported subjective symptoms and the type of HRT (i.e., oral, injection or transdermal patch; data not shown).

Wysocki and colleagues (11) reported on a survey conducted among 8081 postmenopausal women. In this group, 3046 reported at least one symptom commonly associated with vulvar and vaginal atrophy (VVA). The most commonly reported symptom was vaginal dryness (55%), followed by dyspareunia or pain during intercourse (44%) and vaginal irritation (37%). In our study, the reported prevalence of vaginal dryness was lower among the Post-M Non-HRT group showing significant vaginal atrophy (33%). Only 27% of this group reported difficulties with intercourse (Figure 9.1). Surprisingly, there was no evidence that HRT improved these subjective symptoms. In fact, the Post-M HRT group reported a directionally higher incidence of vaginal dryness and difficulties with intercourse than the Post-M Non-HRT group, although these differences were not significant. From this study, it appears that HRT may be associated with relief from external itch (Figure 9.1). The percentage of women reporting this symptom was equivalent in the Pre-M and Post-M HRT groups (7% in each). In the Post-M Non-HRT group, the percentage was significantly higher at 47%.

An interesting observation in the course of this study related to the number of tape strips tolerated by panelists in each test group. Although the genital skin of postmenopausal women is generally considered quite fragile, the Post-M Non-HRT group tolerated a greater number of tape strips at each anatomic site compared to the other two groups (Table 9.2). The difference was significant at the introitus compared to the Pre-M group, and at all sites compared to the Post-M HRT group. This is consistent with previous observations that vulvar sensitivity to mechanical stimuli declines after menopause, but is restored by estrogen supplementation (12).

Physical Measurements

Surface skin temperature is the result of the equilibrium between the body's internal sources of heat supplied to the skin by vascular perfusion and heat loss to the external environment. In this study, differences in skin temperature at all of the anatomic sites were small, but statistically significant at

Table 9.2 Number of Tape Strips Tolerated by Subjects

Body site	Premenopausal (Pre-M) (N = 15) Adjusted mean ± SE	Postmenopausal, non-HRT (Post-M Non-HRT) (N = 15) Adjusted mean ± SE	Postmenopausal with HRT (Post-M HRT) (N = 15) Adjusted mean ± SE	Pairwise comparisons (p-value) Pre-M vs. Post-M Non-HRT	Pre-M vs. Post-M HRT	Post-M Non-HRT vs. Post-M HRT
Introitus	4.4 ± 0.6	6.5 ± 0.8	4.5 ± 0.8	**0.039**	0.96	**0.034**
Labia minora	6.5 ± 0.7	8.1 ± 0.8	5.1 ± 0.9	0.11	0.19	**0.002**
Labia majora	9.3 ± 0.5	10.1 ± 0.5	8.2 ± 0.6	0.27	0.13	**0.006**

Source: Farage MA et al. *J Clin Gynecol Obstet* 2015; 4(3): 237–50. Reprinted with the kind permission of Elmer Press.
Abbreviation: HRT: hormone-replacement therapy.

the labia minora and the labia majora (Figure 9.2a). At the labia minora, surface skin temperature was lower in the Post-M Non-HRT subjects compared to Pre-M and Post-M HRT subjects ($p = 0.0087$ and 0.0388, respectively). At the labia majora, surface skin temperature was significantly higher in the Pre-M group when compared to either postmenopausal group ($p = 0.0025$ for Non-HRT and $p = 0.0035$ for HRT). The lower skin temperature in postmenopausal women reflects the underlying decrease in blood perfusion.

The vaginal pH of premenopausal women without VVA is typically reported as 4.5 or less (13,14). Prior to menopause, the glycogen released from the epithelial cells that are exfoliated from the vaginal wall is converted to glucose, which is acted upon by lactobacilli to produce lactic acid. This lactic acid maintains the acidic vaginal pH. With menopause, estrogen production is reduced, resulting in a thinning of the vaginal epithelial cell layer, with a subsequent reduction in the number of exfoliated cells, ultimately leading to less production of lactic acid. This allows the postmenopausal pH to increase to the range of 5.0–7.5 (13,14).

In our study, measures of skin pH (Figure 9.2b) show that the premenopausal women had a significantly lower vaginal pH (pH 4.72) compared to the Post-M Non-HRT group (pH 6.77; $p < 0.0001$). The mean vaginal pH of the Post-M HRT group was similar to that of the Pre-M group (pH 4.36). The mean pH values at the introitus and at the labia minora were also significantly different when the Pre-M group was compared to the Post-M Non-HRT group ($p = 0.0033$ and 0.0463, respectively). Interestingly, the pH of the introitus in the Post-M HRT group was similar to that of the Post-M Non-HRT group at this site, and was significantly higher than that of the Pre-M group ($p = 0.022$). For the Post-M HRT group, the pH of the labia minora was similar to that of the Pre-M group. There were no significant differences in pH at the labia majora.

To our knowledge, this is the first time skin surface temperature and pH on the external genitalia of anatomic sites on the genitalia have been reported for pre- and post-menopausal women.

Histamine and Histidine Levels

Histamine is derived from the decarboxylation of the amino acid histidine, and has been found to mediate a wide variety of biological processes (15,16). It is commonly associated with inflammatory and allergic reactions. When tissues are inflamed or stimulated by exposure to allergens, local mast cells release histamine and, once released, histamine induces excitation of a subset of unmyelinated C-fibers, resulting in itch (17). Further, histamine is known as a common cause of pruritus or itch. A dose-dependent cause-and-effect relationship between histamine and itching has been demonstrated many times using a variety of test methods. However, histamine has a wide variety of other biological effects, including as a neurotransmitter and in the stimulation of smooth muscle contraction, vasodilation, and exocrine secretions (16).

Histamine levels in skin have been reported to decrease in older subjects. Gilchrest and colleagues (18) evaluated the difference in inflammatory responses in the skin of a small number of older and younger individuals subjected to minimal erythema doses of ultraviolet light. Fluid from suction blisters induced on exposed sites demonstrated significantly lower ($p < 0.05$) levels of histamine during the inflammatory response in the older subjects (seven individuals aged 62–86 years) compared to the younger subjects (four individuals aged 22–26 years).

We measured the levels of histamine and histidine recovered from the introitus, the labia minora, and the labia majora. As shown in Table 9.3, the levels of both histamine and histidine were higher at all three anatomic sites for the premenopausal group compared to both postmenopausal groups (Non-HRT and HRT). For histamine, the differences between the Pre-M and the Post-M Non-HRT groups were statistically significant at all three sites (introitus, $p = 0.0003$; labia minora, $p = 0.0001$; and labia majora, $p = 0.006$). Similarly, when the Pre-M group was compared to the Post-M HRT group, the differences were significant (introitus, $p = 0.041$; labia minora, $p = 0.003$; and labia majora, $p = 0.003$). Levels of histidine were significantly different between the Pre-M and the Post-M Non-HRT groups at the labia minora ($p = 0.045$) and labia majora ($p = 0.006$). For the Pre-M and Post-M HRT group comparison, the levels of histidine measured at the labia minora were significantly different ($p = 0.010$). Due to the higher levels of histamine, the histidine/histamine ratio was lower for the premenopausal group at all three sites. The differences were significant between the Pre-M and the Post-M Non-HRT groups at the introitus ($p = 0.030$) and the labia minora ($p = 0.017$).

To explore the potential relationship between histamine levels and the presence of self-assessed, subject-reported symptoms, levels of histamine for those individuals who reported symptoms of skin and vaginal dryness, external and vaginal itch, and difficulties with intercourse were compared to those of individuals who reported an absence of symptoms. As shown in Figure 9.3, women from the entire test population who reported having symptoms (i.e., regardless of group assignment) showed consistently lower levels of histamine compared to women who did not have those symptoms. This observation was consistent for all of the specific genital symptoms included in the questionnaire (i.e., skin and vaginal dryness, external and vaginal itch, and difficulties with intercourse).

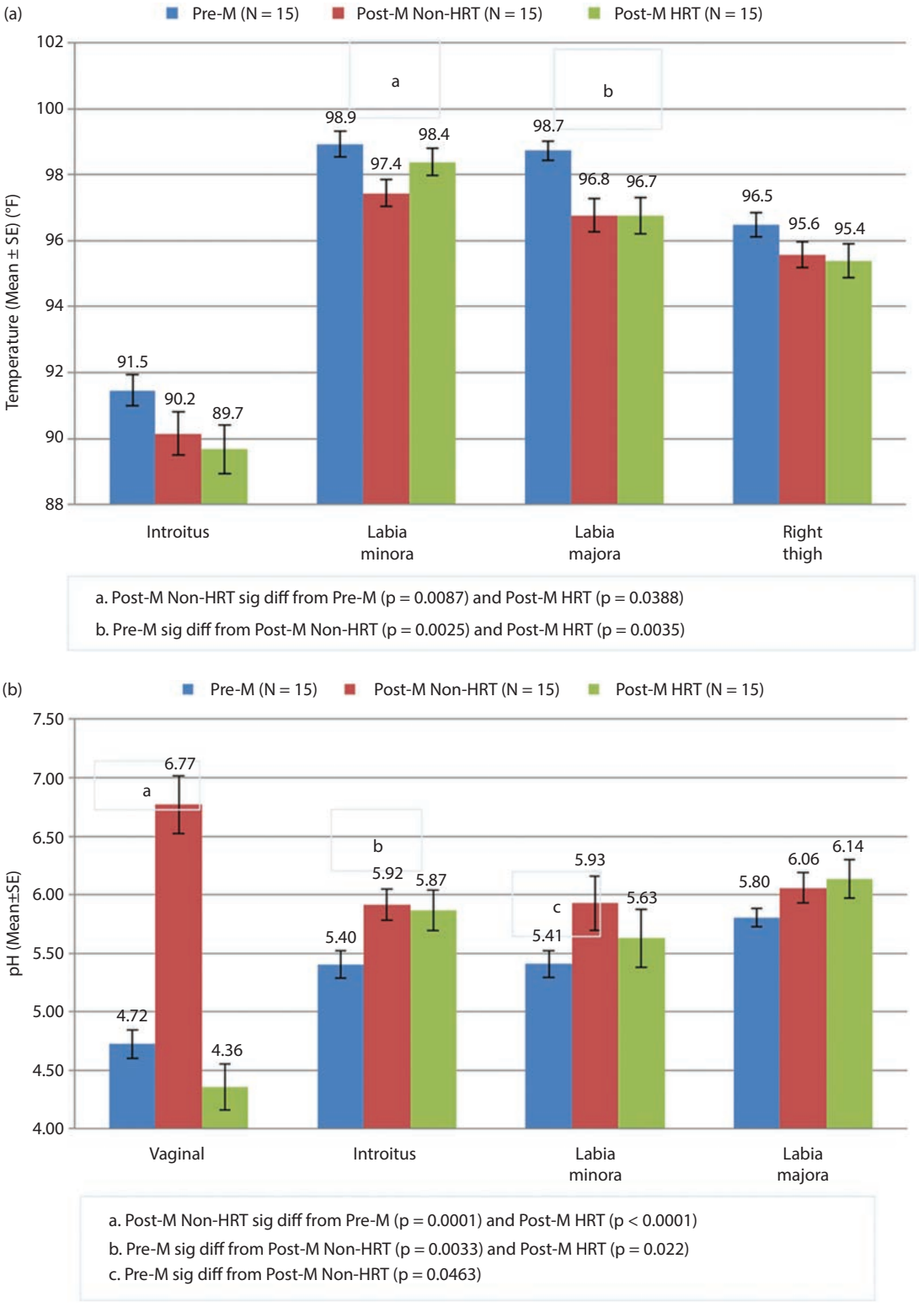
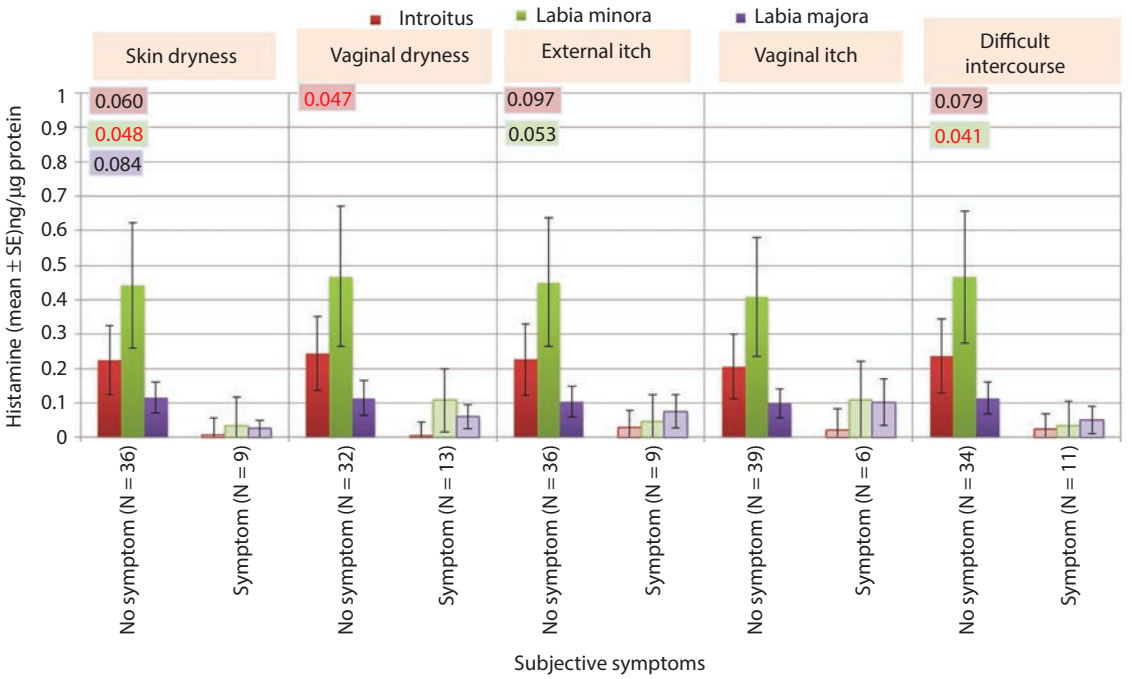


Figure 9.2 Skin temperature and pH among test groups. Skin temperature (a) and pH (b) were obtained from three different body sites; labia majora, labia minora, and introitus. The upper thigh was used as a control site for the skin temperature measurement. In addition, vaginal pH was measured using litmus paper against the middle to upper third of the lateral wall of the vagina. Pairwise comparisons were conducted using a mixed linear model. Significant differences between groups are indicated on the graph. (From Farage MA et al. *J Clin Gynecol Obstet* 2015; 4(3): 237–50. Reprinted with the kind permission of Elmer Press.)

Table 9.3 Measurements of Histamine and Histidine

		Pre-menopausal group (Pre-M)		Post-menopausal, non-HRT group (Post-M Non-HRT)		Post-menopausal with HRT group (Post-M HRT)		Pairwise comparisons (p-value)		
	Body site	N	Adjusted mean ± SE	N	Adjusted mean ± SE	N	Adjusted mean ± SE	Pre-M vs. Post-M Non-HRT	Pre-M vs. Post-M HRT	Post-M Non-HRT vs. Post-M HRT
Histamine/histidine										
Histamine (ng/μg)[a]	Introitus	11	0.126 ± 0.096	14	0.004 ± 0.003	7	0.014 ± 0.018	**0.0003**	**0.041**	0.16
	Labia Minora	15	0.295 ± 0.186	15	0.012 ± 0.009	12	0.022 ± 0.021	**0.0001**	**0.003**	0.43
	Labia Majora	15	0.061 ± 0.034	15	0.009 ± 0.006	15	0.006 ± 0.005	**0.006**	**0.003**	0.65
Histidine (ng/μg)	Introitus	12	9.6 ± 4	13	3.3 ± 1.6	7	7.1 ± 5	*0.058*	0.65	0.19
	Labia Minora	15	16.3 ± 4.7	14	7.3 ± 2.6	12	5.1 ± 2.1	**0.045**	**0.010**	0.36
	Labia Majora	15	31.5 ± 8.3	15	11.2 ± 3.5	14	16.6 ± 6	**0.006**	0.10	0.25
Histidine/histamine	Introitus	11	80.6 ± 88	13	990 ± 1181	7	510 ± 1004	**0.030**	0.18	0.57
	Labia Minora	15	55.2 ± 48	14	591 ± 646	12	234 ± 320	**0.017**	0.18	0.34
	Labia Majora	15	519 ± 312	15	1303 ± 956	14	2407 ± 2082	0.20	*0.053*	0.38

Source: Farage MA et al. *J Clin Gynecol Obstet* 2015; 4(3): 237–50. Reprinted with the kind permission of Elmer Press.
[a] Analyses were adjusted to reflect quantitative values of the material of interest per μg total protein.
Abbreviation: HRT: hormone-replacement therapy.



p values are color coded to correspond to body sites (blue for vaginal, red for introitus, green for labia minora, and purple for majora, and are given for significant values (i.e., $p \leq 0.05$) and trends (i.e., $p \leq 0.1$)

Figure 9.3 Relationship between histamine levels and subjective symptoms. The levels of histamine detected from individuals who claimed the presence of subjective symptoms were compared to those from individuals who did not claim to experience the symptoms. The entire test population was considered as a whole, regardless of group assignment. Pairwise comparisons were conducted using Fisher's exact test. Significant differences ($p \leq 0.05$) and trends ($p \leq 0.1$) between groups are indicated on the graph. (From Farage MA et al. *J Clin Gynecol Obstet* 2015; 4(3): 237–50. Reprinted with the kind permission of Elmer Press.)

As mentioned earlier, histamine is commonly associated with itch in a dose-dependent manner. However, the sensation of itch can be caused by several other biochemical mediators (19), and possibly other stimuli, such as dryness. In our study, claims of external itching in the genital area were significantly higher in the Post-M Non-HRT group (Figure 9.1). However, histamine levels were significantly lower in this group compared to premenopausal women (Table 9.3). Figure 9.4a illustrates the striking change in histamine levels at the different life stages. Histamine levels at the introitus showed a 32-fold decrease when Pre-M women were compared to Post-M Non-HRT women, and a 9-fold decrease when compared to Post-M

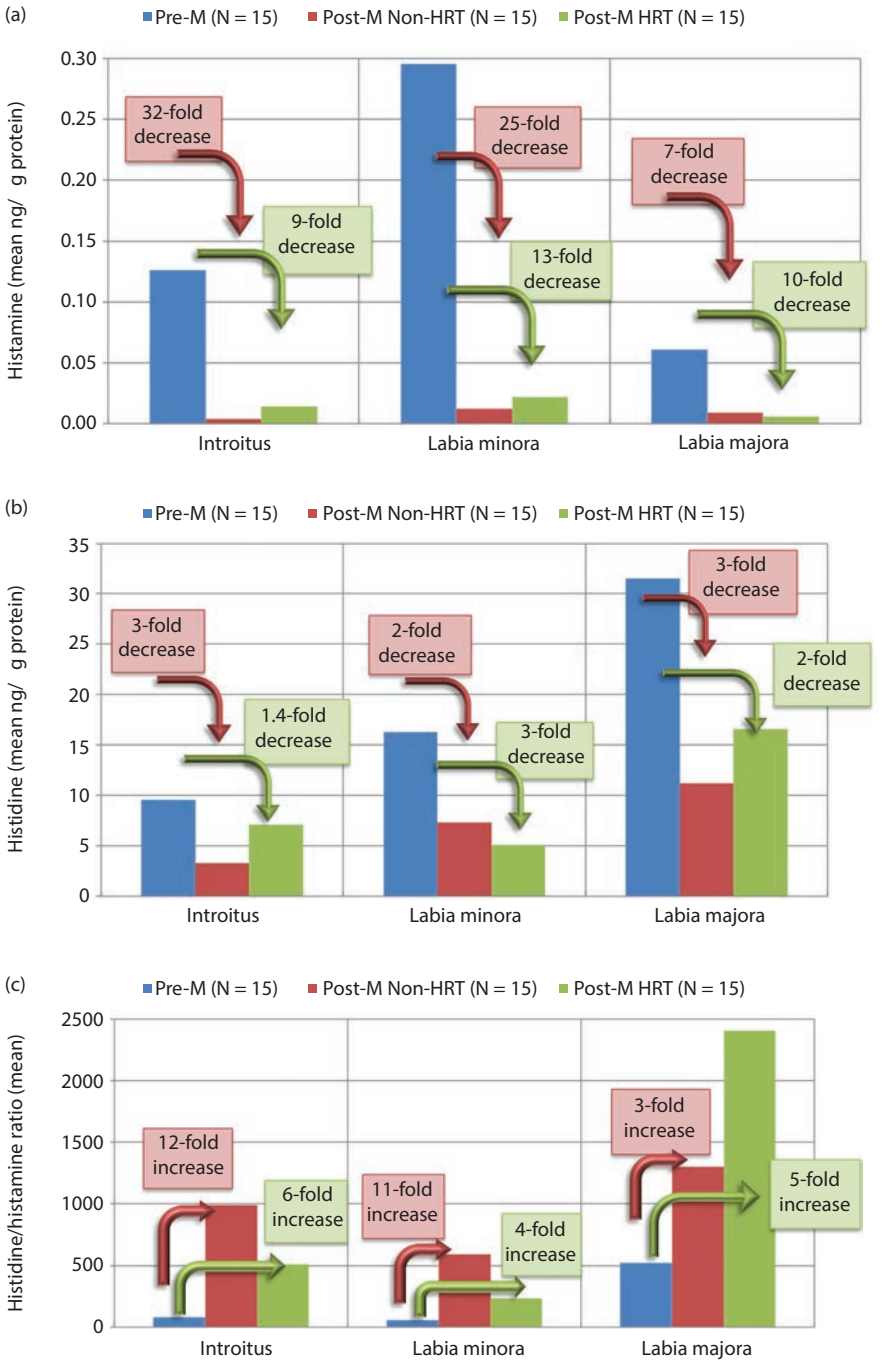


Figure 9.4 Changes in histamine and histidine at different life stages. The histamine (a), histidine (b), and histidine/histamine ratios (c) at three anatomic sites (given in Table 9.3) are plotted for each group to illustrate the change from the premenstrual group to the postmenstrual groups. Decreases from Pre-M levels for the Post-M Non-HRT group are illustrated by the pink arrows and text boxes, and for the Post-M HRT group by the green arrows and text boxes. (From Farage MA et al. *J Clin Gynecol Obstet* 2015; 4(3): 237–50. Reprinted with the kind permission of Elmer Press.)

HRT women. A similar pattern was observed at the labia minora, with a 25-fold and 13-fold decrease, and at the labia majora, with a 7-fold and 10-fold decrease, respectively.

Interestingly, histidine levels were also lower in both Post-M groups compared to the Pre-M group (Figure 9.4b). However, the ratio of histidine to histamine showed an increase (Figure 9.4c) that reached significance when the Pre-M group was compared to the Post-M Non-HRT group at the introitus and the labia minora (Table 9.3). Since histidine is a precursor of histamine, lower histidine levels in postmenopausal women will result in a decrease in histamine. Further, an altered ratio of histamine to histidine may indicate a change in the induction of histidine decarboxylase or a shift in the equilibrium between these two materials.

Several roles have been identified for histamine that are related to sexual function (15). At a central level, histamine receptors are important in the brain areas involved in sexual arousal (20). As a neurotransmitter, histamine levels are related to sexual desire (21); a decrease in histamine causes a decrease in sexual desire, and an increase causes the reverse. At a local level, histamine has effects on smooth muscle and blood vessels that is critical to physiological sexual arousal (22). In women, this involves an increase in clitoral cavernosal artery inflow and an increase in clitoral intracavernous pressure, which lead to tumescence and extrusion of the clitoris (21). Engorgement of the genital vascular network increases pressure inside the vaginal capillaries and results in lubrication of the epithelial surface of the vaginal wall (21). Histamine also causes the sexual flush that occurs during arousal. Orgasm is triggered when histamine is released from the mast cells in the genitals, and sufficient histamine (and its precursor histidine) must be present in order to trigger an orgasm. For some women who fail to achieve sexual pleasure and orgasm, the problem may be a result of a biochemical imbalance.

We propose that the reduced level of histamine in the genital area may be related to sexual and lubrication difficulties in postmenopausal women, and not related to a subjective perception of itch. Further, histamine may be an important biomarker for genital tissue health with regard to blood perfusion and sexual function. To our knowledge, this is the first report on histamine levels of the external genitalia for women in different life stages.

Natural Moisturizing Factor

NMF represents about 20%–30% of the dry weight of the stratum corneum and is composed of a number of water-soluble compounds, including 2-pyrrolidone-5-acid and urocanic acid, proline, lactic acid, urea, citrate, and sugars (23). There are intrinsically lower levels of NMF present in aged skin compared to younger skin (24).

Measures of NMF were not significantly different when groups were compared, with the exception of NMF at the labia minora, where the Pre-M group measurement was significantly higher than that of the Post-M HRT group ($p = 0.016$) (Table 9.4). The levels of NMF tended to increase as the tissue type changed to a more keratinized type (i.e., introitus < labia minora < labia majora). When amino acid components were measured, there were no significant differences between the Pre-M and the Post-M Non-HRT groups, except in proline at the labia majora ($p = 0.033$). Comparisons of the Pre-M and the Post-M HRT groups indicate 2-pyrrolidone-5-acid was higher for the Pre-M group at the labia minora ($p = 0.024$), and proline was higher at the labia minora and labia majora ($p = 0.0023$ and 0.0040, respectively). One significant difference was also noted when amino acid levels were compared for the two postmenopausal groups; proline was higher in the Post-M Non-HRT group at the labia minora ($p = 0.0045$). *Cis*-uronic acid was evaluated but not detected in these samples.

Overall, we did not find a consistent reduction in the components of NMF in the genital epithelium. In those instances where significant differences were found, the postmenopausal groups with and without HRT exhibited lower amounts compared to the Pre-M group.

Cytokine and Other Measures

The cytokines IL-1α and IL-6 are considered proinflammatory mediators, while IL-1ra and IL-10 are considered anti-inflammatory mediators (25). The cytokine IL-1α is produced by epithelial cells, and the normal human epidermis acts as a major reservoir of this material. Regulated cytokine expression is essential to the quality and function of the epidermal barrier, and deregulation of this complex signaling mechanism can result in multiple consequences for skin barrier function (26). The cytokine IL-1ra functions as a competitive inhibitor to block the response to IL-1α (27). Hirao et al. (28) reported that the content of IL-1α and IL-1ra in the stratum corneum varied between body sites. The stratum corneum of an area of skin unexposed to sunlight (e.g., the inner side of the upper arm) contained more IL-1α than a sun-exposed area (e.g., the face). In contrast, the IL-1ra content was reversed, with the unexposed area containing lower amounts than the sun-exposed area. The ratio of IL-1ra to IL-1α was 8 in the unexposed area, and over 100 in the sun-exposed area (28). These same authors reported that the IL-1α content in the unexposed site increased with age, while the content of IL-1ra decreased, resulting in an age-dependent decrease in the IL-1ra/IL-1α ratio.

Our results are consistent with these observations in that the IL-1α content measured in the Post-M groups (Non-HRT and HRT) tended to be higher at all three sites (Table 9.4). When the Pre-M group was compared to Post-M Non-HRT group, the differences achieved significance at the labia minora ($p = 0.0091$) and labia majora ($p = 0.045$). When the Pre-M group was compared to the Post-M HRT group, the difference was significant at the labia majora ($p = 0.014$). Levels of IL-1ra and the ratio of IL-1ra/IL-1α did not show consistent trends. Levels of IL-6 and IL-10 were evaluated but not detected in these samples.

Analysis of Squame is a means of quantifying dry skin (29). Squame was lower for Post-M Non-HRT at the introitus compared to both the Pre-M ($p < 0.0001$) and Post-M HRT groups ($p = 0.0021$). Conversely, this material was lower for Post-M HRT at the labia minora and labia majora when compared to the Pre-M group ($p < 0.0001$ and $p = 0.0080$, respectively) and Post-M Non-HRT group ($p < 0.0001$ and $p = 0.0002$, respectively).

The level of human serum albumin (HSA) measured at the labia minora was significantly increased at the labia minora in the Post-M Non-HRT group. Albumin is the most abundant plasma protein, accounting for 55%–60% of such protein (30). Each day, 120–145 g of albumin is lost into the extravascular space; 41% of the extravascular HSA is in the skin (30). Albumin does not diffuse freely through intact vascular endothelium, thus the loss of albumin into interstitial spaces may be an indication of increased vascular permeability (31).

Involucrin is a soluble protein precursor of the cross-linked envelope in human stratified squamous epithelium (32).

Table 9.4 Measurements of Natural Moisturizing Factor, Cytokines, and Other Biomarkers

		Premenopausal group (Pre-M)		Postmenopausal, non-HRT group (Post-M Non-HRT)		Postmenopausal with HRT group (Post-M HRT)		Pairwise comparisons (p-values)		
	Body site	N	Adjusted mean ± SE	N	Adjusted mean ± SE	N	Adjusted mean ± SE	Pre-M vs. Post-M Non-HRT	Pre-M vs. Post-M HRT	Post-M Non-HRT vs. Post-M HRT
NMF and components (2-pyrrolidone-5-acid, proline, *trans*-urocanic acid, and *cis*-urocanic acid)										
NMF (ng/μg)[a]	Introitus	11	42.5 ± 18	14	23.3 ± 10	7	48.3 ± 32	0.25	0.84	0.18
	Labia minora	15	72.9 ± 18	15	53.5 ± 16	12	28.1 ± 10	0.37	**0.016**	*0.066*
	Labia majora	15	286 ± 53	15	193 ± 42	15	179 ± 44	0.13	*0.091*	0.75
2-pyrrolidone-5-acid (ng/μg)	Introitus	12	16.9 ± 6.8	14	9.5 ± 4.2	7	21.6 ± 15	0.27	0.70	0.14
	Labia minora	15	31.7 ± 9	15	22.3 ± 7.5	12	11.8 ± 4.9	0.35	**0.024**	0.10
	Labia majora	15	141 ± 27	15	94.4 ± 21	15	89.8 ± 22.9	0.14	0.12	0.84
Proline (ng/μg)	Introitus	12	7.2 ± 1.9	14	5.4 ± 1.5	7	8.4 ± 3.5	0.40	0.72	0.23
	Labia minora	15	9.2 ± 1.4	15	8.1 ± 1.4	12	4.3 ± 0.9	0.54	**0.0023**	**0.0045**
	Labia majora	15	22.5 ± 3.5	15	13.9 ± 2.6	15	11 ± 2.3	**0.033**	**0.0040**	0.28
Trans-urocanic acid (ng/μg)	Introitus	12	5.7 ± 2.9	14	4.1 ± 2.2	6	11 ± 10	0.59	0.41	0.16
	Labia minora	15	10.3 ± 3.4	15	12.8 ± 5	11	5.6 ± 2.8	0.61	0.22	*0.069*
	Labia majora	15	73.1 ± 15	15	71.4 ± 18	15	55.5 ± 16	0.94	0.38	0.36
Cis-urocanic acid	Evaluated, but not detected									
Cytokines										
IL-1a (pg/μg)	Introitus	15	1.5 ± 0.3	15	2.1 ± 0.5	15	2.7 ± 0.8	0.31	*0.079*	0.36
	Labia minora	15	1.4 ± 0.3	15	3 ± 0.7	15	1.8 ± 0.5	**0.0091**	0.41	*0.056*
	Labia majora	15	8.3 ± 1.7	15	14.8 ± 3.6	15	17.8 ± 4.9	**0.045**	**0.014**	0.48
IL-1ra (pg/μg)	Introitus	15	60.4 ± 14	15	36.7 ± 9.8	15	50.9 ± 15.3	0.11	0.60	0.27
	Labia minora	15	59.7 ± 16	15	48.7 ± 15	15	77 ± 27	0.57	0.50	0.17
	Labia majora	15	8 ± 2.5	14	4.9 ± 1.9	13	2.9 ± 1.3	0.25	**0.032**	0.22
IL-1ra/IL-1a	Introitus	15	40.2 ± 15	15	17.9 ± 7.7	15	19 ± 9.3	*0.090*	0.14	0.89
	Labia minora	15	41.8 ± 15	15	16.3 ± 7.2	15	42.5 ± 21	*0.053*	0.97	**0.038**
	Labia majora	15	1 ± 0.5	14	0.3 ± 0.2	13	0.2 ± 0.1	*0.097*	**0.011**	0.24
IL-6	Evaluated, but not detected									
IL-10	Evaluated, but not detected									
Other										
Squame (%Abs, 850 nm)	Introitus	15	5.9 ± 0.5	15	3.4 ± 0.3	15	5.1 ± 0.6	<**0.0001**	0.27	**0.0021**
	Labia minora	15	4.4 ± 0.3	15	4.4 ± 0.4	15	2.6 ± 0.3	0.94	<**0.0001**	<**0.0001**
	Labia majora	15	6.5 ± 0.3	15	6.8 ± 0.4	15	5.2 ± 0.4	0.50	**0.0080**	**0.0002**
HSA (ng/μg)	Introitus	8	1.9 ± 1.3	9	1.9 ± 1.3	5	1.3 ± 1.4	0.98	0.65	0.64
	Labia minora	14	1.2 ± 0.4	15	2.9 ± 1.1	11	0.8 ± 0.4	**0.044**	0.51	**0.0083**
	Labia majora	15	1.7 ± 0.4	15	1.6 ± 0.4	13	0.9 ± 0.3	0.86	0.074	*0.070*

(*Continued*)

Table 9.4 (*Continued*) Measurements of Natural Moisturizing Factor, Cytokines, and Other Biomarkers

		Premenopausal group (Pre-M)		Postmenopausal, non-HRT group (Post-M Non-HRT)		Postmenopausal with HRT group (Post-M HRT)		Pairwise comparisons (p-values)		
	Body site	N	Adjusted mean ± SE	N	Adjusted mean ± SE	N	Adjusted mean ± SE	Pre-M vs. Post-M Non-HRT	Pre-M vs. Post-M HRT	Post-M Non-HRT vs. Post-M HRT
Involucrin (ng/μg)	Introitus	8	0.4 ± 0.2	9	0.8 ± 0.3	5	0.6 ± 0.4	0.15	0.47	0.61
	Labia minora	14	0.2 ± 0.1	15	0.3 ± 0.1	11	0.3 ± 0.1	0.25	0.45	0.76
	Labia majora	15	0.1 ± 0	15	0.1 ± 0	13	0 ± 0	0.68	0.23	0.36
Keratin-1, 10 (ng/μg)	Introitus	8	2 ± 0.9	9	1.6 ± 0.7	5	0.7 ± 0.5	0.70	0.11	0.14
	Labia minora	14	1.8 ± 0.3	14	1.1 ± 0.2	11	1.4 ± 0.4	**0.041**	0.37	0.28
	Labia majora	13	1.2 ± 0.2	11	1.1 ± 0.3	7	1.3 ± 0.4	0.85	0.69	0.56
Protein (cytokine) (μg/mL)	Introitus	15	41.9 ± 6.3	15	39.5 ± 7.1	15	33.1 ± 6.6	0.78	0.30	0.38
	Labia minora	15	31.9 ± 4	15	38.6 ± 5.7	15	34.8 ± 5.8	0.29	0.65	0.54
	Labia majora	15	12.3 ± 1.5	15	12 ± 1.7	15	9.4 ± 1.5	0.89	0.15	0.14
Protein SkinMAP (μg/mL)	Introitus	8	47.3 ± 9.8	9	54.8 ± 12	5	63.4 ± 20	0.59	0.39	0.64
	Labia minora	14	46.5 ± 7.8	15	44.3 ± 8.5	11	44.3 ± 11	0.83	0.85	1.00
	Labia majora	15	21.6 ± 3.6	15	15.5 ± 3	13	10 ± 2.3	0.16	**0.0041**	*0.059*

Source: Farage MA, Wehmeyer K, Fadayel G, Carpenter S, Cheng R, Wang B, Ledger WJ. Urogenital biomolecular and physical measures in pre- and post-menopausal women. *J Clin Gynecol Obstet* 2015; 4(3): 237–50. Reprinted with the kind permission of Elmer Press.

[a] Analyses were adjusted to reflect quantitative values of the material of interest per μg total protein.

Abbreviation: HRT: hormone-replacement therapy; IL: interleukin; NMF: natural moisturizing factor.

Keratins are major components of the epithelial cytoskeleton and are important for mechanical integrity at the cellular and tissue level (33). Our measurements indicated no differences between groups in terms of the content of involucrin or keratin-1, 10, with the exception of a single comparison of keratin-110 at the labia minora, where the Pre-M group had a significantly higher level compared to the Post-M Non-HRT group ($p = 0.041$). Similarly, we observed no differences in the general measure of total protein cytokine. The protein SkinMAP was significantly lower at the labia majora in the Post-M HRT group compared to the Pre-M group ($p = 0.0041$).

Study Limitations

In this study, no attempt was made to recruit equal numbers of women on different types of therapy (i.e., oral, genital, or dermal/patch). Half of our panelists were on oral therapy, and those on local vaginal therapy had been using this form for a relatively short time. Differences have been reported in the effectiveness of different therapeutic approaches. Long et al. (34) conducted a comparison of oral and vaginal estrogen therapy in postmenopausal women and found that the vaginal therapy had a greater impact on sexual function compared to the oral preparation, despite a lower serum estradiol concentration in the vaginal group. Vaginal estrogen therapy was reported by the North American Menopause Society (35) as being effective in 80%–90% women for relieving symptoms of VVA compared to 75% of women on oral estrogen therapy. Studies of cytokines and physical markers in larger numbers of women using different HRT approaches (i.e., oral, vaginal, and dermal) may provide insights into the benefits of the different types of therapies and thus will need further investigation.

In this study, a wide range and many types of data collection were conducted. This restricted the group sizes to a manageable number of 15 per group. These numbers of subjects were adequate to demonstrate statistically significant differences for some of the measured parameters. However, evaluations of other parameters, such as subjective symptoms, may have benefited from a larger study group.

SUMMARY

There is growing interest in quantitating biomolecules in the skin as a means of monitoring skin disorders or other clinical conditions. Using minimally invasive methods, we evaluated physical measurements such as temperature and pH, and quantified cytokines and other biomarkers from genital tissue in order to establish a baseline for premenopausal and postmenopausal women (with and without HRT). To our knowledge, this is the first published report of cytokine measures for the genital area. Parameters such as skin surface temperature, pH, and histamine levels obtained from anatomic sites on the external genitalia (i.e., labia minora and labia major) could be indicators of vaginal atrophy. Further, biophysical changes in external tissue can be monitored in a noninvasive manner in order to evaluate the potential benefits of treatments or products intended for postmenopausal women.

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PART 2

Management of Clinical Issues: Disorders, Diagnoses, Symptoms, Toxicity, and Therapies

Are vaginal symptoms ever normal?

Matthew Anderson and Alison Karasz

INTRODUCTION

Vaginal complaints—discharge, odor, itch, and irritation—are among the most common reasons for primary care visits. Current practice focuses on finding and treating infectious causes, primarily candida, bacterial vaginosis, and trichomoniasis. This approach is somewhat limited because there is often no clear association between infection and symptoms. Some women have symptoms but no infections, while other women have infections but no symptoms. The literature on vaginal complaints often describes a "physiologic discharge," but usually without citation to primary literature (1,2).

In 2004, we performed a systematic review in order to examine the evidence that some vaginal symptoms are normal phenomena misinterpreted by women as evidence of disease (3). We found few primary observational studies of normal women that assessed the incidence of vaginal symptoms in the absence of infection. The seven articles we found suggested that the quantity and quality of vaginal discharge in healthy women varied considerably both between individuals and in the same individual during the menstrual cycle. Most studies indicated that discharge is greatest at midcycle (4). Vaginal fluid does contain malodorants, and one study of intact vaginal fluid found it to be malodorous. Two studies found that normal women reported irritative symptoms in the course of their menstrual cycle.

This chapter updates our 2004 review with a focus on original research that reported on the prevalence of four major symptoms—discharge, odor, itch, and irritation—in women who were healthy.

METHODS

We used Google Scholar to identify papers reporting on original research related to vaginal irritation, odor, discharge, and itch that had been published after 2003. Studies were excluded if they included women with atrophic vaginitis, if they were not written in English, if the focus was urinary symptoms, and if they included children. One article from India was excluded because vaginal discharge represents a specific cultural construct within Indian medicine. We sought articles that attempted to measure and define the presence of vaginal irritation, odor, discharge, and itch in women who were not infected and/or not seeking care for symptoms.

To locate articles, we combined the terms "vaginal irritation," "vaginal odor," "vaginal discharge," and "vaginal itch" with the terms "measurement," "physiologic," and "normal." These combinations produced 12 potential search terms. We also crossed the term "vaginal discharge" with the terms "weight" and "quantity." These combinations produced 14 possible different combinations of search terms. The first 100 hits for these combinations on Google Scholar were reviewed. If the title of the article seemed appropriate, the abstract was obtained. In theory, this search retrieved 1400 Google Scholar listings, but many studies showed up multiple times and most of the retrieved literature was not original research. Selected abstracts were reviewed for appropriateness and to locate additional papers.

RESULTS

Only three studies met the criteria for inclusion in our review. They are summarized below.

What is Normal?

In 2014, Gungor and his colleagues sought to determine whether vaginal symptoms might have an effect on female sexual functioning as measured by the Female Sexual Function Index (FSFI) (5). Lacking existing definitions, they proposed the following definitions: "Abnormal color was defined as a yellow or green discharge. Abnormal odor was defined as malodor that did or did not increase with sexual intercourse. Abnormal consistency was defined as a cottage cheese-like or thickened discharge." The study's only significant finding was that a slightly higher FSFI score (indicating improved sexual function) was reported in women with abnormal odor.

While this study did not demonstrate that Gungor and colleagues' definitions of normality were correct, it does offer a definition that could potentially be tested in further studies.

Measuring Discharge, Odor, and Itch

In 2011, Hassan and his colleagues published a paper on the effects of different forms of douching in treating malodor in women who had no infectious cause (6). In order to assess symptom relief, they relied upon a visual analogue scale that was used to assess change in symptoms.

Do Healthy Women Report Symptoms?

In 2004, Veres and colleagues published a crossover randomized controlled trial comparing various outcomes of women using the vaginal ring and oral contraceptives (7). As part of their study, they measured symptoms including vaginal wetness, vaginal odor, yellow-colored discharge, vaginal discomfort/pain inside, vulvar discomfort/pain outside, and vulvar itch. These symptoms were scored on a 0–4 scale. A score of 0 signified "no problem/normal," 1 signified "mild," 2 meant "moderate," 3 was "worse," and 4 was "severely abnormal problem." Subjects rated their symptoms every day. Women underwent multiple microbial evaluations and, when positive, were treated.

This study found very low rates of self-reported vaginal symptoms. A woman with severe symptoms could potentially have a symptom score of 24 (four points on six symptoms). In the four study groups, the average (50th percentile) of symptom scores was 6.7 (when on the ring) and 1.7 (when on oral contraceptives). The difference between study arms was driven by higher rates of vaginal wetness in women when they were using the vaginal ring.

DISCUSSION

In repeating our review of the normalcy of vaginal symptoms, we were only able to locate three studies. Patient self-assessment of symptoms continues to be the "gold standard." Veres and colleagues' study suggests that while most women are asymptomatic, symptoms can occur in healthy women. Gungor and colleagues have presented a simple definition of "normalcy" that could be tested in further studies.

Almost all of the literature in this field continues to be focused on the abnormal. Ma and colleagues have argued—speaking of the vaginal microbiome—that "new strategies and personalized treatments" require "addressing a fundamental issue as to what constitutes a 'normal' and 'healthy' vaginal micobiota and understanding its function in health and diseases" (8). This change in focus suggests that, as clinicians, we need longitudinal studies in healthy woman that would correlate symptom diaries and medical evaluations (as needed) in order to determine which sets of symptoms are concerning and which are not.

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Common diseases of the vulva

Diane Elas and Colleen K. Stockdale

INTRODUCTION

All females, regardless of age, are vulnerable to vulvar irritation and disease. Sometimes the symptoms are short lived and may not cause the individual to seek treatment. Symptoms can be mild to severe, intermittent to constant, and predictable or unpredictable. Women may try over-the-counter treatments or follow recommendations from family, friends, or internet-based resources. Typically, a woman decides to see a health care provider when self-diagnosis and treatments have been ineffective or worsen her condition, or she has begun to experience a disruption in her daily activities. The symptoms can affect her self-esteem and lead to depression (1–4). The clinician is then given the challenge of obtaining an accurate diagnosis and providing effective treatment. Adding to the complexity of diagnosis and treatment is that many women with vulvar vaginal problems have bladder, bowel, and pelvic floor muscle and pain comorbidities (4–6).

This chapter identifies and describes common vulvovaginal symptoms and the associated conditions that health care providers encounter frequently in clinical practice. This chapter also provides the clinician with a practical approach for the assessment, diagnosis, and treatment of these conditions. Treating vulvovaginal disorders appropriately requires the health care provider to incorporate their knowledge and skills in gynecology, dermatology, infectious diseases, and psychology, and to consider that multiple conditions can coexist.

ASSESSMENT

A carefully focused symptom history is essential. A general history that includes gynecologic, obstetric, medical, surgical, social/abuse, and family history of dermatologic and immunologic conditions provides essential information, before physical examination, testing, and patient education.

Women present with any combination of symptoms of vulvar burning, itching, pain (day-to-day activities and/or with sexual activity), ulcer, lesions, and discharge/bleeding as their chief complaint. The intake interview should include information about the onset and duration of symptoms, aggravating/alleviating factors, and response to any prior self-initiated or prescribed treatments. Some vulvar vaginal conditions are correlated with the menstrual cycle (i.e., before, during, or after) or with the circadian. Symptoms that worsen during the sleeping hours can then lead to sleep deprivation problems. Pain with sexual activity can occur with insertion, thrusting, and/or irritation after sexual activity. Evaluating the partner's symptoms with regard to sexual activity can be useful as well. It is useful to obtain subjective and objective information when assessing symptoms. A simple subjective symptom scale such as: "Are your symptoms better, unchanged, or worse?" or an objective scale, such as a Likert 0–10 scale (with 0 being the absence of symptoms and 10 being the most severe symptom) is also useful.

Vulvar hygiene and lifestyle practices can also expose the vulvar vaginal tissue to additional insults that cause symptoms to worsen (7,8). Identify any chemical, mechanical, and moisture irritant exposures to the vulva that she may change, avoid, and minimize. Chemical irritant exposures might include certain laundry detergents, fabric softeners, body soaps/washes, perfumes, depilatory creams, hygiene wipes, douches, lubricants/spermicides with sexual activity, topical prescription/nonprescription medications and activities such as extended swimming in a chlorinated pool or using a hot tub. Mechanical exposures may include scrubbing with a wash cloth, shaving, genital piercing, tight-fitting clothing (e.g., exercise clothing, swim suits, and thong-type undergarments), or harsh daily pads. Activities that might cause mechanical irritation include bicycling and sexual practices including the use of vibrators. Moisture exposures can result from vaginal discharge (normal or abnormal), menstrual discharge, urination, perspiration, or urinary/fecal incontinence.

The importance of lifestyle changes and behavioral modification can be difficult to appreciate for many women. Education is important for self-care in the healing process of all vulvar vaginal conditions described in the following sections. This includes adherence to vulvar hygiene as listed above and the use of a bland occlusive dressing to protect and act as a moisture barrier to irritated vulvar skin. Products such as zinc oxide ointment, vegetable oil, coconut oil, or olive oil have proven to be useful for this purpose. Comfort measures of lukewarm water soaks with either baking soda or colloidal oatmeal and cool compresses to the vulva for 5–10 minutes can be useful tools for symptom relief (9).

PHYSICAL EXAMINATION

For the vulvar examination, the clinician must identify the normal anatomic structures of the vulva (Figure 11.1). The clinician should identify and examine the external structures of the mons pubis, labia majora, inner labial sulci, labia minora, and clitoris. Evaluation of the introitus includes Hart's line (lateral and medial), the major vestibular ducts (Bartholin's gland ostia), and the lesser vestibular ducts, periurethral ducts, urethra, Skene's ducts, and the hymenal ring.

After identifying the normal anatomy, the clinician should inspect the vulva visually to identify any primary lesions, such as macules, papules, plaques, nodules, pustules, vesicles, bullae, or hives, as well as any secondary lesions, such as scaling, crusting, erosions, ulcerations, fissures, atrophic tissue, and scars. Frequent changes of the vulva include erythema,

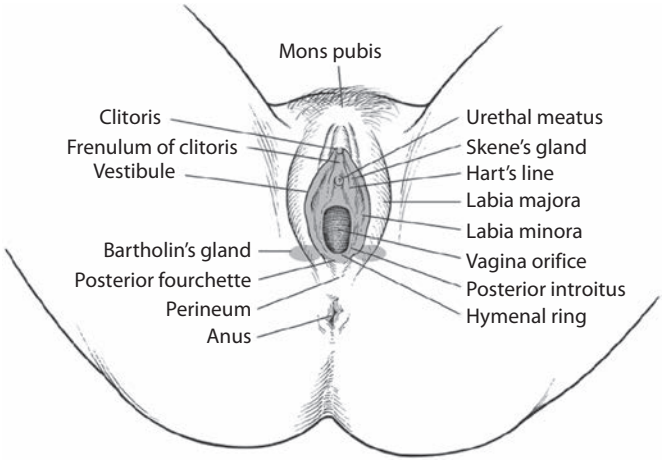

Figure 11.1 Anatomy of the vulva. (From Farage MA, Miller KW, Summers PR, Sobel JD, Ledger WJ. Chronic pain of the vulva without dermatologic manifestations: Distinguishing among a spectrum of clinical disorders. *Clin Med Womens Health* 2010; 3: 1–13, with permission.)

edema, atrophy, hyperkeratosis, fissures, and hypopigmented or hyperpigmented areas/lesions.

Next, the vaginal discharge should be evaluated microscopically. This is accomplished with a wet-smear preparation of the vaginal discharge. From this sample, a maturation index is performed to identify the maturity of squamous cells in order to determine the presence/absence of basal or parabasal cells, which are indicative of an atrophic or erosive condition occurring. The sample should be evaluated microscopically for the presence or the absence of white blood cells, red blood cells, lactobacilli, budding yeast, hyphae, or trichomonads. A yeast culture of the vaginal discharge is useful either for identification of a subclinical yeast infection or for yeast strain identification.

A biopsy may be necessary for diagnosis or to rule out a precancer/cancer condition. Additional cultures and hematologic and/or serologic testing may be indicated as well.

DISEASES THAT CAUSE VULVAR BURNING

The vulvar diseases that present with burning as the predominant symptom are contact dermatitis of the vulva, atrophic vaginitis, vulvar intraepithelial neoplasia (VIN), and *Candida glabrata* yeast infection (10).

Contact Dermatitis of the Vulva

Contact dermatitis of the vulva is an inflammatory condition that can occur at any time during a woman's life in response to primary exposure to an irritant or from an allergic response to an irritant. Contact dermatitis may occur secondary to another condition, such as a vaginal yeast infection or urinary or fecal incontinence. Common causes of irritative contact dermatitis of the vulva might include certain laundry detergents, fabric softeners, body soaps, fragrances, and hygienic practices. In addition, many over-the-counter topical treatments as well as medications that have alcohol in the base, such as creams, can be chemical irritants. Typically, a patient describes vulvar/vaginal burning that is at its lowest intensity upon awakening

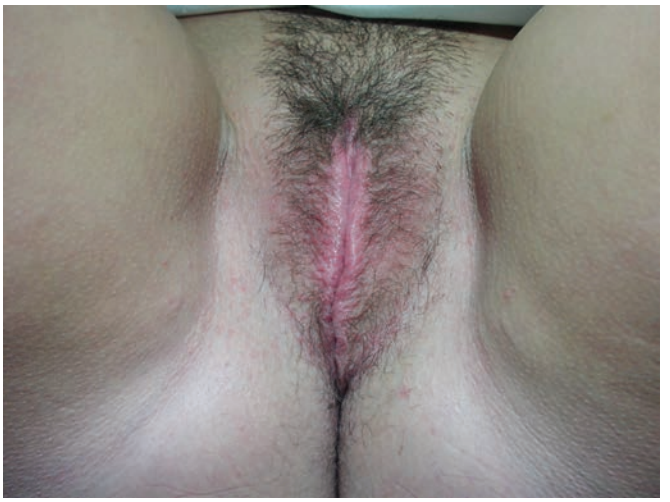

Figure 11.2 Contact dermatitis—irritant: uniform, well-demarcated erythema of the labia majora.

in the morning but increases as the day goes on or with direct exposure to the irritant. Symptoms can be aggravated during and after urination and by touching or wiping the area. There may be an associated vulvar discharge, which in advanced cases is from "weeping" of the vulvar tissue, rather than being a vaginal discharge.

On examination, the vulvar vaginal area has uniform, symmetrical, and well-demarcated erythema, with or without edema (Figures 11.2 through 11.4).

Treatment for contact dermatitis of the vulva requires removing the offending irritant(s). As discussed earlier, adherence to vulvar hygiene guidelines, application of a skin occlusive barrier and comfort measures will be helpful for avoiding irritants and protecting the skin from urine and vaginal discharge. The application of a low-to-moderate- to high-potency

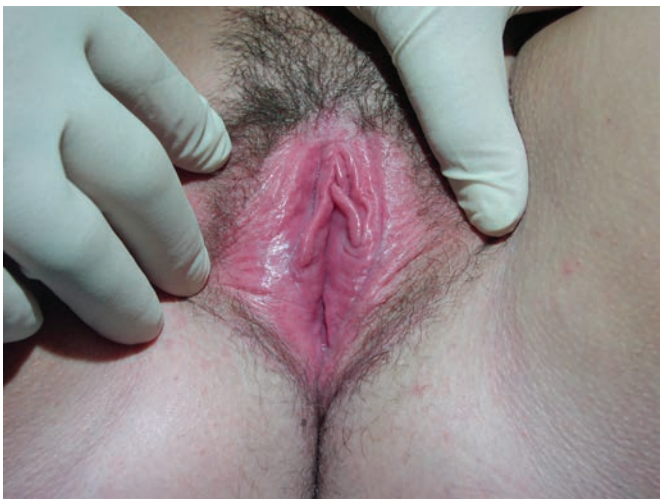

Figure 11.3 Contact dermatitis—irritant: uniform erythema and edema of the labia minora and introitus. (Same patient as in Figure 11.2.)

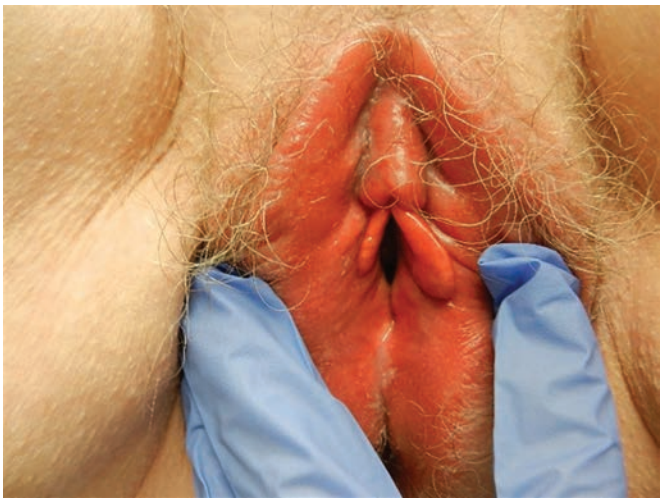

Figure 11.4 Contact dermatitis—allergic: well demarcated erythema and edema. (Courtesy of Diane Elas, ARNP, private collection.)

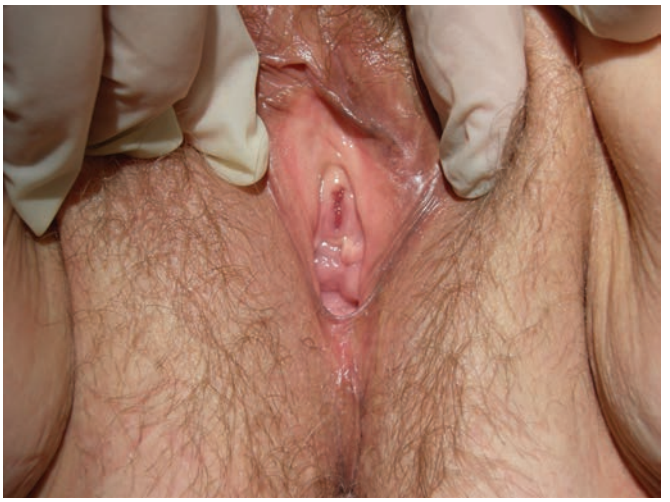

Figure 11.5 Atrophic vaginitis: thin, pale tissue with urethral caruncle. (Courtesy of Diane Elas, ARNP, private collection.)

topical steroid ointment can hasten the resolution of the symptoms of contact dermatitis of the vulva. However, the patient must be cautioned that overuse of steroids on the genital tissue can cause steroid atrophy. If an allergic component is suspected, adding an over-the-counter antihistamine can be helpful. If symptoms are severe and affect the sleep cycle or a neuropathic pain component is present, low-dose tricyclic antidepressant (amitriptyline) or anticonvulsants (gabapentin) can be prescribed (11–13).

Atrophic Vaginitis

Atrophic vaginitis is a condition that occurs when the vulvar vaginal tissue lacks estrogen. It occurs most commonly in postmenopausal females, but can also occur in situations that induce a hypoestrogenic state, such as when women are breastfeeding or taking medications such as Depo medroxyprogesterone or tamoxifen. Atrophic vaginitis does not affect all women. Typically, women with atrophic vulvovaginitis experience burning that can range from intermittent to constant, vaginal dryness, and pain with sexual activity. Some women experience urinary urgency, frequency, nocturia, and/or frequent urinary tract infections. Symptoms can be exacerbated during and after urination. In advanced cases, the skin becomes so thin and fragile that it will bleed with minimal trauma such as wiping or patting with toilet tissue after urination. Examination of the vulvar tissue demonstrates a pale to erythematous mucosa. A urethral caruncle can be present (Figure 11.5). The maturation index from microscopic evaluation of the vaginal discharge demonstrates a decrease in the number of mature squamous epithelial cells and an increase in the number of basal and parabasal epithelial cells. Frequently, there is an increase in white blood cells seen microscopically (14).

Treatment for atrophic vaginitis is estrogen replacement. Intravaginal topical estrogen can be prescribed as a vaginal cream, vaginal ring, or vaginal tablet. Systemic estrogen replacement, prescribed as either an oral tablet or a topical patch, can also be used, but this should be reserved for women who have other systemic-associated estrogen deficits. If systemic estrogen replacement is used and the patient has a uterus, a progestin is required in order to protect the uterus from the increased risk of endometrial cancer with unopposed estrogen. Low-dose vaginal estrogen has been shown to be safe and effective in the management of atrophic vaginitis and not to require a progestin (14–17). Ospemifene is an oral selective estrogen receptor modulator (SERM) that has been Food and Drug Administration (FDA) approved for moderate to severe dyspareunia, but as with all SERMs there are systemic effects that should be considered before prescribing. For women with a history of breast cancer or women who desire not to use estrogen, oral pilocarpine, vaginal hyaluronic acid gel, and over-the-counter moisturizers and lubricants are available (15,18). Once again, adhering to vulvar hygiene guidelines, use of an occlusive bland dressing, and warm water soaks help eliminate additional insult to the delicate skin as it heals.

High-Grade Squamous Intraepithelial Lesions (VIN)

High-grade squamous intraepithelial lesions (HSIL), formerly termed VIN or vulvar squamous dysplasia, are a common cause of vulvar burning that can be intermittent or constant. Women may or may not have a prior documented history of human papilloma virus (HPV) infection. The vulvar examination can be normal or there may be unifocal or multifocal lesions present. When lesions are present, their appearance can vary (10). A 3% solution of acetic acid-soaked cotton balls can be applied to the vulvar area for 3–5 minutes for aceto-white changes in order to assist with targeted symptomatic areas or lesions for pathological confirmation of the diagnosis of VIN (Figures 11.6 through 11.8).

Historically, VIN was categorized as VIN I (mild dysplasia), VIN II (moderate dysplasia), and VIN III (severe dysplasia/carcinoma *in situ*). In 2015, the International Society for the Study of Vulvovaginal Disease (ISSVD) approved a new standard of terminology for vulvar squamous intraepithelial lesions in order to more accurately categorize these histologic findings (19–21).

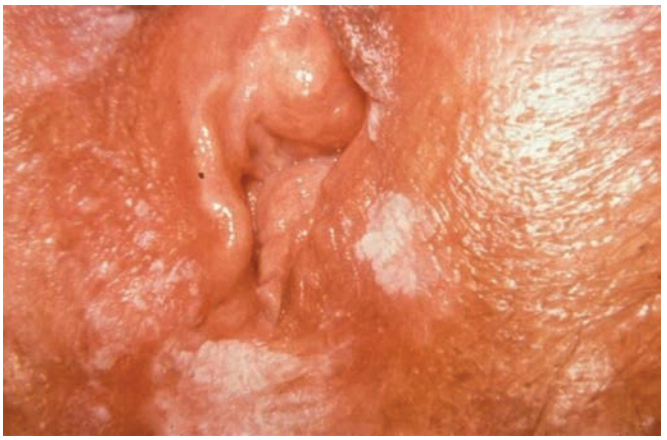

Figure 11.6 LSIL: aceto-white changes in the posterior fourchette and the left labia.

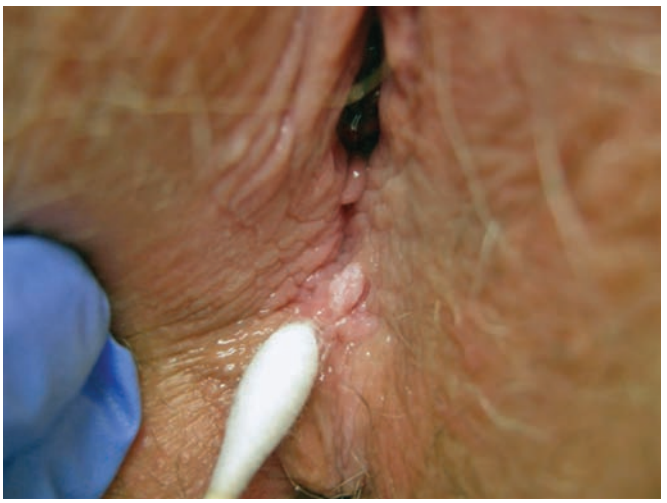

Figure 11.7 HSIL: focal lesion in fourchette. (Courtesy of Diane Elas, ARNP, private collection.)

Low-grade squamous intraepithelial lesion (LSIL) corresponds to the older terminology of VIN I, encompassing flat condyloma or HPV effect. Typically, this is not a precancerous condition, and treatment is based on symptom and is self-limiting (19–21).

HSIL is also referred to as VIN usual type (uVIN), which corresponds to VIN II and III. This is associated with high-risk HPV subtypes of 16, 18, and 33 and it tends to occur in younger women (19,20).

VIN differentiated type (dVIN) tends to occur in postmenopausal women with chronic skin conditions such as lichen sclerosus (LS) or lichen simplex chronicus (LSC) and may not be HPV related. This corresponds to VIN III/carcinoma *in situ* and has a higher rate of progression to invasive squamous cell cancer than does uVIN (19,20).

LSIL can be treated topically with imiquimod cream for symptomatic patients, as well as reassurance that this is

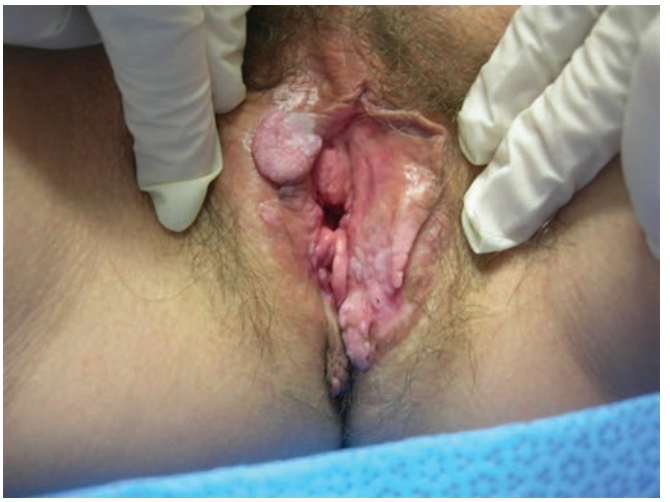

Figure 11.8 HSIL: multi-focal lesions. (Courtesy of Diane Elas, ARNP, private collection.)

self-limiting. For uVIN (HSIL) or dVIN, individualized treatment may include topical therapy or destructive treatments (cryotherapy or light amplification by stimulated emission of radiation [LASER]) versus excision. Patients should have regular follow-up. HPV vaccination at a young age and smoking cessation are advised for optimizing health against HPV (21).

C. (Torulopsis) glabrata

Yeast infection due to *C.* (*Torulopsis*) *glabrata* may cause vulvar burning. Typically, women describe constant vulvar burning without an associated increase in vaginal discharge. Usually, these women have seen multiple providers and tried many over-the-counter as well as prescription medications without relief.

On vulvar examination, the genitalia can appear normal or there can be generalized erythema. Microscopic evaluation of the vaginal discharge may be normal or numerous budding yeasts may be present. A yeast culture is necessary for stain identification that *C.* (*T.*) *glabrata* is present. Treatment can be challenging, as this strain is resistant to azole therapy typically used for candidal infections (22–24). Boric acid capsules or suppositories have shown some efficacy for the treatment of *C.* (*T.*) *glabrata* vaginal infections (boric acid 600 mg, in either a gelatin capsule or suppository, inserted intravaginally twice daily for 14 days) (23). The application of 1% or 2% gentian violet intravaginally prior to initiation of the boric acid capsules has been helpful for some women. A single course of boric acid capsules may not be curative and, therefore, retreatment may be required. Other treatment regimens for *C.* (*T.*) *glabrata* cited in the literature include boric acid with flucytosine or combined flucytosine and amphotericin B topically (22,24). Biofilm formation by *C.* (*T.*) *glabrata* has been shown to be affected by pH, and the presence of acetic acid may increase the susceptibility of this yeast strain to fluconazole (24,25).

Additional Diseases

There are other less common causes of vulvar burning such as Sjögren's syndrome, an autoimmune disease that affects the

lubrication glands of mucous membranes and typically causes ocular and oral dryness, but can also cause vulvar/vaginal dryness.

DISEASES THAT CAUSE VULVAR ITCHING

Lichen Simplex Chronicus (LSC)

LSC of the vulva is a dermatologic condition that causes pruritus. Women may have mild to intense itching, which can occur during the day or night. If the LSC is severe, a woman may commonly scratch the vulvar area in her sleep or be awakened by intense vulvar itching. Many times, a partner identifies that the woman is scratching without awakening.

The etiology of LSC of the vulva tends to be mechanical in nature. Whenever there is irritation that occurs long enough for the itch–scratch cycle to develop, the epidermis and stratum corneum of the vulva thicken (26). The skin of the vulva appears lichenified and fissures and excoriations can be present. The vulvar skin can appear white and crinkled, red, or even take on a violaceous hue. The skin changes are localized to the area of the itch (Figures 11.9 and 11.10).

Treatment for LSC requires removing any exposures contributing to the skin irritation and breaking the itch–scratch cycle. Low- to high-potency topical steroid ointments are used to tailor treatment to the severity of the lichenification for women who scratch during their sleep; the short-term use of antihistamine or low-dose amitriptyline at bedtime can help the patient sleep through the itch sensation (26). Also, vulvar hygiene, skin protection and comfort measures are useful tools for the patient. Zinc oxide ointment provides an effective moisture barrier that also has a slight drying effect, which is especially useful in warm climates. Lukewarm water with baking soda or colloidal oatmeal also provides symptomatic relief. If the skin is severely lichenified and macerated, an aluminum acetate 1:40 solution soak or compress (Domeboro Astringent Solution, Bayer, Morristown, NJ, USA) can assist with comfort and healing.

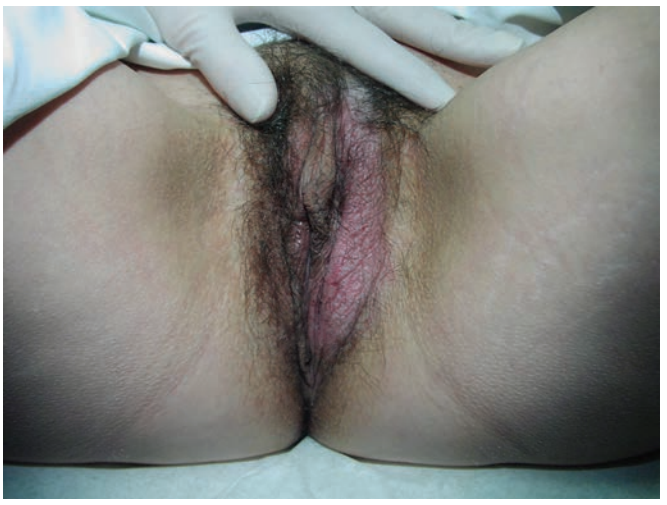

Figure 11.9 Lichen simplex chronicus: hyperkeratosis and erythema of the left labia majora.

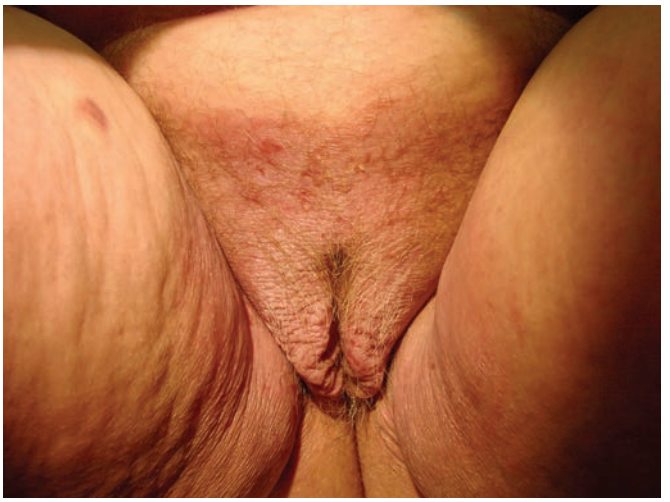

Figure 11.10 Lichen simplex chronicus: hyperkeratosis extending from the base of mons pubis to the labia majora bilaterally.

Lichen Sclerosus (LS)

LS is a cutaneous disease that has an affinity for the anogenital region and can occur across the lifespan. LS can be an intensely pruritic disease and sleep disturbance is a common complaint. The exact etiology is not known, but there is evidence that hormonal factors, autoimmune disorders and genetics may all have a role in this disease (27). Women with LS have higher prevalence rates of thyroid disease, bladder dysfunction, bowel dysfunction, pain comorbidities, and vulvar squamous cell cancer than women without LS (6,28,29).

The vulvar appearance with LS varies depending on the severity and length of time that the patient has had the condition. The disease process disrupts the normal vulvar anatomy, with typical changes including phimosis of the clitoral hood, involution of the labia minora, and scarring of the introitus. The affected skin can have a thin, white, parchment paper-like appearance, it can be thin and red, or it can be thickened and white. All three of these skin variations can appear on the vulvar anogenital region together. There may be an "hourglass" pattern seen over the anogenital region, which can extend into the genitocrural folds (Figures 11.11 through 11.14). A vulvar biopsy can be performed if histologic confirmation is needed or to rule out dysplasia or cancer.

Treatment for LS is aimed at alleviating symptoms, preventing disease progression, and minimizing squamous cell cancer development risk. LS treatment varies among experts and specialties (29,30). Low- to high-potency steroid ointments tend to be the first-line treatments, with some providers using intralesional steroids as well as topical tacrolimus (29–32). Recently, it has been shown that long-term individualized management of LS with regular use of topical steroids can manage symptoms and decrease the incidence of squamous cell cancer compared with episodic treatment (30).

Candida albicans

Candida albicans vulvovaginitis is a common infection, the true incidence of which is unknown, as many women will self-diagnose a vulvovaginal yeast infection based on symptoms and

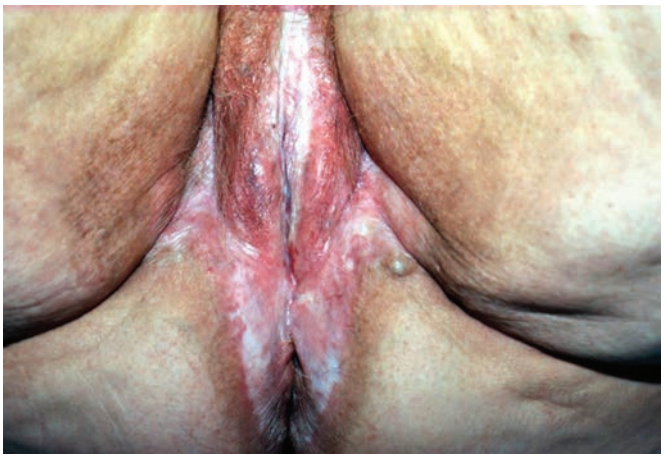

Figure 11.11 Lichen sclerosus: classic changes of lichen sclerosus of the vulva and perianal area in a postmenopausal woman, with areas of thin erythematous skin, white parchment paper-like skin in the perianal area, and thickened white skin.

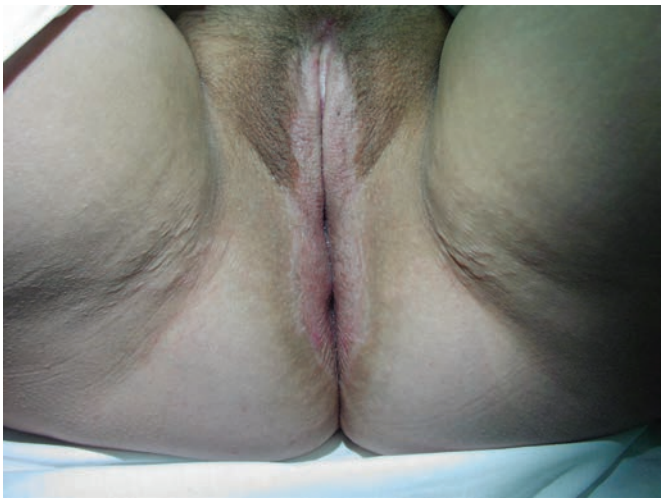

Figure 11.12 Lichen sclerosus: vulvar and perianal changes of lichen sclerosus in a young woman.

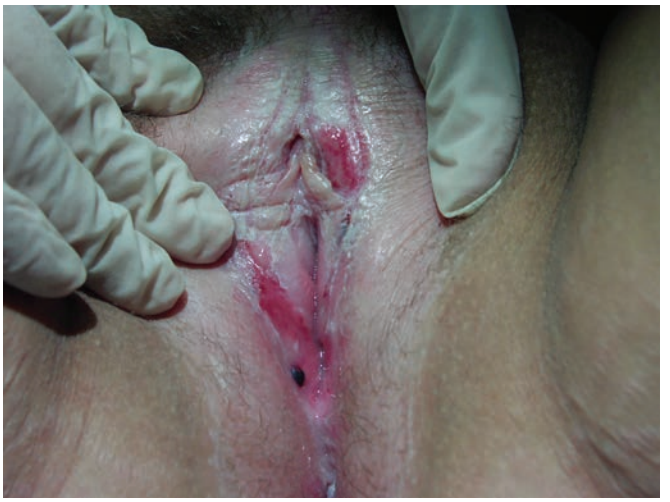

Figure 11.13 Lichen sclerosus: vulvar examination of the same patient as in Figure 11.10, with thin, erythematous skin and white hyperkeratotic skin.

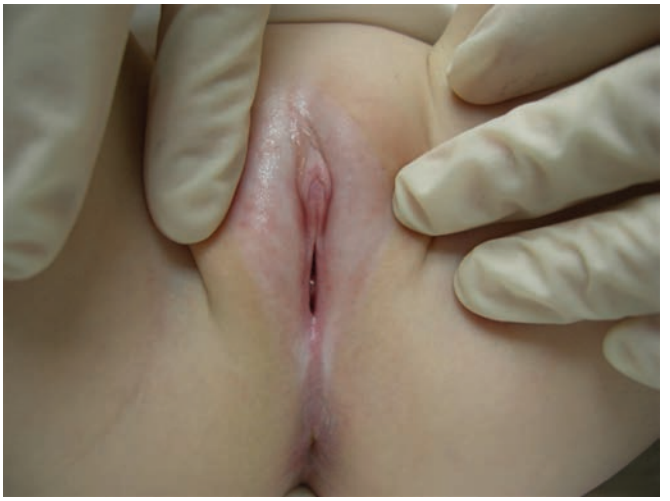

Figure 11.14 Lichen sclerosus: changes of lichen sclerosus in the peri-clitoral area and medial aspects of the labia majora in a 4-year-old girl. (Courtesy of Diane Elas, ARNP, private collection.)

treat with over-the-counter antifungal products. It is estimated that 75% of women will have one episode of vulvovaginal candidiasis, 40%–50% will have more than one episode, and 10%–20% will have complicated vulvovaginal candidiasis (33).

C. albicans is the most common strain of *Candida* to cause infection in the vulvovaginal area (23). Women complain of vulvar itching and/or vaginal discharge. On examination, the vulvar skin and associated affected skin have an irregular or asymmetrical pattern, mild to intense erythema, edema of the labia minora (usually), and edema of the labia majora (possibly). Satellite pustules and excoriation may be present when *C. albicans* infection involves the adjacent skin in the genitocrural folds and the perianal area. Vaginal discharge can be scant to heavy, thin and milky, clumpy and curdy, or "cottage cheese-like." In addition, the woman may describe a foul, sweet, or strong odor associated with the discharge. Microscopic evaluation of the vaginal discharge usually documents the presence of hyphae and budding yeast. If the concentration of yeast is low, a yeast culture is useful in order to document the infection (Figure 11.15).

Usually, *C. albicans* is treated with one of the imidazoles, either with one of the many topical vaginal preparations or with an oral antifungal preparation (23,24,33). Many of the intravaginal preparations can cause burning with application. For symptomatic relief, an antifungal–steroid combination ointment such as nystatin–triamcinolone may be used to decrease inflammation. Lukewarm water soaks, as mentioned before, are also soothing. The role of probiotics for vaginal flora health has not been definitively proven to be of benefit.

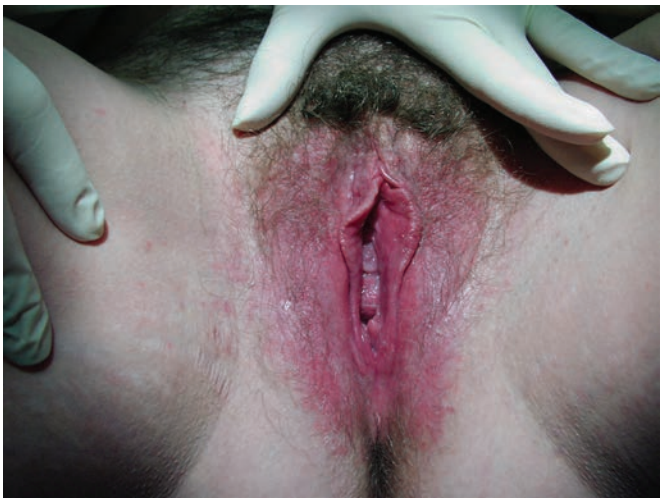

Figure 11.15 Yeast vulvovaginitis: irregular border of erythema, edema of the labia minora, and satellite lesions extending to the right thigh and the perianal area.

Additional Diseases

Less frequently, pruritic vulvitis can be caused by psoriasis, syringomas, pediculosis, and scabies. *Trichomonas*, which cause a pruritic discharge, are discussed later in this chapter.

DISEASES THAT CAUSE VULVAR PAIN

Vestibulodynia (Formerly Termed Vulvar Vestibulitis)

Vulvar pain was documented as early as 1888 by Dr. Alexander J.C. Skene in his textbook *Treatise on the Disease of Women*, in which he identified "hyperesthesia of the vulva" (34). Vulvar vestibulitis syndrome was first described by Woodruff and Parmley in 1983 (35). The criteria for the diagnosis were described by Eduard Friedrich in 1987. His three subjective and objective criteria are (36):

1. Severe pain on vestibular touch or attempted vaginal entry
2. Tenderness to pressure localized within the vulvar vestibule
3. Physical findings confined to vestibule erythema of various degrees

In 2015, the ISSVD in conjunction with International Society for the Study of Sexual Health (ISSWSH) and the International Pelvic Pain Society (IPPS) agreed on the terminology and classification of this pain disorder as vulvodynia–localized–vestibulodynia (37). Women with this condition experience substantial pain with insertion (e.g., tampon, speculum, or insertional sexual activity). When associated with sexual activity, women usually experience relationship difficulties with their partners. When this occurs, lowered self-esteem is common and some women can experience substantial depression (1,38,39). In more severe cases, women can experience pain and burning on a day-to-day basis when walking, sitting, wearing clothing that comes in contact with the vulva, after exercise, and wiping after urination. If the inflammatory process includes the periurethral ducts of the vestibule, women may

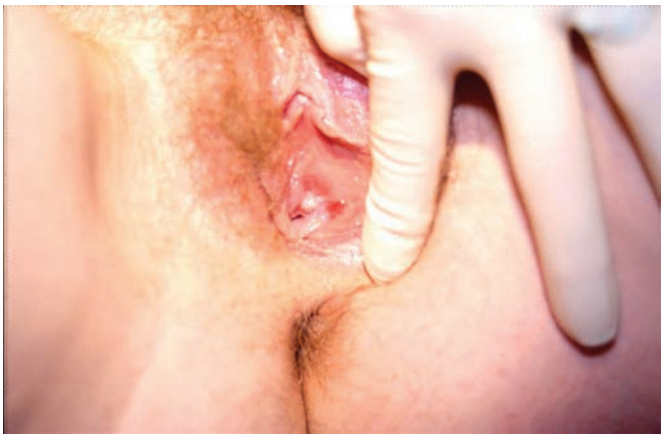

Figure 11.16 Vestibulodynia: localized erythema in the left vestibule.

complain of urgency and frequency in the absence of a urinary tract infection. Symptoms can also be totally unpredictable and unprovoked.

Erythema is limited to the vulvar vestibule and there is a disproportionate pain-to-touch ratio when a cotton-tipped swab is pressed into the erythematous area (Figures 11.16 through 11.18).

The incidence and cause of vestibulodynia is unknown. Definitive treatment can be elusive. The 2013 Vulvodynia Guideline Update reviews treatment strategies. These include the use of topical medications, oral medications, dietary modification, injections, surgery, biofeedback, physical therapy, complementary and alternative therapies, nerve blocks, and counselling (40).

Erosive Lichen Planus

Lichen planus (LP) is thought to be an autoimmune disease. It can occur anywhere on the body. When it occurs in mucous

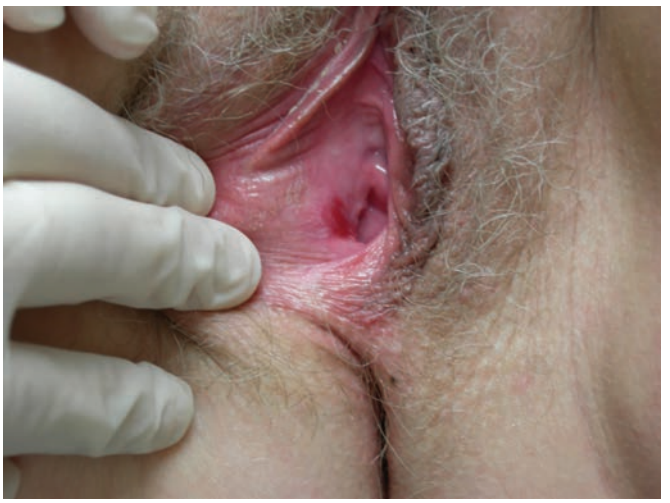

Figure 11.17 Vestibulodynia: localized erythema in the right vestibule. (Courtesy of Diane Elas, ARNP, private collection.)

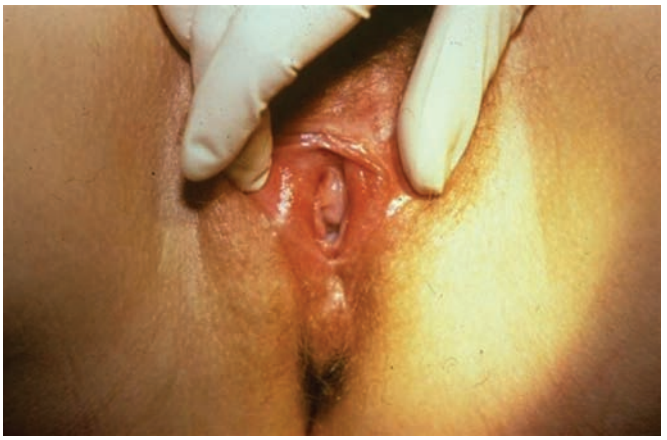

Figure 11.18 Vestibulodynia: localized erythema in the right periurethral area. (Courtesy of Diane Elas, ARNP, private collection.)

membranes, such as the oral mucosa, vulvar introitus and/or vagina, it tends to be erosive in nature (41,42) (Figures 11.19 and 11.20). On the vulva, erosions are quite painful with daily activities, during urination, and can make sexual activity impossible. If there is vaginal involvement, the vagina can coapt, requiring intervention to make the vaginal canal patent (Figure 11.20) (43). Vaginal discharge can be present as a profuse white to yellow to greenish discharge. Examination of the mucous membranes of the mouth, vulva, and vagina demonstrate erythematous and erosive changes. A lacy white pattern, known as Wickham's striae, can be present on the mucosal surfaces.

Treatments for LP are mostly topical in delivery. Low- to high-potency steroid ointments or tacrolimus is applied to the vulva. Similarly, treatments for vaginal disease involve the use of low- to high-potency steroid creams/suppositories or pimecrolimus. In addition, the use of vaginal dilators in order

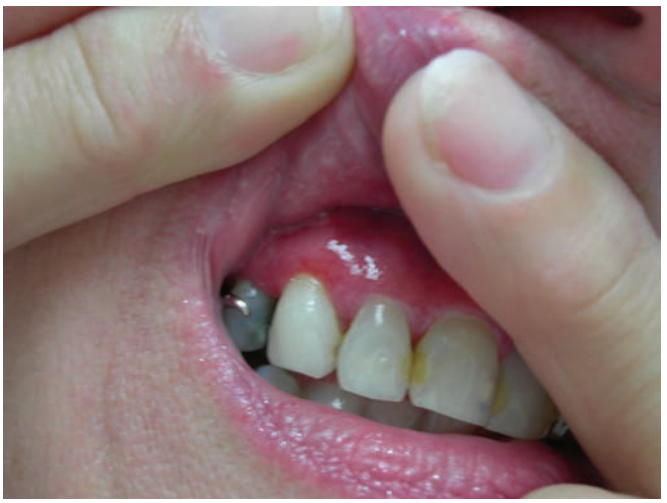

Figure 11.19 Erosive lichen planus: upper gingival erosive changes. (Courtesy of Diane Elas, ARNP, private collection.)

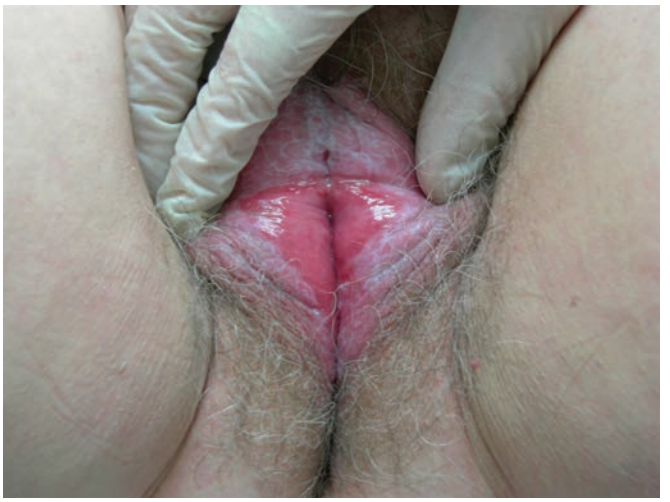

Figure 11.20 Erosive lichen planus: erosive changes of the vulva and introitus with Wickham's striae.

to maintain patency of the vagina may be advised. Oral treatments include oral steroids and, most often, methotrexate (44).

Ulcers

Ulcers of the vulvar vaginal area also cause pain. While it is beyond the scope of this chapter to review genital ulcers, one of the most common causes of genital ulcers is herpes simplex virus (HSV). HSV presents with exquisite pain and a vesicular rash on an erythematous base. HSV lesions are self-limiting, but with rapid identification, lesions can be treated with antivirals to limit the length of the outbreak (33).

Additional infective organisms such as syphilis or lymphogranuloma venereum can present as ulcers. Ulcerations can occur from dermatoses, such as aphthous ulcers, Behçet's syndrome, severe contact dermatitis, pyoderma gangrenosum, or benign familial pemphigus (Hailey–Hailey's disease). Malignancies can also present as ulcerations. Systemic disease processes, such as Crohn's disease, may present with vulvar ulcers. Trauma can also induce ulcer formation in the vulva, as is seen in decubitus ulcers.

Additional Diseases

Additional causes of pain include abscesses, Bartholin's duct cysts, Skene's duct cysts, and periurethral duct cysts.

DISEASES THAT CAUSE VAGINAL DISCHARGE

Bacterial Vaginosis

Bacterial vaginosis (BV) is an overgrowth of polymicrobial anaerobic bacteria found in the vaginal ecosystem. Women describe a foul, usually "fishy" odor and a thin to milky discharge that is irritative. Diagnosis can be made by evaluation of the following: Gram stain of the vaginal discharge, microscopic evaluation of the vaginal discharge for the presence of clue cells and the absence of lactobacilli, vaginal pH is elevated to 5 or higher and a positive whiff test, or with the use of DNA hybridization probes. BV can be treated with either systemic or

vaginal medications: metronidazole, clindamycin, or oral tinidazole (33).

Trichomoniasis Vaginalis

Trichomoniasis is caused by a flagellated protozoan that can infect the vagina, causing a thin, watery, foamy discharge that is extremely pruritic. Diagnosis of a *Trichomonas* infection can be made with culture, microscopic evaluation of the vaginal discharge identifying the presence of the protozoan, nucleic acid amplification tests, antigen detection-based tests, and DNA hybridization probes. Treatment for trichomoniasis is oral metronidazole or tinidazole; patients with persistent, recurrent infections should be referred to a medical specialist (33).

Additional Diseases

Additional causes of vaginal discharge include desquamative inflammatory vaginitis, cervical ectropion, fistulas, and *C. albicans* yeast infection, which has been discussed earlier in this chapter.

CONCLUSION

A woman can experience irritation of the vulva at any time during her life. Some common irritative conditions are self-limiting, while others require health care provider treatment and follow-up surveillance. Appropriate diagnosis and treatment are essential.

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Which women develop vulvar cancer?

Allan Maclean

INTRODUCTION

Vulvar cancer (vulvar malignancy) is a rare cancer. However, it is increasing and will occur in certain at-risk individuals or groups. Worldwide incidence studies would suggest large variations in age-standardized incidences between countries. This chapter will discuss some of the factors that are believed to be responsible for this and hopefully encourage further study.

Malignant tumors of the vulva account for approximately 5% of the malignancies found in the female genital tract. Squamous cell carcinoma accounts for 90%–95% of these tumors; the others are basal cell carcinoma, melanoma, adenocarcinoma, and mesenchymal tumors (e.g., aggressive angiomyxoma). Carcinoma from elsewhere in the genital tract and sometimes from the urinary or intestinal tract can metastasize to the vulva (1–3).

I will refer to data collected during my professional lifetime studying vulvar diseases (e.g., from 1992 until 2015, I saw 3590 new vulvar clinic patients and these included 88 with vulvar malignancy; there were 77 cases of squamous cell carcinoma, three basal cell carcinomas, three melanomas, three invasive Paget's disease, one adenocarcinoma (not Paget's), and one metastatic breast adenocarcinoma). Discussion in this article will be restricted to vulvar squamous cell carcinoma.

INCIDENCE

In the UK, there were 1259 new cases of vulvar cancer diagnosed in 2012. It is regarded as a rare cancer and is ranked 20th in the incidence and causes of cancer deaths in females (4). Worryingly, it has increased over the last 20 years. Lai et al. (5) used data collected from cancer registries and the Office for National Statistics for England and reported a statistically significant increased incidence since 1990, especially among women aged 20–69 years. In 1975, only 6% of vulvar cancers occurred in women under 50 years of age, but by 2006–2008, this age group's contribution had risen to 14% of the vulvar cancers. The incidence remains stable in women over the age of 80 years, but the age-standardized rate per 100,000 is 22 (cf. 2.5 for all ages in England, 3.3 in Wales, and 2.8 in Scotland). A similar increasing incidence is reported in the USA. Data collected on 8553 women in the USA (6) show that 21% were in women aged less than 50 years, and 24% occurred in women over the age of 80 years, where the cancer is more likely to be of an advanced stage at diagnosis, treatment is less likely to be surgical, and risk of death is seven-fold higher than in those women aged less than 50 years.

International data suggest that some regions, including the USA and Canada, Great Britain and Europe, South America and Oceania, have high age-standardized incidences of vulvar cancer (e.g., >2 per 100,000 women), whereas South-eastern Asia and North Africa have incidences of 5–10-fold less.

HISTORICAL BACKGROUND

In 1869, a description was given by Hulke of the Middlesex Hospital, London, of the association between leukoplakia of the tongue and the subsequent development of cancer, and from the same hospital, Sir Henry Morris described similar leukoplakic appearances that preceded vulvar cancer. Sir Comyns Berkeley and Victor Bonney, again of the consulting medical staff of the Middlesex Hospital, described the relationship between leukoplakia of the vulva and cancer as "closer than that of any pathological lesion with the exception of the entirely modern X-ray dermatitis"; all 58 cases of vulvar cancer seen over the previous 10 years had shown leukoplakic vulvitis (7). Rather surprisingly, Professor Howard Kelly, of Johns Hopkins, in his textbook of the same time (8), made no mention of vulvar cancer, but devoted 30 pages to describing cancers of the uterus and cervix.

Many subsequent papers debated the clinical significance of vulvar "leukoplakia" or white lesions, and whether vulvectomy was the appropriate treatment. Advances in terminology improved understanding.

Advances in Understanding of Pathogenesis and Terminology

More than 100 years ago, Cullen (9) described changes in the epithelium along the margin of a squamous cell carcinoma of the cervix, and used the term "carcinomatous transformation." Rubin (10) recognized similar appearances, called them "incipient carcinoma," and suggested that such changes preceded the development of invasion. Broders (11) described "carcinoma *in situ*" existing without migration beyond the basement membrane. Richart (12) introduced the generic term "cervical intraepithelial neoplasia" (CIN) to include the spectrum of intraepithelial abnormalities ranging from mild dysplasia through to carcinoma *in situ*. It was overwhelmingly accepted that all cervical squamous cell carcinomas developed from this lesion, CIN.

Terminology for the vulva developed in parallel, with the International Society for the Study of Vulvar Disease (ISSVD) supporting the use of vulvar "carcinoma *in situ*" in their 1976 recommendations, and then "vulvar intraepithelial neoplasia (VIN)" in 1986. However, it was becoming clear that only a minority of vulvar cancers arose from a background of intraepithelial neoplasia. Buscema and colleagues (13,14) from Johns Hopkins had examined histological appearances adjacent to 98 squamous cell vulvar cancers and found only 33 had VIN; the others arose in proximity to atypical or typical hyperplastic dystrophy, lichen sclerosus (LS), or mixed dystrophy—to be explained in detail later. While oncogenic human papilloma virus (HPV) types were found within almost 100% of cervical cancers, only a minority of vulvar cancers were associated with

HPV (15). Those cancers arising from VIN were more likely in younger women and to be HPV positive, while older women were more likely to have cancer arising in association with "dystrophy" or LS, and to present with more advanced-stage disease. Differences in geography and population ethnicity (see later) might also explain these differences.

In the textbook *Diseases of the Vulva* (16) by Janovski and Douglas (a previous professor in my department in London), both Founding Fellows of ISSVD, it states:

> *It is found mostly in postmenopausal women, more than half of the patients being over the age of 60 years. Occasionally primary squamous cell carcinoma does occur in younger patients, more often in patients of the Negro race. As with most cancer the etiology is unknown but there are certain factors which have a considerable association. Among older patients single nulliparous women predominate; in the younger group the history of venereal disease is common. Carcinoma of the vulva may develop in apparently normal skin, but in 30 to 40 percent of patients there appears to be a close association with previous dysplasia, which is believed to exist for approximately 10 years before the development of frank carcinoma. Chronic irritation, a previous history of granulomatous disease and poor social conditions clearly play a part in the development of the lesion.*

It is now apparent that vulvar cancer develops from at least two separate pathways: one with usual-type VIN (see below for an explanation) and sexually transmitted HPV; and the other from differentiated VIN and LS (less frequently from hypertrophic lichen planus). In my series from 1992 to 2015, the 77 cases of squamous cell carcinoma arose from VIN in 41, LS in 34, and hypertrophic lichen planus in 2. The remainder of this chapter will examine our understanding of these two pathways and what factors can be influenced.

VULVAR CANCER ARISING FROM VIN

Terminology of VIN

Although there is an appeal to use similar terminology when describing neoplastic and pre-invasive lesions of the lower genital tract (cervix, vagina, and vulva), it is increasingly evident that VIN is not the same as CIN. The depth of cell maturation and differentiation from the cervical basement membrane and extending through the extent of the epithelium lends itself to divisions of CIN 1, CIN 2, and CIN 3, or the more recent Bethesda classification of low-grade and high-grade squamous intraepithelial lesions. However, the vulva is skin, or epidermis, often with variations in the thicknesses and undulations of the layers, especially the strata spinosum and corneum (prickle cell and cornified layers). The shape and length of the rete pegs or ridges, especially with different pathologies, show considerable variation. Therefore, attempts to define the basal third or half of this skin, as for VIN 1, becomes inconsistent. Secondly, in the cervix, CIN 1 occurs more frequently than higher-grade intraepithelial neoplasia, and over time may progress from CIN 1 to CIN 3. However, VIN 1 is uncommon compared with VIN 3, and there is little evidence of a continuous spectrum of neoplastic progression from VIN 1 to VIN 3; in fact, what we have previously called VIN 1 may have no neoplastic potential and may represent alterations in the prickle cells from infection with low-oncogenic HPV types or in response to scratching.

Therefore, the ISSVD Vulvar Oncology subcommittee recommend that the VIN terminology should be modified (17). They stated that the term VIN should apply only to histologically high-grade lesions, and the term VIN 1 should no longer be used. High-grade VIN was subdivided into differentiated VIN (described later) and usual-type VIN (further subdivided into warty, basaloid, or mixed types, according to histological appearances). This is the terminology to be preferred, and I will use it in this chapter.

Increasing Incidence of VIN

Recent publications from New Zealand (18), Norway (19), Austria (20), and North America (21–23) have reported a growing incidence of VIN. For example, Judson et al. (23) used Surveillance, Epidemiological and End Results (SEER) databases from 1973 to 2000 and found a 411% increase in carcinoma *in situ* of the vulva (compared with a 20% increase in vulvar cancers). Some of this increase is due to greater clinician awareness and the use of biopsies if a diagnosis of VIN is suspected (24).

What is the Evidence to Connect VIN to Vulvar Cancer?

Among the 233 patients referred to me with possible or biopsy-proven VIN were 12 patients with invasive carcinoma (5%) in whom the use of colposcopic magnification or illumination led to the suspicion of early invasion (e.g., a change in lesion contour or altered vascular pattern [neo-angiogenesis; see later]) and this was confirmed by biopsy. Four of these 12 women were found with perianal or anal verge carcinoma. Subsequently, 19 of the remaining 221 (8.6%) VIN patients had invasive carcinoma diagnosed at microscopy of excised lesions. Then 10 of the other 202 (5%) patients progressed to invasion over time intervals of 13 months to 13 years (Figure 12.1).

Association of VIN with Occult Invasion

Chafe et al. (25) from Gainesville, Florida, reported that among 69 women with VIN were 13 (18.8%) who had unsuspected invasion found in the surgical specimens from excision of all visible lesions; this was <1 mm deep (i.e., stage Ia carcinoma) in eight women and >1 mm deep in four women, while one patient

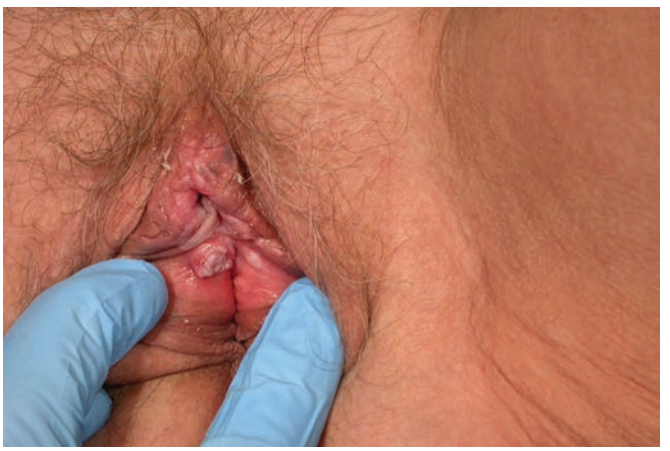

Figure 12.1 Invasion occurring adjacent to VIN.

had a verrucous carcinoma. Patients with occult invasion were older; the youngest was 35 years of age and the median age with unrecognized invasion was 58 years compared to 36 years for those with VIN without invasion.

Herod et al. (26) of Birmingham, England, reported that 26 of 159 women (16%) had superficially invasive carcinoma. Modesitt et al. (27) of Chapel Hill, North Carolina, found 16 of 73 (22%) patients who underwent surgery for VIN 3 had underlying invasion, 10 <1 mm deep, five 1–2 mm deep, and two >2 mm deep. Husseinzadeh and Recinto (28) of Cincinnati, Ohio, reported 16 of 78 (20.5%) patients undergoing surgical excision of VIN had invasion, seven <1 mm deep and nine >1 mm deep. Thuis et al. (29) of Sydney, Australia, reported occult invasion in 6 of 40 patients undergoing management of VIN.

Therefore, occult invasion is found in 15%–22% of women undergoing management of VIN, a much higher risk than for invasion being found with high-grade CIN. The studies referred to above emphasize that invasion is more likely in older patients, that up to 82% of VIN patients had used tobacco products or been smokers (currently or previously), and up to a half had current or previous cervical cytological abnormality. Chafe et al. (25) commented that lesions that were raised and had an irregular surface pattern were more likely to be invasive. These authors warned that the high chance of occult invasion means that treatment should include adequate excisions and biopsy in order to avoid missing invasions to depths >1 mm.

Reports of Progression to Invasion

The invasive potential of carcinoma *in situ* of the cervix has been reported by various authors, but especially McIndoe et al. (30), who reported on a group of women in Auckland, New Zealand, who continued to have abnormal smears after no or inadequate treatment. In this group, 18% developed invasive cancer after 10 years and 36% developed invasive cancer after 20 years. It has been presumed that VIN will show a similar risk of developing invasion, but the presence of symptoms and concerns about potential to invade have meant that very few patients with VIN are left untreated in order to determine the natural history. Arising from the same Auckland group, Jones and McLean (31) described four patients who had vulvar biopsy alone before developing invasive carcinoma 2–8 years later. A fifth patient was kept under observation for 4 years before undergoing a simple vulvectomy and then developing carcinoma within a year. Among the 31 treated patients, four returned with recurrence and one returned with carcinoma 17 years after her original treatment. In a follow-up to their experience with 406 patients with VIN, invasive vulvar, perianal, or urethral carcinoma occurred in 17 (3.8%) of the treated patients. Nine represented treatment failure and eight represented new carcinomas occurring outside the previously treated areas. Ten untreated cases developed carcinoma 1.1–7.3 years after the diagnosis of VIN, but spontaneous regression of VIN occurred in 47 women who were generally younger (mean age 24.6 years) and with a recent pregnancy (median time to complete regression was 9.5 months). Spontaneous regression is well documented (32,33).

Jones et al. (34) commented on the high recurrence of VIN after treatment (50% of those with positive surgical margins required at least one further re-treatment within 5 years), and a review of older series would suggest that the risk of developing cancer subsequent to treatment was due to inadequate removal of the VIN. Thus, Collins et al. (35) described 41 patients with intraepithelial carcinoma, of whom 40 underwent radical vulvectomy. One patient refused and developed an invasive cancer 3 years later. Other authors (13,14,36) report invasion occurring after VIN had been treated with topical 5-fluorouracil or CO_2 laser. Ragnarsson et al. (37) from the Karolinska in Stockholm reported 74 women with vulvar carcinoma *in situ*, of whom three progressed to invasion (two after irradiation). Fiorica et al. (38) reported from Florida that five of 125 patients returned with early invasion, emphasizing the need for long-term follow-up.

Van Seters et al. (39) performed a systematic review of 97 articles relevant to this dilemma and found data on 3322 patients with VIN; 6.5% were said to progress, although 3.2% had occult invasion at assessment, and only 3.3% appeared to progress over an interval of 12–96 months. The authors concluded that the progression rate to invasion was low, but in subsequent correspondence my colleagues and I raised concerns about this interpretation (40). Our concerns are that 96% of these collected patients had been treated and only 4% had not been treated, that progression in only 8 of 88 patients seemed low when these contained seven of eight patients described from Auckland and the outcome of the remaining 80 was unclear, and that a mean follow-up of 33 months was too brief. VIN has significant invasive potential, and the contributing factors are described below. Jones (41) believes that while the annual progression rate for untreated CIN 3 to cancer is 2%, for untreated VIN, this may be in excess of 10%.

Factors Increasing the Risk of Progression to Cancer

The risks of progression are increased with a patient's age, but also one or more of the factors discussed below.

In epidemiological studies of vulvar cancer, a history of genital warts (HPV) and a history of smoking were the most significant; Brinton et al. (42) estimated a 35-fold risk for women with both factors against those with neither.

HPV and Interactions

A retrospective review by Gargano et al. (43) used polymerase chain reaction to amplify viral DNA and linear array HPV genotyping for 37 HPV types in order to test invasive and preinvasive vulvar lesions for HPV presence and so assess the background prevalence within the USA before the impact of HPV vaccination became apparent. Of 176 invasive vulvar cancers, 69% were HPV positive and 48.6% had HPV16; for 68 cases of VIN, 97% were HPV positive and 80.9% had HPV16. The findings are similar to those of Sutton et al. (44) in Oklahoma, where HPV was found in 70% of invasive vulvar cancers, and 80% of these had HPV16; HPV33, 45, 52, 6, 18, 53, and 62 were found in the others. As described above, only a subset of vulvar cancers has HPV, but HPV is responsible for almost all cases of VIN. Van de Nieuwenhof et al. (45) described finding usual-type VIN adjacent to 25 of 130 vulvar cancers, and that 24 demonstrated integration of high-risk HPV DNA. It is thought that integration of viral DNA into the host cell genome increases the risk of progression (46) by interfering with the function of tumor suppressor genes (e.g., HPV16 transforming protein E6 complexes with p53 and E7 with protein products of the retinoblastoma gene) (47). It is of interest that neither CIN nor cervical carcinoma show overexpression of p53, but HPV-positive vulvar cancer does (48); in their study, only three of 73 cases of VIN

expressed p53, but these three patients had concurrent or previous invasion (48). Do Val et al. (49) reported overexpression of p53 among VIN lesions that recurred or progressed. Further discussion of the significance of p53 can be found in the "LS and vulvar cancer" section.

Fu et al. (50) described a study of nuclear DNA content within VIN, believing that aneuploid lesions with low-ploidy stem lines (less than 3N as measured using Feulgen microspectrophotometry) had a greater risk of progression, and polyploidal lesions were more likely to regress. Certainly, invasive carcinomas of low-ploidy stem cells were more likely to have lymph node metastasis than those having high-ploidy stem cells. A similar study by Evans et al. (51) led the authors to comment that the nuclear abnormalities in VIN were different to those seen in carcinoma in older women, but the differences might reflect those cancers arising in association with HPV, and those who did not arise in association with HPV.

Previous CIN

There are many reports that women who have previously had abnormal cervical smears have an increased risk of VIN. Evans et al. (52) used data from the Thames Cancer Registry (principally in and around London) to show that the standardized incidence rates (SIRs) for vulvar cancer was 4.4 after an earlier diagnosis of CIN 3 and 1.9 after cervical cancer. Kalliala et al. (53) used Finnish data and reported a SIR of 4.1 (95% confidence interval: 1.5–8.9) after treatment for CIN. The risks will be less if the patient no longer carries HPV in follow-up testing or gives up smoking. All doctors and nursing professionals who take smears in the follow-up of patients treated for CIN should be aware that any vulvar symptoms may be significant and due to VIN.

Smoking

There is a clear association between smoking and cancer of the lung and upper airways, but the associations between smoking and lower genital tract cancer are more obtuse. Fifty years ago, Naguib et al. (54) suggested that smoking was linked with cervical cancer, and Moore et al. (55) reported that several recent large studies demonstrated that smoking was associated with a greater incidence of cervical, vulvar, penile, anal, oral, and head and neck cancers in a dose-dependent fashion, that smoking was related to higher-grade lesions of the cervix and vulva, and that progression of dysplasia, or pre-cancer, was more likely with smoking.

It has been possible to measure nicotine and cotinine in cervical mucus (56,57), and it was found to correlate with smoking history, leading to postulation that associated carcinogens might have a direct or synergistic effect on the cervical transformation zone. However, changes in cervical mucus may have less effect on the vulvar skin, and the authors (58–60) emphasize that male factors may contribute. Carstairs and Morris (58) showed a correlation between cervical cancer and a score of deprivation relating to postcode and based on the men of the house being unemployed or in semi-skilled or unskilled occupations, overcrowding in the home, and ownership (or not) of a car; a likely explanation for this is inadequate diet and greater smoking consumption. Reid et al. (59) described differences in the basic proteins, histone, and protamine of sperm, and suggested that protamine in the sperm head (showing a correlation with social class, with a greater proportion of protamine being associated with lower social class) might have an etiological role in cervical cancer; there was no mention of smoking in this study, but this might be the underlying factor. Zenzes et al. (60) demonstrated that smoking increases benzo(a)pyrene diol epoxide–DNA adducts in sperm, showing a new aspect of passive exposure of women to cigarette smoke. Passive exposure, whether by inhalation or exposure to seminal fluid, might explain why, in studies from Taiwan (61) and Singapore (62), cervical neoplasia is found in women who do not smoke but whose husbands do.

Percivall Pott (1714–1788), surgeon at St Bartholomew's Hospital, London, described a cancer that developed in genital skin (cancer scroti) of men who had been chimney sweeps. Initial theories included the lodging of soot in the rugae of the scrotal skin, or the friction generated between the sweep's overalls and his scrotum (63,64). In much later laboratory research using the application of an ethereal extract of soot, cancer could be induced in the skin of mice (65). Gerrard (66) described that women working in the cotton and wool mills of Lancashire and Yorkshire who were exposed to oil-impregnated material directly or via their clothing were twice as likely to develop vulvar cancer than women of similar ages employed in other occupations.

Berenblum (67) reviewed a lifetime spent studying carcinogenesis and recalled that the earliest scientific work concentrated on induction/promotion stages with viral oncogenesis, the consequences of hormonal compounds on breast tissue, and the carcinogenic properties of polycyclic aromatic hydrocarbons and aminoazo compounds; Yamagiwa of Japan produced cancers with coal tar. We now recognize that cigarette smoke causes damage via polycyclic aromatic hydrocarbons that react with DNA to form characteristic "adducts." Levels of DNA adducts can be measured using a ^{32}P post-labeling method (68–70) or by an immunohistochemical method (71). Differences in DNA adduct levels between smokers and nonsmokers have been reported for the cervix (72–74), anus (75), and vulva (76–78). Although the majority of my VIN patients were smokers, there were some who were not and had never smoked. My colleagues and I postulated that some who had raised levels of DNA adducts in vulvar biopsies may have been passively exposed via seminal fluid, environmental exposure, or diet. Pott was aware that many chimney sweeps were exposed to soot at a young age and did not develop cancer. Similarly, exposure to seminal fluid containing possible carcinogens may require cofactors such as HPV and critical polymorphisms or genotypes of cytochrome P450 or glutathione-S-transferase (79–81) before the carcinogenic process could be induced or promoted.

Immune Suppression

Among the 233 cases of VIN and occult or early cancers were 11 transplant patients (liver, renal, and bone marrow), seven HIV-infected patients, and three who were iatrogenically immune suppressed in order to treat systemic lupus. Of the 10 patients who progressed from VIN to invasion while under surveillance, five had altered immunity.

In the 50 cases of VIN described by Friedrich et al. (82), there was one case that progressed to invasion, and she was a 21-year-old with "severe immunosuppression." Buscema and colleagues (14,83) at Johns Hopkins followed 102 patients with VIN (carcinoma *in situ*), and of the four who developed invasion, two were young and immunosuppressed, with cancer occurring at the anal margin. Lindeque et al. (84) described a

26-year-old women who developed invasive vulvar cancer in association with a T-lymphocyte deficiency. Choo (85) described 17 patients under the age of 35 years who developed invasive vulvar cancer, usually in association with carcinoma *in situ*; one patient had her treatment withheld because of advanced Hodgkin's lymphoma.

From the early years of understanding HIV, cervical carcinoma was grouped as an AIDS-defining illness. More recently, it has been suggested that a diagnosis of VIN warrants HIV screening.

Ellerbrock et al. (86) followed a large group of 328 women with HIV for 3 years and found 20% of them developed squamous intraepithelial lesions on their cervix, a four-fold greater percentage than in non-infected women. Thus, women with HIV are often coinfected with HPV. Brown et al. (87) reported three young women with HIV who developed vulvar cancer in association with low CD4 counts and evidence of AIDS-defining illnesses. Better use of antiretroviral drugs reduces this risk, but two of the young women who developed vulvar cancer while under my care for their VIN were known to be HIV positive. Dedes et al. (88) reported that HIV-infected women were more difficult to treat for anogenital intraepithelial neoplasia, with high relapse rates of anal, vulvar, and vaginal intraepithelial lesions and a subsequent invasive potential.

Role of Transplantation

Penn (89) reported that anogenital carcinomas occurred in 65 of 2150 renal transplant recipients who had presented with 2298 different malignancies; there was a 100-fold increase in the incidence of carcinomas of the vulva and anus in these patients compared with the general population. A viral etiology was suggested, and the cancers occurred on an average of 88 months (range, 9–215 months) after transplantation. The article does not implicate specific anti-rejection or immunosuppressive drugs or regimens. Van Leeuwen et al. (90) reported that reduction of immunosuppression after transplantation (e.g., after the transplant failed and the patient returned to dialysis) was associated with a reduction in certain cancers, including anogenital ones.

Harwood et al. (91) reported organ transplant recipients with skin cancers tended to be 15 years younger than immunocompetent individuals with similar cancers, and the outcome for squamous cell carcinoma was worse than for immunocompetent individuals.

Other Factors

It has been noted that the incidence of vulvar cancer in Aboriginal women of less than 50 years of age and living in East Arnhem, Northern Territory, Australia, was at least 70-fold higher than the national incidence of the same age group (31.1; cf. 0.4 per 100,000 women). It was postulated that this isolated population might exhibit increased autozygosity, but this could not be demonstrated (92). Nevertheless, this cluster phenomenon would support the possibility of a genetic risk.

Clinical Features and Diagnosis of VIN

Appearances

Examination of the vulva is sometimes handicapped by inadequate exposure and poor illumination. Koller (93) suggested that the colposcope, and colpophotography, would have advantages. This is applicable to observation of subepidermal vessels. Stafl and Mattingly (94) described the restructuring of the terminal vessels when cervical columnar epithelium underwent metaplasia, and then the prominence of these vessels when neoplastic epithelial changes developed. They described the neovascularization that occurred when intraepithelial disease became invasive, with the development of horizontally running and varying-diameter vessels becoming visible. These changes are not always apparent in vulvar neoplasia, being obscured by associated hyperkeratosis. My colleagues and I (95) used LASER Doppler perfusion indices and then immunohistochemistry to demonstrate vascular endothelial growth factor (VEGF) in the majority of invasive cancers, but only 6% of VIN biopsies. We speculate that detection of altered vascularity or VEGF expression may indicate an increased risk that VIN is progressing to invasion.

Cytology has underpinned the reduction of cervical cancer over the last 70 years, but has received little enthusiasm for its use in detecting or following VIN. Dennerstein's technique (96,97) used the collection of cells by directed scraping, which requires targeting an identified lesion. The study by Nauth and Schilke (98) included 20 precancerous and 111 malignant vulvar lesions; all smears from the precancerous lesions showed dyskeratotic cells of mild to severe degree. In malignant lesions, anaplastic cells were noted in 57%. Our unit (99) used brush sampling of vulvar skin and a cytospin monolayer application to microscope slides followed by Papanicolaou staining. Of the 11 slides containing dyskaryotic cells, 10 had matching biopsies that confirmed vulvar or anal intraepithelial neoplasia (AIN) on histology, and the 11th had basal atypia (see later). Those cases that did not contain dyskaryotic cells did not have neoplastic histology on matching biopsies, but relatively acellular specimens should be regarded as inadequate and require repeating or other techniques in order to assess the vulva and exclude VIN/AIN.

Examination and Biopsy

The paper by Howson and Montgomery (100) from Philadelphia, Pennsylvania, assessed why the diagnosis of gynecological cancer was delayed and reported that five of the seven vulvar cancers they assessed had not been examined. Stanley Way (101), one of the pioneers in the UK in the management of vulvar cancer, expressed concerns that delays in diagnosis still occurred because the patient was shy and reluctant to be examined, because the general practitioner or family doctor had not examined the patient, or because the consultants, usually gynecologists, had failed to take a biopsy. The issue of where to take the biopsy is partly helped by magnification, the use of the colposcope, and the finding of altered vascularity, but the application of 1% toluidine blue solution, as originally described by Richart (102) for the cervix and Collins et al. (103) for the vulva, has much to recommend it (104,105). Thickened areas with extensive hyperkeratosis may give false-negative results, and false-positive staining can occur (e.g., within the vestibule or the anal margin). Techniques for taking biopsies under local anesthesia are described (e.g., by McCullough et al. (106)).

An additional method to keep lesional areas under observation is "self-examination" (77). When patients are seen in colposcopy, the videophotography enables them to understand their anatomy, where biopsies have been taken, and where surgery has been performed. Subsequent examination with good lighting and a magnifying mirror enables them to review the area from time to time and report back if changes are noted (Figure 12.2) (107).

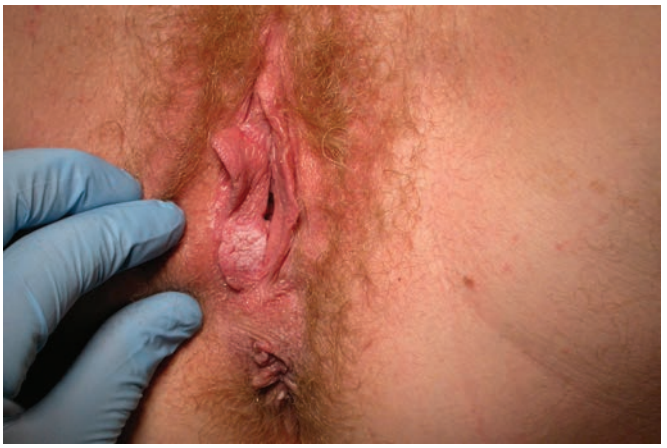

Figure 12.2 An area of VIN showing hyperkeratosis and needing biopsies.

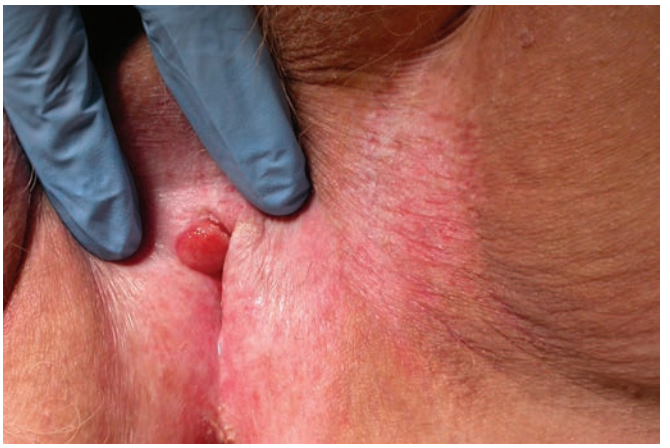

Figure 12.3 Invasion occurring within an area of lichen sclerosus.

Cancer Research UK lists the symptoms and signs of vulvar cancer as:

- A lasting itch
- Pain or soreness
- Thickened, raised red, white or dark patches
- An open sore or visible growth
- Burning pain on passing urine
- Vaginal discharge or bleeding
- A spot that changes shape or color
- A lump or swelling

These features are not specific and may herald many possible gynecological pathologies. Among 1000 women referred to a specialist vulvar clinic with the above symptoms (particularly itch or irritation), only 26 had vulvar cancer (108).

LS AND VULVAR CANCER

Between 1992 and 2015, I saw 3590 new vulvar patients, and these included 757 (21%) with lichen sclerosus (LS); 19 (2.5%) had vulvar cancer present when their LS was first seen, and six progressed to develop cancer 2–12 years after their LS diagnosis. Nine patients (including some of the above) attended the clinic for management of symptoms after previous radical vulvectomy for carcinoma, but with persisting areas of LS (e.g., involving the perineum), and were found to have recurrent carcinoma (Figure 12.3).

The association between these premalignant lesions and cancer has been discussed for more than 100 years. Berkeley and Bonney (7) described their experience with "leukoplakic vulvitis," and Graves and Smith (109) with "kraurosis vulvae." There were inconsistencies across the Atlantic on the criteria for each diagnosis, and Jeffcoate and Woodcock (110) recommended that the way forward was to group these premalignant conditions as "chronic epithelial dystrophies." Further changes in terminology led by the ISSVD saw the replacement of "dystrophy" with "lichen sclerosus" (111,112), but grouped with squamous hyperplasia and other dermatoses as "non-neoplastic epithelial disorders of skin and mucosa." The problem was that some of these patients went on to develop cancer, so the term "non-neoplastic" was misleading. Thus, Wallace (113) described details of 290 women with LS, of whom 12 (4.4%) went on to develop vulvar cancer with an average follow-up interval of 12.5 years. Meyrick Thomas et al. (114) described that 19 of their 357 women with biopsy-proven LS had cancer. Micheletti et al. (115) reported the development of 26 cancers among 976 women managed over 33 years in Turin. In Table 5 of the article by Hart et al. (116), 10 articles published between 1951 and 1969 and describing 465 patients with LS (et atrophicus) included 16 (3%) who had developed cancer of the vulva. Friedrich (117) reported that cancer was found in 4.1% of 1356 patients in 17 published articles; if only articles published in the prior 17 years were included, the rate was 2.6%. Meffert et al. (118) analyzed 5207 published cases of LS and reported 5.4% led to cancers. Thus, the risk of cancer developing with LS is small, but are there factors that might lead to greater risk?

Age

Women who develop vulvar cancer against a background of LS are older than those who have had VIN. Jones et al. (119) reported that the median age of 46 women with vulvar cancer plus LS was 75 years, but the median age of 213 women with LS only was 63 years. However, there are reports of young women who have developed vulvar cancer with LS. Cario et al. (120) reported an 18-year-old who presented with a 1-month history of a painful lump. Examination found LS and a raised ulcerated lesion; biopsy confirmed cancer arising in an area of LS plus hyperplasia with focal atypia. Lindeque et al. (84) reported a 26-year-old with several years of pruritus, extensive dystrophy, and random biopsies that showed hyperplastic dystrophy with severe atypia and areas of squamous carcinoma. Roman et al. (121) reported a 22-year-old with a 3-month history of pruritus and a painful lesion; 2 months later, multiple biopsies found squamous carcinoma and LS.

Symptoms

The majority of patients who develop cancer have increased symptoms of itch and irritation, usually ascribed to inadequate response to treatment, "allergy" to the treatment, or superimposed "thrush." Scurry (122) postulated that "scratching" might be a factor triggering progression to cancer. However, Meyrick

Thomas et al. (114) reported that three of the 19 patients in their series of women with cancer and LS had no symptoms. Jones and Joura (123) reported that of 102 women with vulvar cancer (not all with adjacent LS), 88% had experienced vulvar symptoms for more than 6 months, or for 5 years in 28%. A third of the women had three or more medical consultations for vulvar symptoms prior to the diagnosis of cancer and 25% had undergone vulvar biopsy without cancer being suspected (but see below).

Clinical Appearances

Leibowitch et al. (124) described the clinical findings of 48 women with carcinoma associated with LS, and, along with tumor, include hyperkeratotic plaques, induration (hardening or thickening of the skin), erosion, and ulceration; some of these features are due to the invasion and proliferation when cancer occurs. The significance of white or leukoplakic areas within the vulva has challenged the management of vulvar disease and whether prophylactic vulvectomy should be advised for many years. Jones et al. (119) found that hyperplastic skin changes were more frequent in cases (LS plus cancer) than controls (LS only). They advised that areas of hyperplasia, particularly if localized, should be treated intensively with topical potent corticosteroid and excised if not showing prompt response (125,126).

Histopathology

Since the publications from the 1950s (summarized in (110)), the significance of cellular "atypism" in the basal and parabasal epidermal layers, which is particularly found in hyperplastic or hypertrophied rete ridges, has been recognized. Woodruff and colleagues (127,128) used histology and tritiated thymidine to demonstrate unexpected cellular and metabolic activity in some lesions, and speculated that 25% of such lesions would eventually become malignant. The ISSVD classifications of 1976 (111) included hyperplastic (or the preferred "hypertrophic") dystrophy with or without atypia and mixed dystrophy (LS with foci of epithelial hyperplasia) with or without atypia, and this was replaced in 2005 when VIN was redefined to include VIN, differentiated type (dVIN) (17). Such changes included "basal atypia" that was found in older women in association with carcinoma arising with LS and/or squamous hyperplasia (45,124) and were not always recognized by pathologists. My colleagues and I have suggested (125) that any patient with LS and a previous diagnosis of dVIN, or where the pathologist expresses concern but cannot make a definite diagnosis of dVIN, should be referred to a specialist/specialist clinic.

> *In this setting the clinician can choose between a limited period of intensive medical therapy with follow-up biopsy, or excision at the outset.*

Molecular Markers

The use of immunohistochemistry to help with diagnosis or to define risk of malignancy is now common. Mulvany and Allen (129) used immunoreactivity of Ki67 and p53 to define dVIN and distinguish it from normal squamous epithelium. My colleagues and I (130) used Ki67 and p53 staining to examine biopsies taken from a patient who previously had vulvar cancer arising from LS. She had residual LS within vaginal introital and perianal skin areas, and after 11 years had histological confirmation of malignant recurrence; the overexpression of p53 and Ki67 anticipated the histological diagnosis. A series of mutations within exon 5 of the p53 molecule was identified, sometimes preceding the cancer (131). A frequent mutation found in our LS plus cancer patients was at codon 136, where the pyrimidine cytosine was replaced by thymine; this mutation results in the triplet for the amino acid glutamine being replaced by a stop codon. It is thought that these transitions are due to endogenous inflammatory processes, but still this does not allow identification of which patients need more frequent follow-up. Expression of p53 and Ki67 may also be induced during treatment with ultrapotent topical corticosteroids (132).

Duration of Diagnosis

Micheletti et al. (115) calculated the cumulative probability of progressing to neoplasia (including intraepithelial neoplasia and dVIN) as 1.2% at 2 years to 36.8% at 300 months (25 years), and this risk was greater in patients aged 70 years or older. The authors indicated that they were unable to correlate these risks with the adequacy of treatment or frequency of follow-up.

Adequacy of Treatment

Some of my patients had comorbidities (e.g., obesity or arthritis) that restricted their ability to apply topical corticosteroids and, I believe, increased their risk of developing cancer.

The British Association of Dermatologists have given recommendations on how to treat LS with topical ultrapotent corticosteroid ointment (i.e., clobetasol propionate) (133,134) and there is a recommendation to refer such patients to a "specialist clinic" if symptoms are not improved on these protocols (125).

Renaud-Vilmer et al. (135) described responses to treatment with topical clobetasol of 83 women with LS, and documented that relapse occurred in 50% at 16 months if treatment were discontinued. Complete clinical remission was obtained in 54%, but was less in older women. Six women had cancer diagnosed when they first presented. Additionally, one woman had no follow-up and 3 years after the end of her treatment returned with cancer. Furthermore, one developed cancer due to infrequent treatment because of severe depression. Cooper et al. (136) described the responses to treatment with clobetasol of 327 patients with LS, and noted that 22 (9%) showed only minor or no improvements in clinical signs. Six developed carcinoma and they were likely to have a delay in diagnosing LS (15.3 vs. 4.4 years), but there is no description of adequacy of response to treatment.

Recently, Lee et al. (137) showed that among 357 patients who adhered to the treatment instructions of using potent steroids initially and then low- to moderate-potency steroids for maintenance, there were no cases of subsequent cancer. Among 150 patients (30% of the total group) who did not carry out the advised treatment, there were three (after 36, 120, and 360 months of treatment, aged 70, 60, and 60 years, respectively, and with treatment-resistant hyperkeratotic plaques) who developed cancer and four with dVIN.

Use of Immunosuppression

Among the patients of mine who progressed to carcinoma was one who, 8 years after her first consultation at the vulvar clinic, re-presented with troublesome symptoms and 3 months of application of pimecrolimus. Fischer and Bradford (138) had reported a similar case of cancer developing soon after exposure to pimecrolimus. Pimecrolimus and tacrolimus are calcineurin inhibitors that have potent immunomodulatory effects. The U.S. Food and Drug Administration added a "black box"

warning to tacrolimus in 2006, and current advice is that topical calcineurin inhibitors should not be used on malignant or potentially malignant skin conditions.

I had another patient with LS who had been well controlled with intermittent topical corticosteroids, but after 10 years was diagnosed with polymyalgia rheumatica and commenced on oral corticosteroids; soon after, she had further vulvar symptoms and was found with an early carcinoma. I have other patients with LS who take medication to control other inflammatory conditions (e.g., ulcerative colitis and rheumatoid arthritis) and have few vulvar symptoms and require minimal topical steroid use. We all have concerns that excessive topical corticosteroid use may increase the risk of malignant progression and advise increased surveillance of women who need to apply steroid more than three times a week or use more than 30 g of ointment in 6 months (125).

Blood Groups

Sir Richard Doll, medical epidemiologist, published (139) an association between gastric carcinoma and blood group A. We know now that gastric cancer has links with *Helicobacter pylori*, hypochlorhydria, altered E-cadherin expression, and interleukin-1β polymorphisms, and that blood group antigens may reflect a genetic predisposition. My colleagues and I found (140) that while our control population was blood group A in 38% and O in 43%, those women with vulvar cancer and LS were group A in 72% and O in 17%. Women with LS alone were group A in 57% and O in 13%, and vulvar cancer with VIN were group A in 30% and O in 50%. We postulate that the naturally occurring blood group antibody anti-A (as found in those individuals who are blood group O) may be protective, and its absence may increase the chance of LS and the risk of progression to malignancy.

Vitamin D Deficiency

Vitamin D deficiency has been associated with autoimmune disorders and some cancers. It is caused by inadequate dietary intake and reduced sun exposure. The hypothesis of my colleagues and I (141) was that such a deficiency might explain the geographic distribution of LS (it appears to be rare in equatorial countries) and why vulvar cancer is 5–10-times more prevalent in Europe, North and South America, and Australasia than in, for example, Asia. Severe vitamin D deficiency (serum 25-hydroxyvitamin D levels <25 nmol/L) was found in 13% of our LS patients, but the four patients with LS plus cancer had levels of 30, 32, 50, and 95 (optimal 25-hydroxyvitamin D levels are >75). Women who develop vulvar cancer may be vitamin D deficient because of infrequent sun exposure, obesity, altered skin pigment due to ethnicity (two women with LS who progressed to cancer were of Asian ethnicity), and poor diet; this deficiency may be coincidental and not causal.

LICHEN PLANUS AND VULVAR CANCER

Among the patients I have seen with vulvar cancer were two whose cancers had arisen from lichen planus (Figure 12.4). Zaki et al. (142) reported that of 50 cases of squamous cell carcinoma, 24 had LS, 20 had VIN 3, and three had lichen planus. The association with oral lichen planus and buccal cancer is well known, but because lichen planus of the vulva is less common and may be confused with LS, the association with vulvar cancer is often not considered. It appears that the risk is increased with hypertrophic lichen planus, and progression occurs via pseudoepitheliomatous hyperplasia (143). The question of whether carcinoma can arise against a background of erosive lichen planus was raised by Kennedy et al. (144), who reported finding one patient with cancer among 113 with erosive lichen planus. Day et al. (145) described that some cases of erosive lichen planus that show features of regeneration on histology may cause confusion when distinguishing it from dVIN.

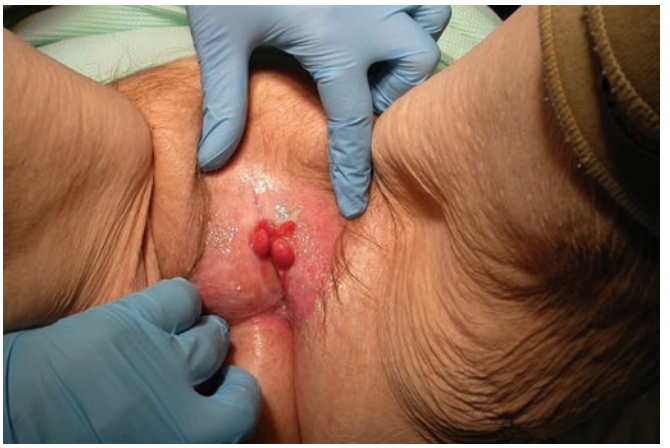

Figure 12.4 Invasion occurring within an area of lichen planus.

FOLLOW-UP OF PATIENTS WITH SIGNIFICANT LESIONS

The follow-up of patients with previously treated CIN has relied on cytology, colposcopy, and now HPV testing. The same advice cannot be given for those patients with VIN or LS, and the occurrence of cancer many years after the original diagnosis requires that assessment is long term or even lifelong.

It is likely that the introduction and coverage of HPV vaccination will eventually limit the numbers who will develop VIN, usual type (146), but in the meantime, smoking cessation and regular scrutiny of transplant and other immune-suppressed patients is advocated.

The large majority of women with LS will not develop cancer. We have advised that women with LS who struggle with symptom control or use increased amounts of topical corticosteroid, those who have hyperkeratosis or localized skin thickening, and those with previous vulvar cancer or VIN should be seen in specialist clinics (125). Some of these women will need 6-monthly assessment and frequent biopsy. This may not prevent cancer from developing, but early diagnosis should result in better prognosis.

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Vulvar cancer and post-vulvectomy complications

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INTRODUCTION

Vulvar cancer is rare and represents 5% of female genital tract cancers. It is considered a disease of older women. In recent decades, there has been an increase in vulvar cancer diagnosis in women aged less than 50 years (1). The gold standard in the treatment of vulvar cancer is surgery. In the past, the preferred operation was radical vulvectomy and bilateral groin node dissection, but these had high morbidity rates, including prolonged hospital stays, infection, and wound breakdown. The first proposed surgical therapy was introduced in 1912 by Basset, performing en-bloc lymph node dissection involving the butterfly technique (2). Although the introduction of this technique increased overall survival up to 70%, it had consequences of prolonged hospital stays and frequent complications such as lymphedema and wound breakdown (2,3). Fifty years later, in 1962, Byron described the triple-incision technique, which was characterized by lower morbidity, even though cases of seroma formation, wound breakdown, and lymphedema were still significant (occurring in more than 50% of the cases) (3,4). In 2003, Gaarenstroom et al. reported that the triple-incision technique was also related postoperatively to psychosexual disturbances and negative body image in the majority of treated patients (5). In recent decades, less invasive procedures have been suggested based on individualization of treatment, including wide local excision of the vulvar tumor, unilateral groin node dissection, and, lately, sentinel lymph node biopsy. In order to reduce further postoperative complications, Rouzier et al. suggested the sartorius transposition: the preservation of the fascia lata and long saphenous vein (LSV) (6). In addition, the preservation of the LSV has demonstrated a 33% decrease in postoperative morbidity (5–8). By using these conservative methods, we achieved decreased postoperative morbidity rates without compromising prognosis and survival, while offering better postoperative quality of life to the patients.

Our aim is to present the postoperative complications of patients undergoing surgery for vulvar cancer. These complications can be divided into early and late postoperative complications. Early complications include wound infection, cellulitis, urinary tract infection, hemorrhage/hematoma, wound breakdown, lymphocyst, deep venous thrombosis (DVT), and pulmonary embolism (PE), as well as prolonged hospital stay. Late complications include leg lymphedema, recurrent lymphangitis, urinary stress incontinence, vaginal stenosis, femoral hernia, rectoperineal or rectovaginal fistula, and psychosexual concerns. Such complications are challenging for the surgeon to deal with and they are usually approached on a specialized team basis involving a multispecialty approach. Optimization of preoperative management can minimize the possible complications. An experienced surgical team, diabetes mellitus control, smoking control, preoperative anesthetic review, thromboprophylaxis using thromboembolic-deterrent stockings, low-molecular-weight heparin (LMWH) injections, and optimization of the surgical technique, as well as correct choice for the optimal time of drain removal and the patient's early mobilization based on enhanced recovery protocols, can optimize the outcomes.

We are going to further analyze each possible complication, focusing on the prevention and possible management of each of them.

INCIDENCE

In the literature, up to 85% of the patients treated for vulvar cancer may report complications, among which the most documented are wound breakdown, lymphoceles, wound-related infection, erysipelas, formation of lymphedema, and cellulitis (5,9). In the early 1980s, the standard surgical treatment of vulvar cancer was considered to be en-bloc radical vulvectomy combined with bilateral lymph node groin dissection (10). The related complications after such a radical approach were relatively high (wound breakdown infection: up to 91%; leg lymphedema: 8%–70%; lymphocyst: up to 31%; genital prolapse: up to 14%; inguinal/femoral hernia: 0%–5%, hospital deaths: up to 12%). The postoperative complications were in direct correlation with the patient's age and the extent of the operation (5,10). In the following decades, morbidity was significantly decreased without influencing total survival through the utilization of the triple-incision technique using separate incisions over the inguinal ligaments (11,12). In order to reduce further the incidence of morbidity without influencing the risk of local recurrence, additional modifications were made, such as hemivulvectomy and/or wide local vulvar excision in an individualized approach (11,13,14). Furthermore, the introduction of the concept of the sentinel lymph node in the treatment of early-stage vulvar cancer has further decreased complication rates (15,16).

RISK FACTORS

Hinten et al. assessed the risk factors related to short-term and long-term complications using univariate analysis (17). Parameters including patient characteristics (age, diabetes, smoking, peripheral vascular disease, body mass index, and continuation of antibiotics), surgical technique (bilateral groin node dissection, en-bloc dissection, ligation of the saphenous vein, number of nodes dissected, and number of positive nodes), postoperative management (duration of the drain *in situ*, drain production on last day, total drain production, adjuvant radiotherapy, and hospital stay), and FIGO (International Federation of Gynecology and Obstetrics) stage were analyzed.

The examination of various risk factors for the development of wound breakdown revealed that "en-bloc" surgery (odds ratio [OR]: 2.72, 95% confidence interval [CI]: 1.16–6.37) and older age (OR: 1.06, 95% CI: 1.02–1.10) both represent independent risk factors (17). Old age can also be related to deterioration of the capacity of the body to wound heal. In addition, "en-bloc" surgery and higher drain production (OR: 1.05, 95% CI: 1.00–1.09) were the only independent risk factors regarding the possibility of wound infection (17). Drain production (OR: 1.05, 95% CI: 1.01–1.10) and younger age (OR: 0.95, 95% CI: 0.93–0.98) were also considered risk factors for the postoperative presentation of lymphocele. In particular, higher drain production on the day of the drain removal (OR: 1.11, 95% CI: 1.04–1.19) and diabetes (OR: 4.10, 95% CI: 1.04–16.05) were found to be risk factors for the development of any short-term complications. Regarding the development of cellulitis/erysipelas, younger age (OR: 0.96, 95% CI: 0.93–0.98) and lymphocele (OR: 3.28, 95% CI: 1.50–7.19) were independent risk factors. Furthermore, younger age seemed to be a risk factor for long-term complications and lymphedema. The latter can be interpreted by the fact that younger women are more physically active and the development of a possible lymphedema might limit their daily activities. Moreover, a higher number of dissected lymph nodes could increase the risk for lymphedema, based on the fact that the more lymph nodes that are dissected, the more the lymphatic drainage is interrupted. However, the prognostic impact of the number of lymph nodes dissected remains unclear. Nevertheless, it is suggested to remove six to eight lymph nodes per groin (18,19). Regarding the duration of drainage, there are no standardized protocols, even though the literature suggests that the drains should be left *in situ* for at least 5 days and should be removed when the production has reduced to less than 100 mL per day (17). As already mentioned, higher drain production on the last day that the drain was *in situ* is associated with increased risk for the development of lymphocele (17). An explanation for this fact is that the negative suction pressure in the drain may prevent the lymphatic leak and blood vessels from sealing off, causing prolonged drainage (17,20,21).

EARLY POSTOPERATIVE COMPLICATIONS

Wound Complications

Wound complications result in significant patient morbidity, require extensive hospital stays and wound treatment, affect quality of life, and elevate hospital costs. Wound dehiscence, infection, seroma, hematoma, wound necrosis, and lymphocyst represent the most common wound complications that could be identified after the surgical treatment of vulvar cancer. Risk factors related to the general status of the patient such as diabetes mellitus, obesity or poor nutritional status, chronic renal failure, advanced age, presence of jaundice, alcoholism or smoking, previous radiotherapy or chemotherapy, and immunosuppressant status are predisposing factors related to wound complications (22). Some medications can also increase the risk of wound complications, including immunosuppressants, cytostatics, corticosteroids, antiphlogistics, anticoagulants, and psychotropics (23,24).

The incidence of such complications varies by institute or even surgeon. Regarding the incidence of hemorrhage/hematoma/postoperative bleeding, Gaarenstroom et al. reported that it can reach 1% and 4% for vulvar and groin locations, respectively (5). Regarding the rate of documented wound infection, there is great variability. Senn et al. reported an incidence of 5.6% (22), while Leminen et al. reported 47% (12). It has been shown that a body mass index of more than 24, age older than 70 years, and extended lymphadenectomy represent significant risk factors for wound infection/dehiscence (6). It has also been suggested in the literature that both wound dehiscence and wound infection are more frequent in the vulvar compared to the inguinal region (22). The tumor location and surgical radicality are also reported as risk factors for wound infections (12,25). Wound infection is significantly correlated with increased incidence of wound breakdown and lymphedema (12). Also, the presence of early complications after groin dissection is related to the development of lymphedema (12,26).

Wound dehiscence often occurs after radical vulvectomies, with incidence rates ranging widely between 13% and 54% according to the current literature (12). The principal predictors of wound breakdown are reported to be wound infection and the extent of surgery (27). Over the past two decades, modifications on the technique of radical vulvectomies and inguinal lymph node dissections have decreased postoperative morbidity. The traditional "en-bloc" resection has been replaced by the triple-incision technique in order to reduce the rate of wound-healing disorders (3). Factors that may have some impact on wound dehiscence and infection rates are the surgical techniques used, the types of drains utilized, and wound closure techniques applied after lymphadenectomy, and these have been analyzed in different studies. For example, Carlson et al., in a randomized clinical trial comparing the impact of fibrin sealant and sutured wound closure, reported a statistically significant higher rate of vulvar infections in the fibrin sealant group (7). In another study, Uyl-De Groot et al. tried to limit wound infection rates and hospital stays by using perioperatively recombinant human granulocyte colony-stimulating factor (r-metHuG-CSF, filgrastim) (28). In this study, 39 patients treated with filgrastim increased their absolute neutrophil count without having any effect on the prevention of wound infection. On the other hand, Morelli et al. reported the application of platelet gel at the site of the surgical field before vulvar reconstruction to prevent wound breakdown (29). Platelet concentrates are commonly utilized in order to facilitate cutaneous reparation. The gel consists of autologous or heterologous platelets that have first undergone centrifugation and then been stimulated by agonist factors that can cause the activation and the release of platelet-derived growth factors, resulting in the acceleration of wound healing (30). After the use of a platelet gel application, a reduction was found in the total rates of wound infection, wound breakdown, and/or necrosis (29). In addition, less postoperative pain and shorter hospital stays were observed in comparison to patients not treated with platelet gel. Nevertheless, these results are reported from preliminary studies and further investigation is necessary. Some other studies reported that the duration of suction drainage and antibiotic prophylaxis did not prevent the presentation of wound infection and late complications, such as lymphedema and cellulitis (12,26).

Treatment of Wound Dehiscence/Infection

Lately, negative pressure wound therapy has been studied in postoperative wound closure, creating a clean, dry wound microenvironment, decreasing postoperative seromas, and accelerating wound healing (31,32). Vacuum-assisted closure (VAC) dressing is the treatment of choice. In the past, there were also other proposed types of treatment, such as hyperbaric oxygen therapy (33). The disposable components of the V.A.C. Therapy

Figure 13.1 V.A.C. Therapy System®. (With permission from KCI, TX, an Acelity Company.)

System® (Figure 13.1) include the foam dressing kits (i.e., V.A.C. GranuFoam™, KCI, TX, USA; V.A.C. GranuFoam Silver®, KCI, TX, USA; or V.A.C. WhiteFoam™ dressing). The therapy accessories are packaged sterile and are latex-free materials. The ActiV.A.C.® (KCI, TX, USA), InfoV.A.C.® (KCI, TX, USA), V.A.C. ATS® (KCI, TX, USA), and V.A.C. Freedom® (KCI, TX, USA). Negative pressure wound therapy systems are dedicated to wound management on an inpatient or outpatient basis. The created negative pressure forms an environment that increases wound healing by secondary or tertiary intention, promoting granulation tissue formation, removing exudates, and reducing edema (34–37).

Urinary Tract Infection

Postoperatively, there is a need for the use of a urinary catheter because of the patient's immobilization during the first days, as well as to keep the wound dry and clean. Through this, an immediate dose of intravenous antibiotics can prevent any possible urinary tract infections.

Lymphocyst

A variety of approaches has been attempted in order to provide perioperative prophylaxis and treatment of inguinofemoral lymphocysts, although so far none has been consistently effective or optimal. The prevention of lymphocyst could be achieved by performing a meticulous dissection including preservation of the saphenous vein and careful ligation of lymphatic vessels (8). Bed rest, pressure dressings, and prophylactic antibiotic treatment are the first-line therapeutic options (32). Other invasive interventions include external drainage using local needle aspiration or local injection of various sclerosing agents (e.g., bleomycin, povidone iodine, polidocanol, doxycycline, octreotide, alcohol, fibrin sealant, collagen powder, and radiotherapy) (38–46). However, such interventions can cause wound infection. Other possible surgical interventions include ligation of leaking lymphatics, lymphaticovenous anastomosis (LVA), use of muscle flaps (sartorius muscle flap), and/or local wound revision and debridement (47–50). The preservation of fascia lata during groin lymphadenectomy was also proposed as an effective technique for preventing lymphocyst (51). In addition, the utilization of subatmospheric or negative pressure techniques has also been proposed for the treatment of persistent lymphorrhea (52,53).

One of the most successful techniques for preventing lymphatic leakage is the mapping of the lymphatic vessels by blue dye and successive ligation of these vessels (54). More specifically, the lymphatic drainage of the lower extremities is utilized to retrieve lymphatic vessel endings. After the inguinal lymph node dissection, lymphatic vessels are frequently left intact and, as a consequence, inguinofemoral lymphocele and leg lymphedema arise. The mapping of the lymphatic vessels begins with the injection of patent blue dye distally to the inguinofemoral region, marking the main lymphatic vessels that drain into the groin. Consequently, surgical exploration of the inguinofemoral area is performed, followed by ligation of the lymphatic endings using titanium clips (55).

Buda et al. proposed another preventive technique using the application of a sterile, absorbable hemostatic surgical patch (TachoSil®, Nycomed, Zurich, Switzerland), which is a fixed combination of a collagen matrix with coagulation factors (such as human fibrinogen and human thrombin), as a means of reducing postoperative complications after groin lymphadenectomy (Figure 13.2) (56). Such a technique seems to be effective in decreasing the rate of complications after lymphadenectomy. TachoSil® has already been utilized in reducing lymphatic leakage as a result of mediastinal lymph node dissection and preventing lymphocyst formation after inguinofemoral dissection (56,57). Its action is based on the effect of coagulation and fibrinolytic factors, produced by lymphatic endothelial cells, on the sealing of lymphatic capillaries. It is shown that patients using TachoSil® had significantly less lymphorrhea, lower rates of complications (such as cellulitis, wound infection, and lymphocysts), and earlier drainage removal (56).

There is a query about whether the use of new energy sources (e.g., Ultracision®, Ethicon Inc., Smithfield, Rhode Island, USA; LigaSure®, Covidien, Maryland, USA; and Ligaclips®, Ethicon Inc., Sommerville, New Jersey, USA) can reduce lymphocyst rates. Madhuri et al. suggested the use of the PlasmaJet® system (Plasma Surgical Ltd, Abingdon, UK) (Figure 13.3), an argon plasma device that heats pressurized argon gas, as a means of preventing lymphocyst formation and other wound complications following inguinofemoral dissection (4). Following groin dissection, the PlasmaJet® sealed the lymph vessels at a setting of 40% over the entire surgical field, at a distance of 10 mm from the surface to the tip of the PlasmaJet®. This application added an extra 5 minutes to the total duration of the operation and had promising results.

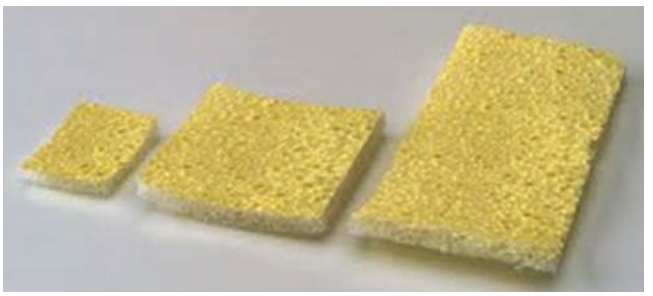

Figure 13.2 TachoSil®. (With permission from TachoSil®, Nycomed, Zurich.)

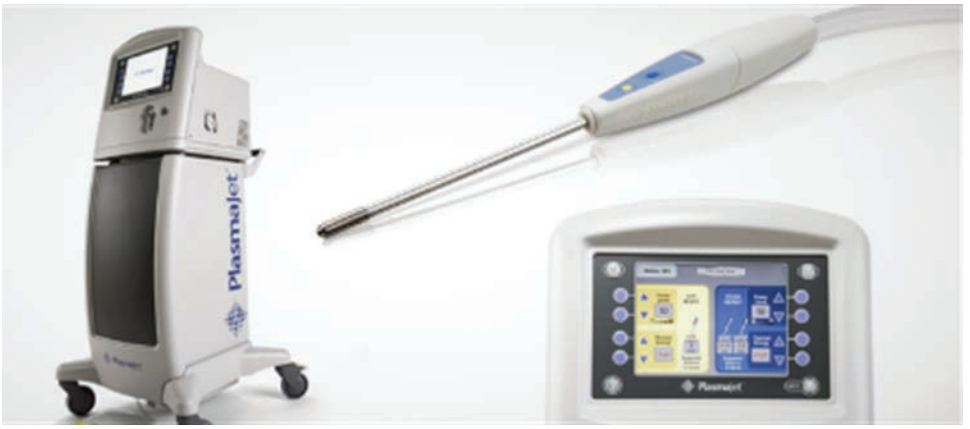

Figure 13.3 PlasmaJet®. (With permission from PlasmaJet®, Plasma Surgical Ltd, Abingdon.)

Nevertheless, spontaneous resolution of even extended lymphoceles after several months of repeated hospitalizations and surgical treatment is presented in the current literature (56). Finally, the sentinel lymph node technique can be expected to decrease the number of complications post-lymphadenectomy, minimizing the need for extensive dissection.

DVT and PE

DVT as well as PE represent the two major complications after gynecologic surgery and can present with significant postoperative morbidity and mortality (58). The prevalence of DVT after gynecologic surgery depends on the method applied for diagnosis. The identification of high-risk patients and the administration of effective thromboprophylaxis can reduce incidence (58). Immobilization is the main risk factor for the development of DVT and PE, with a nine-fold increase seen in patients after extensive bed rest (59). Hospitalization and surgery are also correlated with an increased probability of thrombosis risk, with ORs of 11.1 and 5.9, respectively. Cancer, old age, prior history of venous thromboembolic events, smoking, African–American ethnicity, ankle edema, prolonged surgical time, varicose veins, and history of prior radiotherapy are the main prognostic factors. The prophylactic options can be divided into mechanical and pharmacological. The use of intermittent pneumatic compression (IPC) prophylaxis and LMWH are among the most effective measures against venous thromboembolic event development. Mechanical methods prevent venous stasis and promote endogenous fibrinolysis, while pharmacological methods prevent clot formation (60).

Graduated Compression Stockings

Early postoperative ambulation, elevation of the foot from the bed, and graduated compression stockings (GCSs) prevent venous stasis of blood in the legs (61). Low cost and simplicity are the principal advantages of the utilization of GCSs. A correct fit of GCSs is crucial, and for this reason, limb diameter measurement is advised, as improperly fitted stockings can increase venous stasis at the knee or mid-thigh. Knee-length GCSs are as effective as thigh-length GCSs and should be preferentially used (62).

Intermittent Pneumatic Compression

IPC devices compress the calf with an inflatable pneumatic sleeve and reduce venous stasis as a result. It is proven that the use of IPC devices during and after major gynecologic surgery is as effective as LMWH in reducing DVT risk (60,63). IPC devices should be used continuously until complete ambulation and are discontinued at hospital discharge (58). It is also proven that IPC devices showed a three-fold reduction in the incidence of venous thromboembolic events (60).

Low-Molecular-Weight Heparin

The main advantage of LMWH includes its single daily dosing guaranteeing greater bioavailability (64). LMWH has more anti-factor Xa and less anti-thrombin activity, which decrease iatrogenic bleeding and postoperative wound hematomas. Furthermore, heparin-induced thrombocytopenia is a very rare event with LMWH and screening for this is not necessary (65).

LATE POSTOPERATIVE COMPLICATIONS

Lymphedema

Lymphedema represents one of the most important long-term complications after radical vulvectomy with complete inguinofemoral lymphadenectomy. Lymphedema is a complication that is correlated with dysfunction of the lymphatic system. The incidence rate varies by up to 20% in different studies (66); however, the real incidence rate of lymphedema may even be underestimated due to the methodological quality of the presently available studies. The preservation of the saphenous vein is considered to be a necessary step in order to reduce postoperative morbidity during groin lymphadenectomy. Zhang et al. proved that patients who underwent the saphenous vein-sparing surgery in comparison with those who underwent ligated surgery presented with fewer frequent long-term complications (67). Moreover, chronic lower extremity lymphedema, lower extremity pain, and cellulitis were reduced by about 50% in the saphenous vein-sparing groups, while there was no remarkable difference between the two groups in terms of the rates of postoperative phlebitis and DVT (67). Dardarian et al. showed that, in patients with vulvar carcinoma treated with inguinofemoral lymphadenectomy, the frequencies of cellulitis, wound breakdown, and chronic lymphedema were higher in the

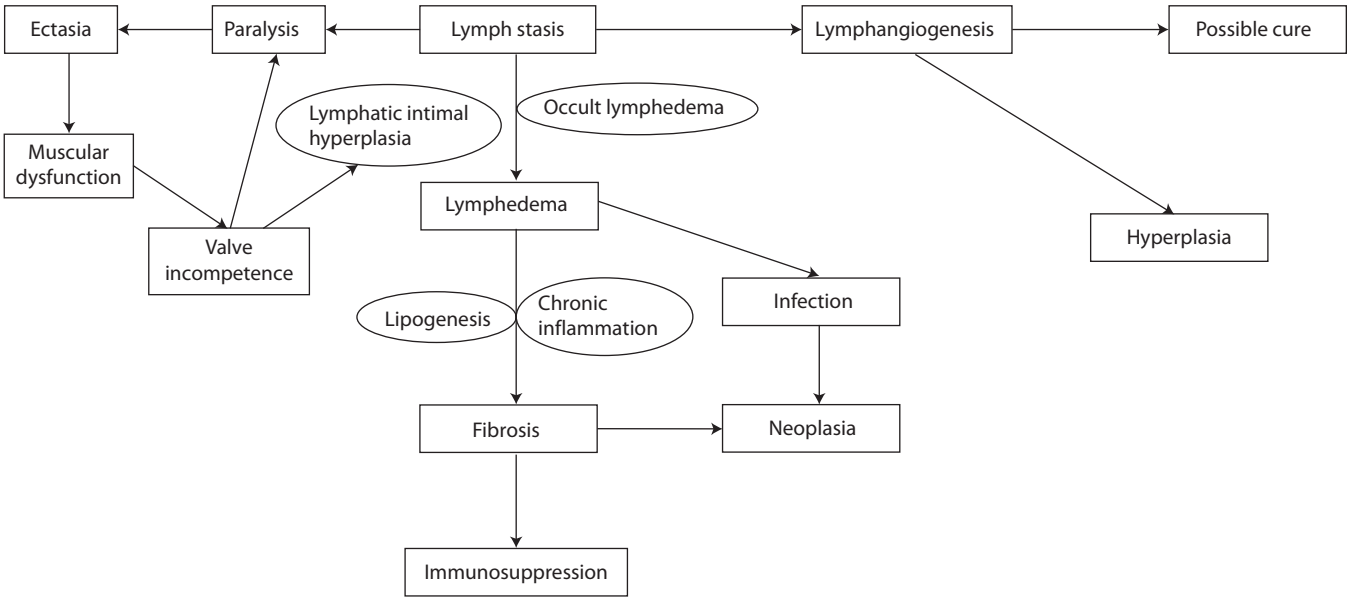

Figure 13.4 Pathophysiologic pathway of lymphedema. (Modified from Saito Y et al. *Biomed Res Int* 2013; 2013: 804675.)

saphenous vein-ligated group than in the vein-spared group (68). However, in the literature, sparing of the saphenous vein does not decrease the rates of lymphedema in all studies (6,8,9). Sartorius transposition also does not reduce morbidity (6,69). Postoperative lymphedema is the result of the accumulation of lymphatic fluid in the affected limb after the disruption of normal lymphatic drainage (Figure 13.4) (66). The first phase of lymphedema is also known as the fluid phase and is characterized by swelling (pitting edema) due to excess lymphatic fluid. The fluid phase, if not treated or treated improperly, then leads to the accumulation of inflammatory lymphatic fluids, which may activate fibrocytes as well as adipocytes, causing the gradual deposition of fat and fibrotic elements (70). The solid phase of lymphedema can be present in many patients with chronic lymphedema and is characterized by non-pitting edema and 90% excess volume in the afflicted limb (71,72). There is great variation in the time of transition from fluid to solid phase among patients (72). Staging lymphedema is based mainly on edema aggressiveness (Table 13.1) (73,74).

The management of lymphedema includes conservative and surgical treatment. In general, the management of lymphedema is focused on conservative treatment, which is based on externally enhanced lymphatic drainage. Such methods include compression therapy, elevation of the affected limb, decongestive physiotherapy (by specific manual lymphatic drainage massage), and external sequential pneumatic compression (75). The conservative treatment of lymphedema has showed success mainly in patients with mild to moderate lymphedema and is associated with great variability due to its dependence on patient compliance (76). As a result, a large number of patients experience little benefit from this type of treatment (70). Furthermore, the external physical methods can be costly, uncomfortable, and time consuming (77,78).

More specifically, conservative treatment for lymphedema has in the past been administered by a lymphedema therapist as an initial course of complete decongestive therapy (CDT) (66). Manual lymph drainage or massage, compression bandaging, and constant skin care are the main components of CDT (79,80). Conservative treatment with CDT can improve lymphedema, particularly in patients in the early stages of disease. However, CDT must be continued indefinitely so as to reach the best possible outcome. Low-level topical lasers as well as mechanical compression pumps have also been applied as alternative treatment modalities (81,82). The great variability in the effectiveness of the treatment and the high treatment costs that are not totally covered by health insurance are some disadvantages of conservative treatment (83,84). Chronic pain, depression, difficulties in activities of daily living, and difficulties fitting into normal clothing are some of the consequences of lymphedema (85,86). In addition, lymphedema increases the risk of developing cellulites/erysipelas in the affected extremities, which generally requires hospitalization, intravenous antibiotics, and continual low-dose antibiotic prophylaxis. Chronic lymphedema is also correlated with an increased risk

Table 13.1 Staging Lymphedema

ISL stage (73)	Campisi stage (74)	Clinical description
0/Ia	1A	• Absence of edema • No difference in volume between legs
I	1B	• Mild reversible edema
	2	• Moderate edema (partially reversible)
II	3	• Severe edema • Recurrent episodes of acute lymphangitis
	4	• Fibrotic lymphedema • Limited lymphostatic warts
III	5	• Elephantiasis • Scleroindurative pachydermatitis • Extensive lymphostatic warts

Abbreviation: ISL: International Society of Lymphology.

of malignancies such as Kaposi sarcoma, lymphangiosarcoma, and lymphoma (87,88).

Pharmaceutical treatment of lymphedema is characterized by limited success (89). Studies have showed mixed results regarding the use of benzopyrones (90,91).

Surgical Management of Lymphedema Patients

Surgical treatment can be distinguished into reconstructive and reductive techniques (Table 13.2) (92–101). The former include procedures/techniques the main intention of which is to reconstruct lymphatic drainage either with microsurgical lymph node transfers or microsurgical anastomoses. This type of treatment is generally recommended in early-stage lymphedema with existing healthy lymphatics combined with compressive therapy (102). In the to-date published studies, 87% of the patients reported subjective improvement and 83% demonstrated significant volume reductions of the area involved (94). Becker et al. treated with free lymph node transfer patients with upper extremity lymphedema after axillary dissection and reported significant volume reductions in 42% of cases (103). Chronic damage of the lymphatic vessels is generally irreversible, and attempts to restore regular flow had poor results. In such cases, the second type of surgical treatment—reductive procedures—can be attempted. This type of surgical therapy is appropriate when the volume and dimensions of the limbs are massive and lymphedema is incapacitating. This technique is principally characterized by the Charles procedure, which, over time, was modified and evolved (104–107). This surgical technique has showed improvements of skin hygiene and reductions of the risk of cellulitis and sepsis, and there has also been a report of a significant improvement in mobility combined with acceptable cosmetic results and fewer complications (108). A modification to the Charles procedure was published by van der Walt et al.; that is, applying negative pressure wound therapy to the wound bed after reductive surgery with the intention of improving its quality for grafting (109). Moreover, Lee et al. reported low complication rates and better overall volume reductions after treating end-stage lymphedema with a modified Auchincloss–Homan operation (78). Suction-assisted lipectomy has proven successful in women with both upper and lower extremity lymphedema secondary to malignancy treatment (110–112). In addition, suction-assisted lipectomy techniques demonstrate that at end-stage lymphedema there is a predominance of fat deposition and that fat is the primary cause of swelling, not the increase of lymphatic fluid, rendering ineffective all of the conservative treatments, as well as all of the lymphatic reconstruction procedures (77,113).

More analytically, we can identify different surgical approaches in the literature that are used to treat lymphedema. The Charles procedure was first reported in 1912 (114). This operation involved an aggressive resection of skin and soft tissue down to the deep fascia, followed by skin grafting over the excised area. The Charles procedure achieved debulking of the limb, but was not as effective at managing ongoing lymphatic stasis. The first attempts at preservation of lymphatic function in the literature were described by Sistrunk and Thompson (115–117). However, these early procedures were often ineffective and disfiguring, and for this reason have been abandoned. Since then, new approaches have been described in the literature with more effective results.

Vascularized Lymph Node Transfer

Vascularized lymph node transfer (VLNT) involves the microsurgical transfer of a lymphatic soft tissue flap along with its arteriovenous supply from a donor site to the affected area (66,118). The first step includes removal of the scar tissue post-lymphadenectomy and then the vascular circulation is re-established through the transferred flap. The lymphatic channels and small peripheral flap vessels are permitted to heal with the respective lymphatics and small vessels present at the recipient site. Most microsurgeons prefer to transfer lymph nodes from the lateral groin to the affected area (100,103,118–122). Some surgeons prefer to transfer the lymph node flap together with the vessel perforator. Post transfer, some patients can have immediate improvement, which can be explained due to the removal of scar tissue in the previously surgically treated lymphatic area, which has been postulated to account for this clinical observation (95). The further healing process of transplanted lymphatics to native lymphatics at the selected area and the drainage of lymphatic fluid by a direct negative pressure mechanism may reduce lymphedema. The major disadvantage of the VLNT technique is the potential risk of donor site morbidity. In order to minimize the risk of disturbing lymphatics at the donor site, the careful selection/collection of lymphatics during the VLNT should be made. In a groin donor site, in order to leave intact the drainage of the leg, only the most lateral lymphatics are

Table 13.2 Surgical Techniques for the Treatment of Lymphedema

Procedure	Level of evidence	Description of the technique	Indications	References
Liposuction	III	Circumferential suction of lymphedematous tissues	Applied in patients with moderate/severe lymphedema who have failed conservative management	(92,93)
Lymphovenous bypass	III	Anastomosis of collecting lymphatics to local veins	Applied in patients with early-stage lymphedema	(94–96)
Skin/subcutaneous tissue excision	IV	Direct excision of lymphedematous tissues	Applied in patients with severe lymphostatic elephantiasis	(97)
Flap transfer	IV	Transfer of vascularized tissues flaps to bypass obstructed areas	Applied in combination with other reconstruction techniques, such as breast reconstruction	(98)
Lymph node transfer	IV	Transfer of lymph nodes to damaged collecting lymphatics	Considered controversial and experimental	(99,100)
Lympholymphatic bypass	IV	Anastomosis of obstructed collecting lymphatics to nearby non-obstructed lymphatics	Applied in patients with early-stage lymphedema	(94,101)

collected. Intraoperatively, lymph node mapping with indocyanine green dye can lead to more selective VLNT lymph node collection (72).

Lymphaticovenous Anastomosis

LVA was first presented 40 years ago. This technique includes the anastomosis of lymphatic vessels with small venules in order to reduce lymphatic leakage. This permits the drainage of excess lymph so as to bypass areas of either reduced or completely obstructed lymph flow. The anastomosis of lymphatic vessels necessitates the use of microsurgical techniques as the majority of most lymphatics have a diameter that ranges from 0.1 to 0.6 mm (95,123–126). The identification of lymphatic vessels during the operation can be achieved with the injection of lymphazurin dye or with indocyanine green. Generally, the surgical risks of LVA are low because the lymphatics that are used for this procedure are superficial and only a small number of them are used for anastomosis.

Lymphaticolymphatic Bypass

Baumeister et al., in 1986, presented for first time a microsurgical technique involving the transfer of healthy lymphatic tissue from a donor area, preferably the inner area of the thigh and connecting the lymphatic vessels of the donor site to the lymphatic vessels of the affected limb (127). Such a procedure improves lymphedema in terms of both limb volumes and the lymphatic transport index. However, there is also the theoretical risk of new lymphedema at the donor collection site (128).

Suction-Assisted Protein Lipectomy

Suction-assisted protein lipectomy (SAPL) removes the excess solid volume remaining in the limb affected by lymphedema after the fluid component has been reduced with nonsurgical, conservative treatment. The procedure is performed under general anesthesia and excess fatty tissue from the affected area is aspirated using power-assisted liposuction cannulas. This particular technique has been shown to reduce large volumes of proteinaceous fatty tissue, with reductions in leg diameter of up to 86% after 1 year of follow-up (72). Moreover, some studies revealed further reductions over an 8–15-year period (93,129). The incidence of cellulitis is also decreased significantly (over 75%) after the SAPL procedure (72,130). After this approach, a specialized lymphedema therapist should be involved early on. Custom-fit compression garments must be placed immediately after the end of the surgical operation in the operating room. SAPL does not influence the pathophysiology of lymphedema and for this reason patients should continue compression in order to prevent lymphedema recurrence. Furthermore, custom-fit, flat-knit garments should always be re-measured as the volume decreases in the follow-up period. The safety of SAPL has been established and it has been shown that there is no further damage caused to the affected lymphatic flow area (131). Among the possible complications of SAPL are nerve damage, vessels disruption, and, rarely, further damage of lymphatic vessels (72).

The initial staging of lymphedema and the selection of the appropriate therapy are the key points in the treatment of lymphedema. It is suggested that patients whose lymphedema is in the fluid phase are treated with a technique that assists the drainage of fluid from the affected limb, such as VLNT, lymphaticolymphatic bypass, or LVA. These patients are typically in the early stages of the disease or may improve with CDT treatment. In patients whose lymphedema has progressed to the solid phase, treatment with SAPL is recommended in order to remove this excess solid proteinaceous fatty tissue. A delay in treatment may allow solid deposits of fatty tissue and may require patients to undergo SAPL treatment. It should be mentioned that VLNT or LVA procedures are less likely to succeed if they are used after SAPL (95,132). Likewise, SAPL does not present good results in ongoing lymphatic stasis and obstruction (72). Moreover, SAPL and VLNT procedures have been utilized in combination in a single-staged approach in order to manage chronic solid-phase lymphedema. In these cases, SAPL is initially performed to remove the proteinaceous solid fats and reduce the excess of volume. At this point, postoperative swelling stabilizes and VLNT is applied in order to improve lymphatic drainage. This aforementioned combined approach is reported to reduce volume by over 83%, while compression garment use is required only in the evenings and at night (133).

Concept of Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy is still new; however, it is now used as the standard of care in some institutes and can definitely be considered as an alternative to systematic bilateral inguinofemoral lymphadenectomy in cases of vulvar cancer when the patients are informed adequately (134). The sentinel procedure is performed in the early tumor stage and morbidity with a 2.3% rate of groin recurrence has been found by Van der Zee et al. (135). Obviously, by minimizing surgical aggressiveness, fewer postoperative complications are expected in the groin node area.

Urinary Stress Incontinence

Another serious complication that has been reported after radical vulvectomy with a combined removal of a portion of the urethra is the probability of severe urinary incontinence, with incidence, according to the literature, ranging from 22% to 100% (136). However, in another study, de Melo Ferreira et al. showed that patients undergoing surgical treatment for vulvar cancer postoperatively showed no decrease in urinary function (137). The presence of urinary incontinence was correlated with patient age and number of deliveries, but not with a history of surgery for vulvar cancer. A study where patients with radical vulvectomy and partial urethra removal were compared with patients without urethra resection did not demonstrate any significant differences regarding urinary incontinence rates between the compared groups (138). During urethrectomy, the urethral length is reduced, causing a decrease in urethral closure pressure and leading to urinary incontinence. Also, paraurethral fibrosis after a radical surgical treatment leads to decreased urethral mobility, resulting in intrinsic sphincter deficiency in the majority of cases. Nevertheless, the management of this condition includes utilization of a pubovaginal sling, artificial sphincter implantation, insertion of mid-urethra tension-free vaginal tape, and injection of bulking agents (139–141). The use of a pubovaginal sling is correlated with high perioperative morbidity, while artificial sphincter implantation has a high risk of discontinuation and complications (such as infection, erosion, and mechanical failure) (140,141). Additionally, the use of a mid-urethra tension-free sling in patients with vulvar cancer seems to be unreasonable due to the fact that these patients generally present severe paraurethral fibrosis and a

short urethra, combined with vulvar and vaginal retraction induced by previous radical vulvectomy. Nonetheless, only one case of the management of severe urinary incontinence after radical vulvectomy has been described in the literature (142). The presented case was treated with an Aldridge sling operation. Recently, the use of urethral bulking agents as a minimally invasive procedure for the treatment of urinary incontinence caused by intrinsic sphincter deficiency has also been proposed. The utility of these agents rests on narrowing the urethral lumen and inducing urethral coaptation during increased intra-abdominal pressure without variating the voiding pressure. Among the most common agents used are collagen, autologous fat, polytetrafluoroethylene, carbon-coated beads, and polydimethylsiloxane (141). The latter of these substances is a soft-textured, permanent implant of a safe, efficient, and long-term durable material (143). Also, polydimethylsiloxane can be implanted as an outpatient therapy with local anesthetic and with low morbidity, especially in patients with a high operative risk (ASA > 3) (American Society of Anesthesiologists [ASA] Physical Status classification) (141).

Vaginal/Introital Stenosis

Introital stenosis can be among the most unusual clinical complications related to the surgical management of vulvar cancer (144,145). The introital stenosis may be the consequence of extended fibrosis due to the primary closure of a large vulvoperineal defect, resulting in complete or partial compromise of sexual function. The surgical strategy regarding the vulvar reconstruction depends on the characteristics of the defect, the patient's general condition, and the availability of the donor site (144). Regarding the latter, there is a probability that the utilization of local tissues may be limited for repairing introital stenosis after a previous surgical operation. The use of a gracilis flap has been proposed in the past, even though the location of the pedicle limits the mobility of the flap and the visible postoperative donor scar restricts the application of this type of flap in clinical practice (146). In 1996, Yii and Niranjan proposed the lotus petal flap, which is an innovative surgical technique (147). A refinement of the lotus petal flap is represented by the use of perforating vessels that have rich arterial anastomoses around the perineum (148). Moreover, a further refinement of the lotus petal technique involves the utilization of subcutaneous vessels as the pedicle instead of the deep fascial layer, creating a thinner and more mobile flap (149). Among the advantages of this flap are its safety and the fact that it is easy as well as fast to perform. In addition, the lotus petal flap can also be used in the reconstruction of the labium in cases of both bilateral and hemilateral vulvectomy, offering a good cosmetic scar and preserving self-esteem, a fact that has great importance in young women (150).

Psychosexual Concerns

Studies on quality of life after surgical treatment for vulvar carcinomas are scarce. Regarding the sexual functioning in survivors of vulvar cancer, there are various studies with conflicting data (151). A number of studies have found no difference in sexual well-being and sexual satisfaction between women treated for vulvar cancer versus healthy women, while other authors reveal significant differences between the compared groups (137,152–154). However, numerous studies have revealed serious disturbances to women's sexual functioning after treatment (155–157). For example, a number of studies have reported reductions in psychological, social, physical, and sexual well-being in patients with gynecological cancers (151,158). Depression, decreased libido, reduction or complete absence of orgasms, and reduced sexual satisfaction may cause psychological vulnerability in women treated for vulvar cancer (156). These kinds of psychological changes can lead to emotional stress and have a negative impact on quality of life and, consequently, can cause relationship problems with partners (157). Old age and the extension of vulvar excision were associated with poorer sexual function and general well-being in women after surgical treatment for vulvar cancer (159). In a study of the quality of life of vulvar cancer patients after sentinel lymph node procedure alone or combined with inguinofemoral lymphadenectomy was reviewed, Oonk et al. analyzed and reported an increase in the patients' complaints regarding the presence of leg lymphedema after inguinofemoral lymphadenectomy, even though there was no difference shown in overall quality of life between the two studied groups (160). It has also been shown that in patients with vulvar cancer who were treated either with extensive or with less extensive treatment, there was no difference between the two groups regarding sexual function. Women treated with wide local excision in comparison to radical vulvectomy revealed an increase in quality of life functional scales (global health status and emotional and cognitive functioning) and in symptom scales (161,162).

CONCLUSION

Surgical approaches for vulvar cancer are still changing in order to minimize morbidity rates. Informed consent of the patient is essential in order to clarify the possible risks and complications of these approaches. In case of such complications, a multispecialty approach is necessary in order to minimize the consequences and improve patients' quality of life.

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14

Dermoscopic and confocal microscopy patterns of vulvar mucosal melanotic macules

Elvira Moscarella, Elisa Cinotti, Jean Luc Perrot, and Giuseppe Argenziano

INTRODUCTION

The differential diagnosis of pigmented vulvar lesions includes benign and malignant melanocytic proliferations such as nevi and melanoma, but also non-melanocytic skin lesions such as basal cell carcinoma, squamous cell carcinoma, and seborrheic keratosis. Moreover, non-proliferative entities marked by increased pigmentation may occur, the most frequent being benign melanosis (1,2).

Vulvar pigmented lesions are estimated to occur in 10%–12% of women (3,4). Because of overlapping clinical and histological features between malignant and benign processes, pigmented vulvar lesions are often challenging. In this chapter, we summarize the distinguishing clinical characteristics of vulvar melanotic macules. We include dermoscopy and reflectance confocal microscopy (RCM) features. These noninvasive imaging techniques may aid in the diagnosis of pigmented vulvar lesions.

Vulvar melanotic macules, also called melanosis, are the most frequent type of pigmented macule of the vulva. They usually occur in reproductive-aged women (2–5). The pathogenesis is largely unknown. When arising in children, the multi-system genodermatoses should be considered (6–10). Clinically, vulvar melanosis presents as single or, more commonly, multiple asymmetric macules or patches with variable shades of tan to black color, irregular and poorly demarcated borders, and variable sizes. A predilection for the mucosal surfaces rather than the keratinized, hair-bearing skin of the external genitalia has been observed (11–15). The labia minora and labia majora can both be involved. In a recent study, vulvar melanosis occurred more frequently on the labia majora as compared to melanoma, which is most commonly found on the labia minora (5).

DERMOSCOPY

Dermoscopy patterns have been described in four large studies and several reports (5,16–20). The most frequently detected pattern is the so-called ring-like pattern. Other common morphologies include homogeneous, parallel, reticular-like, and globular-like patterns (Figure 14.1).

The ring-like pattern is characterized by multiple round to ovoid structures, with regular hyperpigmented, well-defined borders arranged in a grape-like manner in some areas. At dermoscopic–pathological correlation, it is characterized by the presence of "skipped" areas of pigmentation at the top of the dermal papillae (Figure 14.2).

The parallel pattern is composed of linear and curved streaks, lines, or globules running parallel to the skin surface. This parallel pattern may have a fingerprint-like aspect. It is observed mainly in cases with epithelial hyperpigmentation without prominent melanocytic hyperplasia (Figure 14.3).

The homogeneous or structureless pattern shows a diffuse homogeneous brown to gray–blue pigmentation with no additional dermoscopic criteria. Histopathologically, a moderate to marked hyperpigmentation is observed along the basal cell layer, with no significant differences in the pigment distributions between the top and the bottom of the rete ridges (Figure 14.4).

The reticular-like pattern is similar to the pigment network observed in acquired-type nevi on skin. It does not show a typical honeycomb polygonal disposition, but a rather ovoid or round-shaped honeycomb. Histopathologically, it is correlated with the presence of melanin in the epidermal basal cells, with the lines of the network resulting from the projection of the pigmented rete ridges to the skin surface. The epidermis is hyperacanthotic, with thick, hyperpigmented epidermal crests with bridging of their base.

The globular-like pattern shows aggregated round to oval structures, tan to dark brown in color, similar to globules of melanocytic lesions. On histopathologic examination, the lesions show variable distribution of the melanin pigment along the epidermal basal layer and several melanophages in the dermis, with no increase in the number of melanocytes.

REFLECTANCE CONFOCAL MICROSCOPY

RCM features of vulvar melanosis show hyper-reflective keratinocytes at the epithelial–chorion junction (ECJ). These keratinocytes rim the dermal papillae that can be roundish (ringed pattern) and sometimes elongated (draped pattern) (21–26). Dendritic cells are a possible finding in the epithelium of more than a third of cases. They are small in size and mainly confined in the basal layer of the epithelium around the dermal papillae, rendering possible, in the majority of cases, a differential diagnosis with malignant melanocytes that are preferentially located in the suprabasal layer (pagetoid scattering). The presence of gray color in dermoscopy has been associated with dendritic cells in RCM. A recent study suggested that the presence of gray color on dermoscopy, considered as an alerting feature for melanoma, could be related to the presence of melanin-laden inflammatory cells in the superficial dermis on RCM and thus, when it is present as a "pure" feature not associated with other colors than brown or with atypical dermoscopic structures, is related to the diagnosis of melanosis (Figures 14.5 and 14.6) (25).

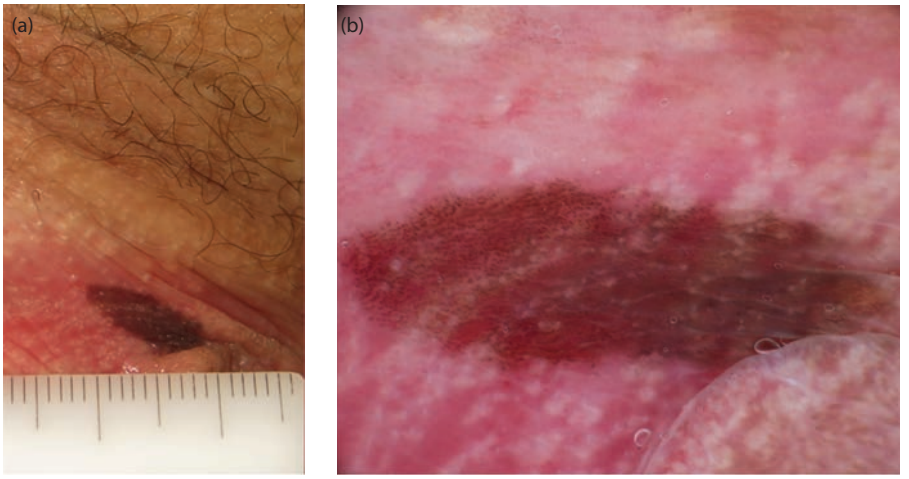

Figure 14.1 Clinical and dermoscopy picture of a vulvar melanosis occurring in a 60-year-old woman. (a) A flat, solitary, brown-colored macule of unknown duration. (b) In dermoscopy, a parallel pattern is detected, composed of lines and globules running parallel to the skin surface. A grayish coloration is visible on one side of the lesion.

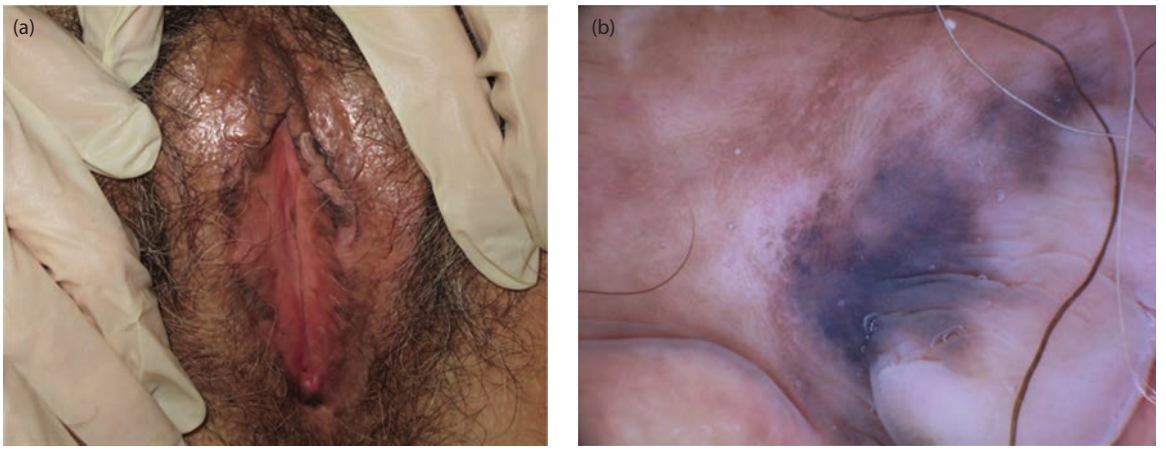

Figure 14.2 Clinical and dermoscopy picture of a vulvar melanosis occurring in a 70-year-old woman. (a) Multiple flat, brown to gray macules on the labia majora. (b) In dermoscopy, a parallel pattern is detected, composed of brown and gray lines parallel to the skin surface.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes mainly vulvar nevi and melanoma.

Vulvar nevi account for 23% of all pigmented vulvar lesions (1,2). A small subset of nevi with peculiar histopathologic features have been described, termed "atypical melanocytic nevi of the genital type" (AMNGT) (27,28). Vulvar nevi may present during childhood and they appear as symmetric macules and flat-topped or dome-shaped papules, ranging in color from pink to dark brown–black, or, rarely, blue. Common nevi are well demarcated with regular borders and uniform pigmentation. Compared with common vulvar nevi, AMNGT are more frequently located on the labia minora (5) and have an equal distribution between mucosal surfaces and hair-bearing skin of the external genitalia in adults. AMNGT may have alarming clinical features, such as dark pigmentation, irregular borders, and large size. The predominant dermoscopic patterns of vulvar nevi are the globular and homogeneous patterns (5). These can be difficult to distinguish from the globular-like and the homogeneous patterns of vulvar melanosis. However, when only brown to gray color is present with no other dermoscopic features, the diagnosis of a benign pigmentation should be favored (5,16–20). The globular pattern is defined by the presence of aggregated roundish to oval structures, tan to dark brown in color, corresponding histopathologically to dermal nests of melanocytes. The homogeneous pattern is characterized by the presence of homogeneous pigmentation in the absence of other dermoscopic structures. In AMNGT, a mixed pattern, defined as the combination of two or more dermoscopic patterns, has been observed most frequently. These lesions are frequently excised in order to exclude melanoma (5). Only two studies up to now have examined the RCM features of vulvar nevi (24,29). RCM showed focal cytological atypia and architectural irregularity without clear features of malignancy

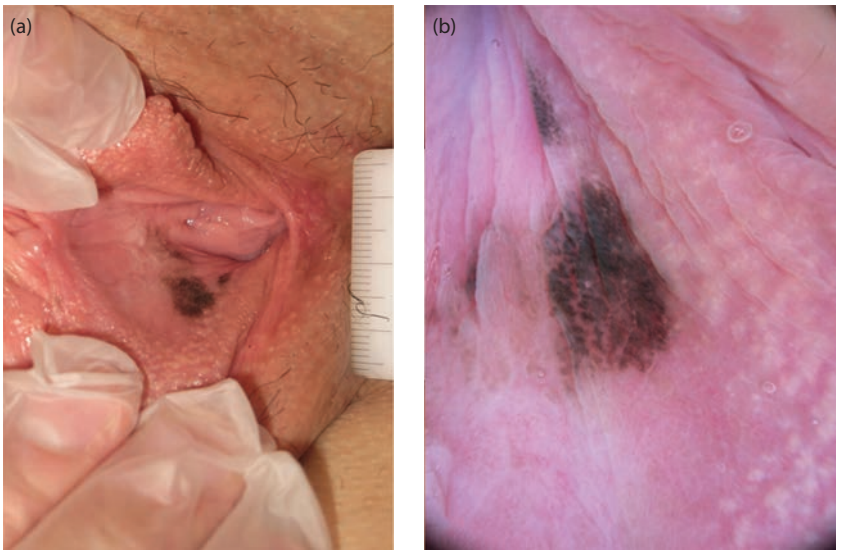

Figure 14.3 Clinical and dermoscopy picture of a vulvar melanosis occurring in a 40-year-old woman. (a) A flat, solitary, brown-colored macule of the vulvar mucosa. (b) In dermoscopy, a globular-like pattern is detected, composed of dark brown, aggregated, round to oval structures, similar to the globules of melanocytic lesions.

in the case of AMNGT (29). Further studies are needed in order to clarify RCM features of vulvar nevi.

Vulvar melanoma accounts for 2% of all melanomas in females (1–3). Most melanomas are located on the labia minora or clitoris (1). The disease can affect women of all ages, but is more common in the older population, with almost half of the patients aged 70 years or older, and a greater prevalence in the white population (almost 90% of cases) (30–34). It may present as macules, papules, or nodules of irregular coloration. Early stages of vulvar melanoma can be in differential diagnosis with benign melanotic macules. However, a recent study highlighted that in vulvar melanomas, a dermoscopic combination of blue, gray, or white color plus structureless zones is highly predictive of melanoma (19). In more advanced stages, a multicomponent pattern composed of irregular dots and globules, multiple colors, a blue–white veil, and atypical vessels can be found, similar to melanomas of the skin (19). *In vivo* RCM of mucosal melanoma is characterized by four major features: presence of pagetoid bright cells in the epithelium (mainly roundish or spindle shaped with a plump body); high density of basal hyper-reflective dendritic cells; loss of the normal architecture of the chorion papillae; and sheet-like proliferation of atypical cells in the chorion (21–23). The diagnosis of early invasive melanoma can be very difficult because the architecture of the epithelium and of the ECJ can be mostly preserved and only few atypical melanocytes can be observed in the epithelium. In these cases, melanocytes could have a similar size to keratinocytes, thus the differential diagnosis with vulvar melanosis can be challenging (21–23). Therefore, it is important to look for the presence of dendrites that characterize the melanocytes. However, hyper-reflective dendritic cells can also correspond to Langerhans cells, which are a frequent finding in inflamed and even normal mucosa. The differential diagnosis with melanoma is sometimes challenging because some melanoses present Langerhans cells around the chorion papillae and among the papillae, as well as in the upper layers of the epithelium (Figure 14.7). In melanoses, roundish, large, medium-reflective cells correspond to melanophages. When melanophages are present, they are usually numerous and can be distinguished from an initial spread of melanocytes towards the chorion because they are less reflective and are associated with edged papillae and a normal epithelium, which are not found in the case of invasive melanoma.

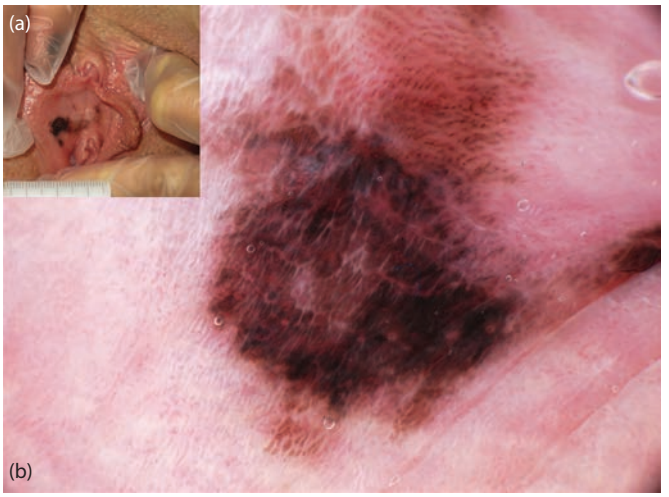

Figure 14.4 Clinical and dermoscopy picture of a vulvar melanosis occurring in a 50-year-old woman. (a) An irregular, flat, solitary, black to dark brown-colored macule of the vulvar mucosa. (b) In dermoscopy, a multicomponent pattern is detected, composed of dark brown to black globular-like structures, white lines in the center, and a ring-like pattern in the periphery. The lesion was showing more than one dermoscopic structure, color variegation from brown to gray and white color, and the presence of dotted vessels. A biopsy was performed that confirmed the diagnosis of vulvar melanosis.

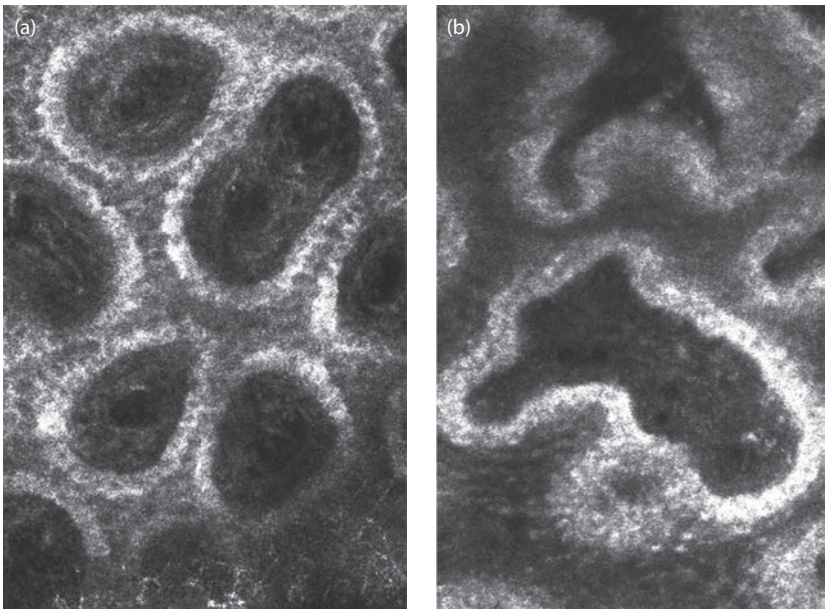

Figure 14.5 The reflectance confocal microscopy features of two typical patterns of vulvar melanosis. Viva images taken with a VivaScope® 3000 (Caliber Imaging & Diagnostics, Inc., Rochester, NY, USA) at the level of the epithelial–chorion junction. (a) In the ringed pattern, the keratinocytes rim the dermal papillae, which appear roundish. (b) In the draped pattern, the dermal papillae appear elongated and rimmed by regular keratinocytes.

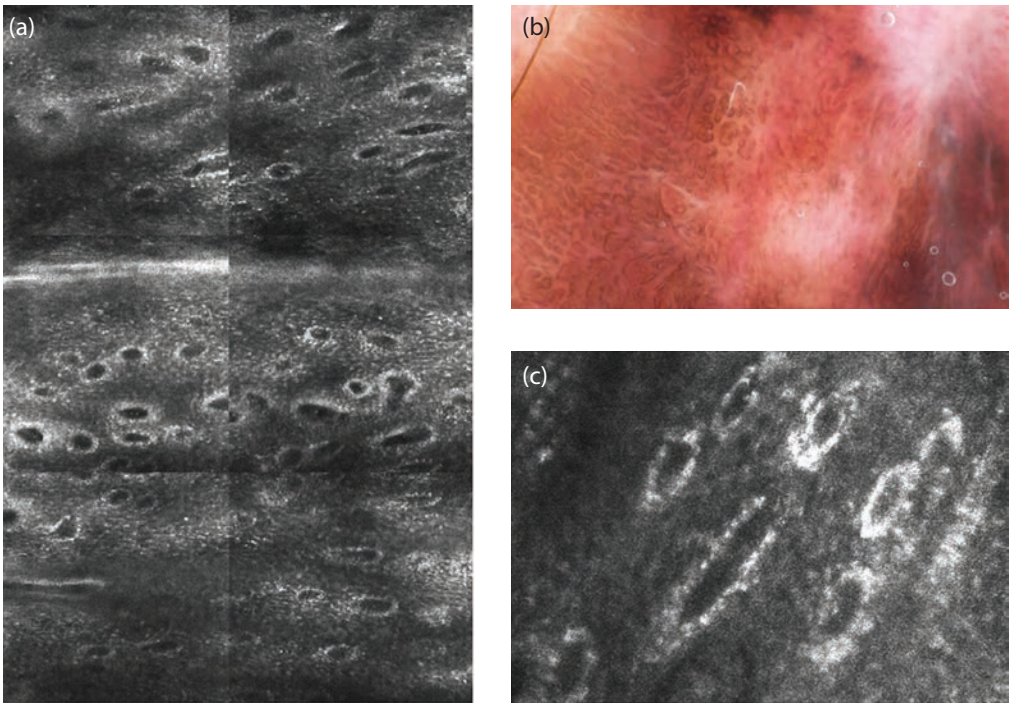

Figure 14.6 Dermoscopy and reflectance confocal microscopy images of a vulvar melanosis in a 53-year-old woman. (a) Mosaic image, taken with a VivaScope® 1500, at the level of epithelial–chorion junction, showing a ring-like pattern. Multiple bright scattered cells are visible, corresponding to melanophages. (b) Dermoscopy showing a ring-like pattern and blue–white structureless areas. (c) Single reflectance confocal microscopy image taken at the level of the epithelial–chorion junction showing ringed dermal papillae.

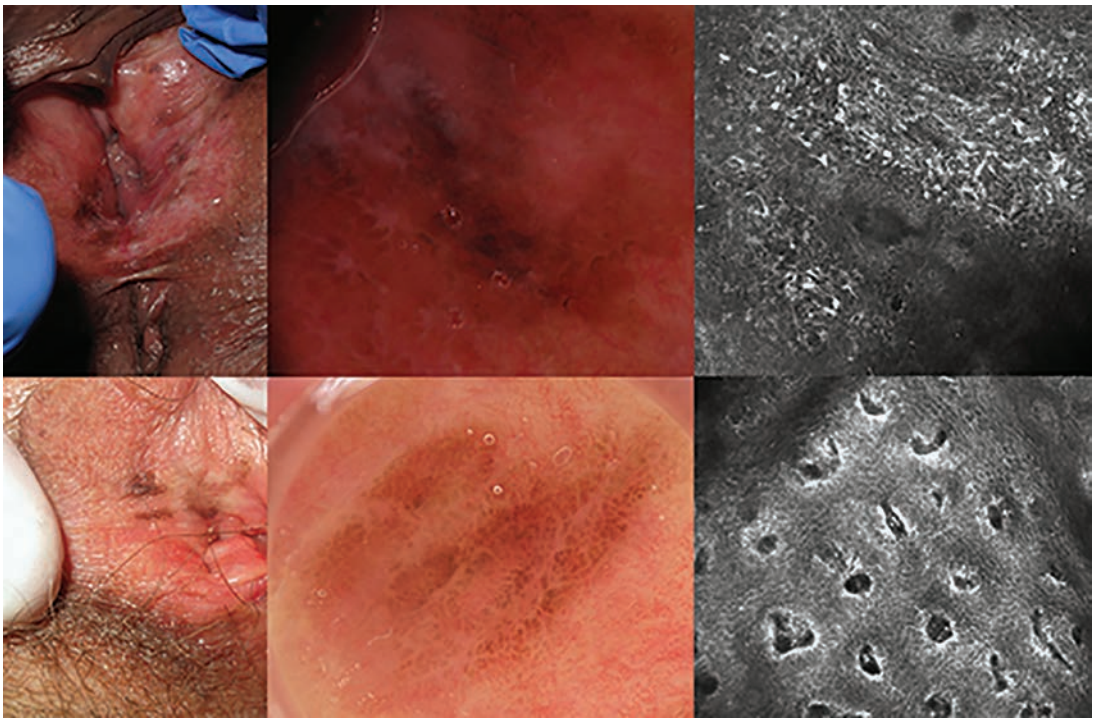

Figure 14.7 Clinical, dermoscopic, and reflectance confocal microscopy images of a melanoma with a 0.38-mm Breslow index (top) compared to a melanosis (bottom), both from the labia minora. Dermoscopy shows gray, white, and brown colors with structureless areas in the melanoma and a brown ring-like pattern in the melanosis. Reflectance confocal microscopy shows hyper-reflective polymorphic melanocytes in the upper part of the epithelium of the melanoma and hyper-reflective keratinocytes and dendritic cells corresponding to Langerhans cells around the chorion papillae at the basal layer of the epithelium of the melanosis.

Moreover, the presence of a homogeneous hyper-reflective rim around the papillae is usually not found in melanoma and favors the diagnosis of melanosis.

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Vulvar procedures

Biopsy and Bartholin abscess treatment

Allison Jackson, Danielle Cooper, and E. J. Mayeaux, Jr.

INTRODUCTION

The anatomy and histology of the vulva create a unique environment for dermatopathology. There are multiple benign, malignant, and premalignant lesions that can present in this anatomic region. The presence of three separate dermatologic tissue types and numerous structures in a small anatomic region can create diagnostic challenges. Dermatopathologies exhibit different characteristics on the modified mucous membranes and the squamous mucosa than they would on keratinized skin, and each skin type has different levels of susceptibility to various skin conditions and infectious agents (1). It is for this reason that good examination techniques, liberal use of biopsies, and consultation with a pathologist are key to the appropriate diagnosis and treatment of diseases on the vulva. The most common vulvar procedures performed include vulvar biopsy, Bartholin's abscess treatment, and treatment of condyloma. With appropriate counseling and anesthetic technique, these procedures are effective and very well tolerated.

Understanding the anatomy of the vulva is fundamental to the successful diagnosis and treatment of lesions. The borders of the vulva are the mons pubis anteriorly to the anal area posteriorly, and the crural folds bilaterally (Figure 15.1). Keratinized, hair-bearing skin extends from the crural folds to the medial edges of the labia majora. From the inside fold of the labia majora, partially keratinized, modified mucous membrane proceeds to Hart's line, which marks the transition to squamous mucosa. This mucosa covers the vestibule and continues into the vagina. Further anatomic detail is discussed in Chapter 1.

Histologically, the vulva is made up of keratinized skin, partially keratinized skin, and mucosa. The Bartholin's glands are pea-sized glands located bilaterally at the 5 and 7 o'clock positions that drain into the vestibule. The body of the gland is composed of mucinous acini that lead to a duct that is predominantly transitional epithelium. This continues to orifices lined with squamous epithelium that are contiguous with the epithelium of the vulvar vestibule (2). These glands are mucous secreting and serve to lubricate the introitus.

VULVAR BIOPSY

When to Biopsy

Liberal use of biopsy is indicated when evaluating vulvar lesions. Indications for vulvar biopsy include (1,3):

- Any pigmented lesion that is not stable in size and clearly identifiable as benign
- Any lesion that is concerning for dysplasia or malignancy
- Any unidentified vulvar mass
- Any unidentified inflammatory or bullous skin disorders
- Any lesion of uncertain etiology or atypical in appearance
- Any lesion that does not respond appropriately to therapy

Adequate visual inspection of the vulva can be accomplished with a good white light and magnifier such as a handheld magnifying glass or colposcope (3). Application of acetic acid (3%–5%) for a minimum of 5 minutes will have the same effect on the keratinized skin of the vulva as it has on the cervix, vagina, and mucous membranes (1). Those cells with higher nuclear:cytoplasmic ratios will stand out as white lesions that should be biopsied. Diffuse acetowhitening may be due to inflammation, in which case a good history for inflammatory diseases or infections should be obtained (1).

Selection of Biopsy Type

Once the decision to biopsy has been made, consideration must be given as to which type of biopsy to perform. The technique used should take into consideration the character of the lesion and the location of the most active pathology. A Keyes punch removes a circular piece of epithelium and often some underlying fat. This technique is good for flat or slightly raised lesions, inflammatory lesions, and scarring lesions. Raised or pedunculated lesions may be easily sampled or removed entirely with scissors, cervical biopsy forceps, or shave procedures. If malignant melanoma is suspected, a punch trephine large enough to excise the entire lesion or an excisional biopsy is preferred in order to maximize tissue sent for pathologic analysis (4). Full excisions are performed using a scalpel, but shave biopsies may be performed with a scalpel or skin blade.

In general, the most abnormal-appearing area (darkest, most raised, or most irregular contour) is the best place to sample (3). When sampling ulcerative, sclerotic, or inflammatory lesions, a biopsy at the edge of the lesion that includes normal skin in the sample will improve diagnostic accuracy, as this is generally where the most active disease is present (1). Including a detailed description of the lesion or photograph can be helpful to the pathologist, especially in more challenging cases. A significant number of vulvar intraepithelial neoplasia (VIN) 2 and 3 cases may be underdiagnosed by single biopsy; therefore, sampling of multiple sites is encouraged (5).

Anesthesia

The vulva is not only a sensitive area on which to perform procedures, but abnormalities of this anatomic region will often cause psychological distress for the patient. For these reasons, patient comfort and adequate counseling is imperative.

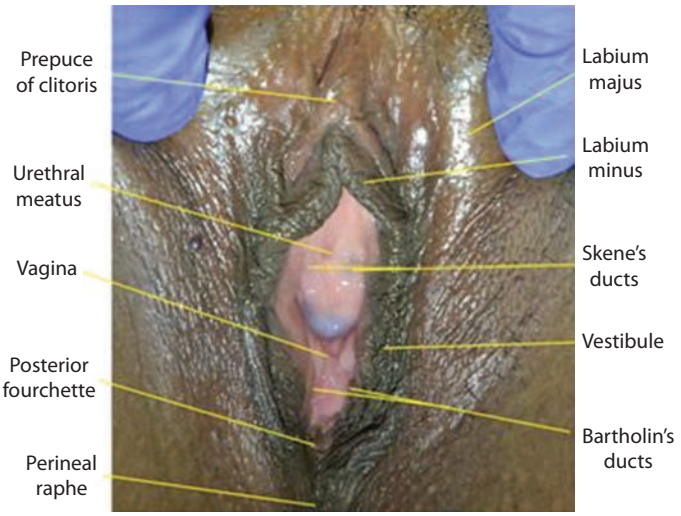

Figure 15.1 External anatomy of the vulva.

A combination of topical and local anesthetic will provide adequate anesthesia and allow for a generous and typically diagnostic biopsy.

If the patient is unable to tolerate local anesthetic injection, topical lidocaine 2.5%/prilocaine 2.5% cream or lidocaine 10% cream can be applied over keratinized skin in a thick layer for 30 minutes prior to the procedure. Less time is needed if applied to the mucous membrane (6). Ice or ethyl chloride topical refrigerant may also be effective in numbing the skin for the local anesthetic administration.

For a punch or shave biopsy, the skin should be infiltrated with lidocaine 1% or 2% with a 30-gauge needle to create a bleb in the dermis (not subdermal). Subdermal anesthetic injections are often effective, but take much longer to work and give less reliable anesthesia. Although intradermal anesthesia injections sting a little more, they provide extremely dense anesthesia and almost never fail. They also expand the dermis, which is particularly good for shave-type excisions (7,8). For most biopsies, 0.5–1.0 mL is sufficient (maximum of 4 mg/kg). Lidocaine with epinephrine is usually used (except on the clitoris) to aid in vasoconstriction for hemostasis and to prolong anesthetic action. The anesthetic effects of the intradermal injection are almost instantaneous and allow generous time for completing an uncomplicated biopsy (4). The lidocaine can be buffered by adding one part 1 mEq/mL of sodium bicarbonate to nine parts 1%–2% lidocaine solution. This will decrease patient discomfort during injection (9). Do not buffer the lidocaine in the vial, since it is less stable on the shelf at the more basic pH (10).

The skin should be prepared with an antiseptic solution such as alcohol, povidone-iodine or chlorhexidine (3). Preoperative shaving for hair removal is associated with higher rates of surgical site infections (11,12). If necessary, clipping hair immediately before a surgical procedure has the lowest rates of associated infection and should be considered to be the preferred preparatory activity for any presurgical hair removal.

Punch Biopsy

The Keyes punch is a circular blade (trephine) that is pressed into the anaesthetized skin and rotated back and forth in a clockwise and counterclockwise fashion until the blade has passed through the dermis into the subcutaneous fat. The sizes available range from 2 to 8 mm, although 3- and 4-mm punches are the most commonly used (Figure 15.2) (3). An intradermal anesthetic injection is performed and the skin is prepared with an antiseptic solution. Use a back-and-forth motion with mild pressure to create the specimen (Figure 15.3), then forceps or a needle can be used to gently lift the specimen free of surrounding tissue (Figure 15.4) and cut it at the base (Figure 15.5). Take care not to crush the sample with the forceps. Depending on the size of the defect created, hemostasis can be obtained with pressure, Monsel's solution, aluminum chloride, or a suture. Monsel's solution should be avoided in pigmented lesions that may require repeat biopsy since it may leave a pigmented artifact that can cause diagnostic problems (4). With biopsies

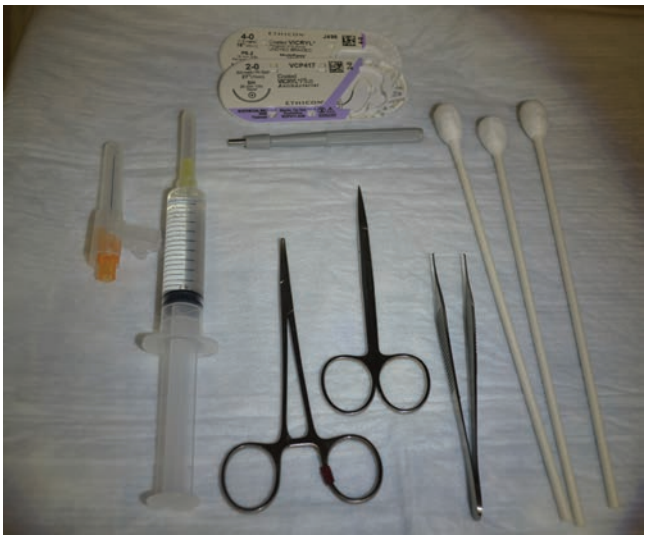

Figure 15.2 Typical set up for punch biopsy including anesthetic, a 3-mm Keyes punch, scissors, forceps, swabs, or gauze, and possibly suture material.

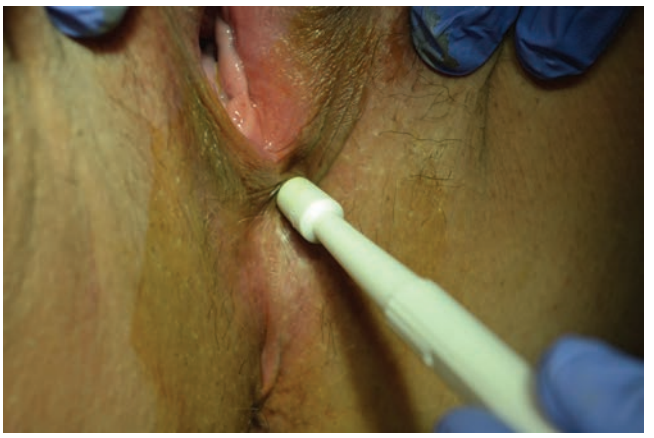

Figure 15.3 Create the specimen by using downward pressure and a back-and-forth motion until a "give" is felt as the trephine passed into the subcuticular fat.

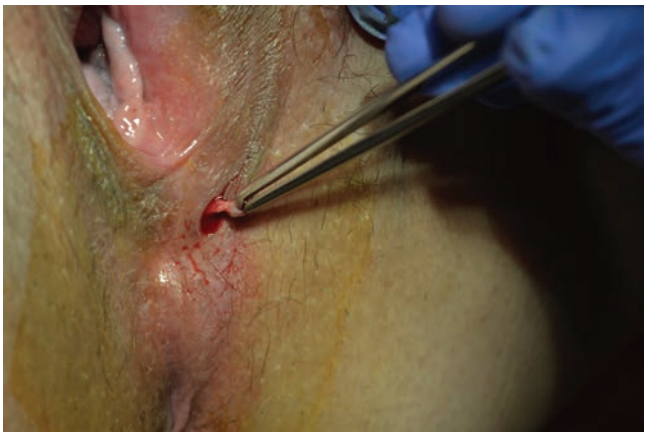

Figure 15.4 Forceps or a needle can be used to gently lift the specimen free of surrounding tissue. Take care not to crush the tissue, since this makes histological diagnosis more difficult.

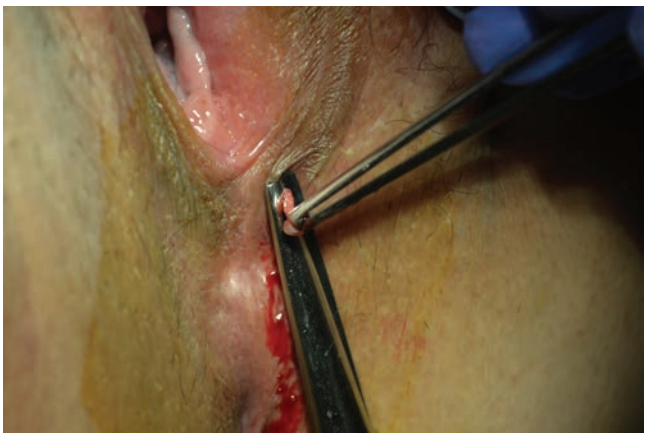

Figure 15.5 If the specimen does not come free on its own, use scissors or a blade to cut it below the level of the dermis.

>3 mm, post-procedure cosmesis is better with suture closure (Figure 15.6) (13). These rounded biopsy sites are easier to close if elliptical in shape, which can be accomplished by stretching the skin perpendicular to the lines of least skin tension as the punch biopsy is being performed (8). Vicryl® (Ethicon, LLC, Cincinnati, Ohio, USA) sutures are better tolerated on the vulva than more stiff sutures, which can irritate the sensitive skin (3). Silk sutures cause more inflammation.

Shave Biopsy

Shave biopsy is used to obtain partial-thickness tissue for histologic examination and is useful for removing superficial lesions in their entirety. Pedunculated lesions above the skin surface are particularly well suited for shave excision, but other types of lesions that are not deep in the dermis can be removed by shave technique (14). Shave procedures are quick, require little training, and do not require sutures for closure. A small, slightly depressed scar about the size of the initial lesion often results (15).

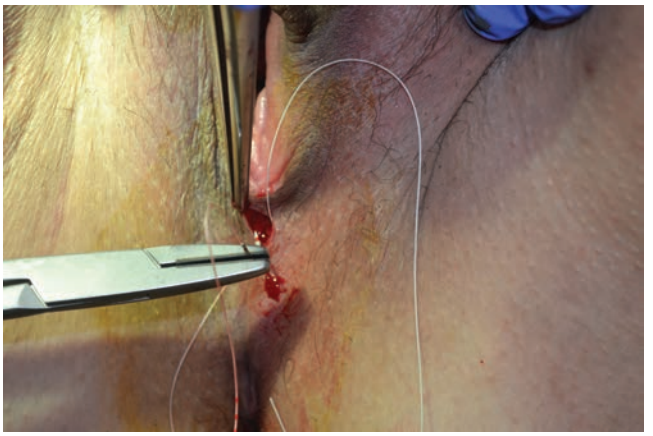

Figure 15.6 Biopsies >3 mm have better post-procedure cosmesis with suture closure, which can also produce excellent hemostasis and less post-procedure pain.

A shave biopsy can be accomplished using one of four techniques. A no. 15 or 22 scalpel blade may be held horizontally in the hand or on a handle to cut below the lesion. This method provides good control of depth. Excision with a flexed razor blade, including modern devices that put the blade in a holder, is safe and easy to perform. Scissor excision can be effectively used to remove lesions and is particularly useful for elevated or pedunculated lesions. Radiosurgical loop or needle removal is effective, but requires more expensive equipment and more training.

Shave biopsy should be performed deep enough to remove the entire lesion but shallow enough to prevent significant damage to the deep dermis. For smaller lesions, shave excision can be performed with scissors. Forceps can be used to elevate the lesion and scissors can be used to excise the lesion in its entirety. Alternatively, a suture can be placed through the lesion and used to elevate the lesion away from the skin, which can then be snipped off at the base with scissors (6). If neither of these methods will completely remove the lesion, a full-thickness excision will be necessary. The deeper the damage in the skin, the more likely scar formation will leave a noticeable, sometimes hypopigmented scar. Depressed scars can result after this technique. If a scoop defect is created, the edges can be feathered (i.e., smoothed) to blend the color change into the surrounding skin.

Historically, it was not recommended to perform shave biopsy on pigmented lesions due to the possibility of transecting a melanoma. The American Academy of Dermatology guidelines for the management of primary cutaneous melanoma states that the ideal method to diagnose a possible melanoma is to perform a narrow-margin excisional biopsy that encompasses the entire breadth of the lesion with clinically negative margins, and to a depth that is sufficient to ensure that the lesion is not transected. This can be accomplished by a fusiform (elliptical) or punch excision or a shave removal to a depth below the anticipated plane of the lesion. This saucerization shave (scoop or deep shave) is more commonly used when the suspicion of melanoma is low and the lesion lends itself to complete removal by this technique (16). Both the shave and punch biopsy have been found to be equally effective in diagnosing subtypes of basal cell carcinoma (17).

Relative contraindications include (18):

- Skin appendage lesions (e.g., cylindromas and epidermoid cysts), should be full thickness
- Subcutaneous lesions (pathology often missed by shave technique)
- Epidermal nevi (removal requires full-thickness excision)
- Local infection
- Severe bleeding disorders (relative)
- Patients on warfarin or clopidogrel (relative)

Procedure

Prepare the site with isopropyl alcohol, povidone-iodine, or chlorhexidine gluconate (11,12). Infiltration of local anesthetic into the dermis can aid in achieving the appropriate depth of biopsy. Intradermal anesthesia thickens the skin, making it less likely that the shave will penetrate the dermis into the subcutaneous fat. Unintentional penetration into the subcuticular layer should prompt transforming the biopsy into a full-thickness fusiform (elliptical) excision. The blade is brought under the base of the lesion with a slight back-and-forth movement until the lesion is removed, leaving a crater in the dermis. For pigmented lesions, the blade should pass through the deep dermis. Lesion removal can sometimes be facilitated by elevating and squeezing the surrounding skin.

Small, pedunculated lesions can be removed easily with scissors. The skin is stretched with the non-dominant hand, and the lesion is removed with sharp scissors. Small lesions can be removed without local anesthesia or with brief application of a skin refrigerant. The scissors must be flush with the skin surface to prevent leaving a residual stump.

Radiosurgical loop excision can be used to perform a shave biopsy. After intradermal anesthesia is placed, the loop or bent wire is activated and moved beneath the lesion until it is excised. The radiosurgical current can be set to provide hemostasis to the wound base if needed.

The wound base can be treated with pressure, coagulation, fulguration, 10%–20% aluminum chloride, or ferric subsulfate (i.e., Monsel's solution) for hemostasis. All of these methods should be applied to a dry wound bed, so the blood must be wiped away and the treatment applied immediately after. White petrolatum (not antibiotic ointment) and a bandage are then applied (18).

Follow-Up

The dressing may be removed in 12–24 hours and cleaned with soap and water once or twice daily. After cleaning, the wound should be covered with the occlusive ointment to promote moist healing. In a randomized trial, similar rates of infection were found in patients who used white petrolatum compared with those who applied bacitracin for postoperative wound care following dermatologic procedures. Therefore, to avoid potential contact dermatitis, use of petrolatum for dressing clean wounds is preferred over antibiotic ointment (19). Histologic evaluation results of the shave specimen should be reported to the patient. If the evaluation of a benign growth reveals that the specimen margin was positive, the lesion can be closely followed or re-excised. Specimens that reveal positive margins for malignancy should prompt re-excision.

Excisional Biopsy

Excisional biopsies are performed for lesions that cannot be adequately sampled due to their size, location, or depth, as well as any lesion that needs to be removed in its entirety for diagnostic or therapeutic purposes. For smaller lesions, excision can be performed completely with a Keyes punch.

Procedure

Use a skin marking pen to outline the planned incisions in a fusiform (elliptical) shape around the lesion to be excised. The long axis of the incisions should be made parallel to the skin tension lines and with a 2–5-mm margin of normal skin (4,20). A no. 15 scalpel blade is used to make an incision in the skin through the entire thickness of the epidermis and dermis, into the subcutaneous fat. The blade should be placed at a slight angle away from the lesion below the dermis to undermine the skin and make closure of the defect easier. The specimen should be gently lifted out, cut away from the subcutaneous layer, and placed in a fixative (20).

Closure of the defect will depend on the size of the lesion. For larger biopsies, two-layer closures provide better cosmesis and decrease the risk of wound dehiscence (21). Interrupted absorbable sutures should be placed in the subcutaneous tissue. If this layer is closed correctly, the skin edges should fall together nicely, allowing the skin sutures to merely provide wound stability. To close the skin, interrupted sutures or a subcuticular stitch will both provide adequate closure.

For interrupted sutures, use a small-gauge nylon suture placed in an interrupted fashion spacing the sutures evenly and taking care to not tighten the sutures so that the skin edges blanch. Blanching is a sign of tissue ischemia and may lead to suture marks and scarring (21). For a subcuticular stitch, run an absorbable suture in the subcuticular space for the length of the wound. This type of closure is especially beneficial in patients with keloid tendencies or in areas of fragile skin (21).

If considerable skin tension is present despite a two-layer closure or where a two-layer closure is inappropriate, vertical mattress sutures may be placed. For these closures, use a small-gauge nylon suture to place a wide stitch across the wound, then a smaller stitch back across the same area. These sutures are tied down on the same side of the wound as the entry site and are helpful in closing wounds with significant skin tension (20,21).

Follow-Up

Tape strips may be placed across the wound to provide support and decreased skin tension if present. The wound may be left exposed to air or covered with a dressing or bandage. Dressings should be changed once or twice daily by the patient for the first 24–48 hours, at which point they should no longer be needed. The patient should be instructed to keep the area clean and dry. A barrier protectant such as petrolatum may be used to prevent crust formation and promote wet healing (4). Follow-up evaluation within 1–2 weeks is generally accepted for re-examination of the surgical site and discussion of pathology.

BARTHOLIN CYST AND ABSCESS TREATMENT

Anatomy of the Bartholin's Gland

The Bartholin's glands are located at 5 and 7 o'clock at the vaginal introitus and normally cannot be palpated. Bartholin's gland cysts develop from dilation of the duct after blockage of the duct orifice, usually by trauma or inflammation (Figure 15.7). Cyst or abscess formation occurs in 2% of all women (3,22). These lesions usually are 1–3 cm in diameter and usually are asymptomatic. When symptoms occur, the patient may report

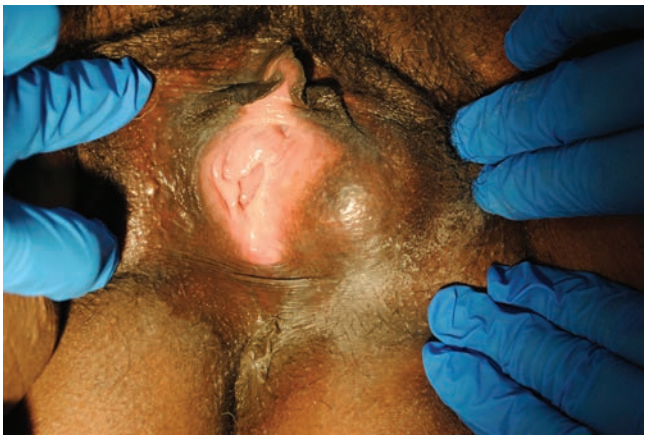

Figure 15.7 Left Bartholin's gland cyst with swelling but no erythema.

vulvar pain, dyspareunia, inability to engage in physical activity, or pain during walking or sitting. The glands' secretions provide some moisture for the vulva, but are not necessary for sexual lubrication. Removal of a Bartholin's gland does not compromise the vestibular epithelium or sexual functioning.

Pathology of Abscess Formation

An abscess forms in a Bartholin's cyst when the cavity is inoculated with local flora and obstruction is present (Figure 15.8). The abscess usually develops over 2–4 days and can become larger than 8 cm in diameter. On examination, there will be a large, tender mass in the vestibule with associated vulvar erythema and edema (23). If left untreated, spontaneous drainage will occur by days 4–5. Culture of the abscess will yield polymicrobial flora similar to vaginal flora (24). Patients may experience severe dyspareunia, difficulty in walking or sitting, or vulvar pain, sometimes to the point of incapacitation. They may also experience more systemic signs such as myalgias, fever, and chills. Rectovaginal fistula formation secondary to Bartholin's cysts or abscesses is a very rare complication (25).

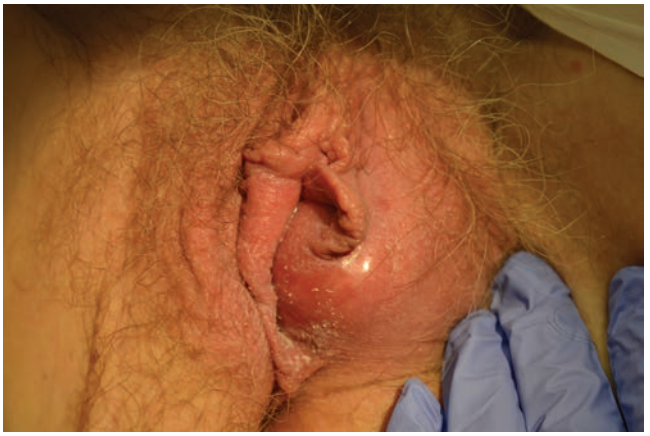

Figure 15.8 Left Bartholin's gland abscess with swelling, erythema, and pain.

Options for Treatment

The best method for treating a cyst or abscess is one that preserves physiologic function with minimal scar formation. When treating an abscess, consider obtaining nucleic acid amplification testing or cultures for gonorrhea and chlamydia; however, sexually transmitted infections are no longer thought to be the most common causes of Bartholin's abscesses. More recent evidence points to methicillin-resistant *Staphylococcus aureus* and *Escherichia coli* as the most common pathogens (26). Consider broad-spectrum antibiotic therapy if the patient has significant risk factors for severe infection, such as diabetes or immune compromise, or if clinical findings indicate a severe infection.

There are many treatment options for symptomatic Bartholin's cysts or abscesses, including simple drainage, fistulization (such as with a Word catheter), marsupialization, or excision of the gland (27). Treatment is not contraindicated in pregnant women, although the increase in blood flow to the pelvis during pregnancy may lead to excessive bleeding from any procedure. If treatment is necessary because of abscess or discomfort, local or regional anesthesia should be considered and most broad-spectrum antibiotics are safe. Simple incision and drainage provides prompt symptomatic relief, but recurrence is common (23). Following incision in the cyst, the wall may be ablated with a stick of crystalloid silver nitrate inserted into the cavity (28). Healing usually occurs within 10 days. Treatments using loops of plastic tubing and carbon dioxide laser have also been described (29,30).

In the 1960s, Dr. Word introduced a simple fistulization technique using a small, inflatable, self-sealing, bulb-tipped catheter (Figure 15.9) (31). The catheter is placed following incision and drainage to allow formation of the fistulous tract in order to maintain future drainage. The recurrence rate is between 2% and 15% (32,33). Other options for the treatment of a Bartholin's gland abscess include the marsupialization or "window" procedure, carbon dioxide laser excision, or surgical excision. The marsupialization procedure is a relatively straightforward procedure that can be performed in the office or in the outpatient surgical suite. It can be used as a primary treatment or can be used if a cyst or abscess recurs after treatment with a Word catheter. The recurrence rate after marsupialization is less than with Word catheter use (27). The Word catheter has been found to be easy to use and well tolerated for the treatment of Bartholin's cysts and abscesses, with few to no serious side effects and little impingement of sexual health (33,34).

Figure 15.9 Word catheter (a fistulization device consisting of a small, inflatable, self-sealing, bulb-tipped catheter).

A cyst that has recurred several times despite office-based treatment may require excision, especially if the patient is over 40 years of age (23,35,36). Excision of a Bartholin's gland cyst is an outpatient surgical procedure that should be performed in an operating suite by an experienced physician because of the possibility of copious bleeding from the underlying venous plexus. Excision is usually performed under general anesthesia. It can result in intraoperative hemorrhage, hematoma formation, secondary infection, and dyspareunia due to scar tissue formation.

Contraindications include:

- Acutely, severely inflamed abscess (relative contraindication)
- Asymptomatic cysts (relative contraindication)
- Latex allergy (e.g., to Word catheter)

Word Catheter Placement

Anesthesia

Apply field block anesthesia by injecting 1%–2% lidocaine with or without epinephrine around and under the cyst or abscess (Figure 15.10). Use caution not to inject directly into the lesion, as this will yield ineffective anesthesia and can also cause the lesion to rupture. Prepare the area with organified iodines. It may cause less pain to simply incise without anesthesia an abscess that has very attenuated overlying skin.

Procedure

Use a stab incision with a no. 11 or 15 scalpel blade to make a 1.0–1.5-cm deep opening into the cyst, preferably just inside or, if necessary, just outside the hymenal ring (Figure 15.11). Do not make the incision on the outer labium minus or labium majus. The resulting scar may cause pain, a poor cosmetic result, or a permanent fistula. Do not extend the incision beyond the width of the blade, or the catheter will require a retention stitch. Break up any loculations with a hemostat or similar instrument (Figure 15.12).

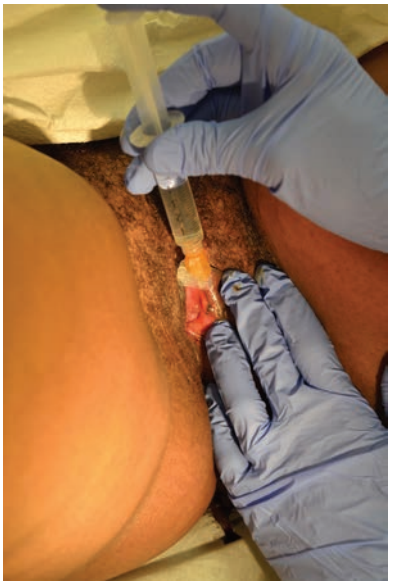

Figure 15.10 To start a Word catheter fistulization procedure, apply field block anesthesia by injecting 1%–2% lidocaine around and under the lesion. Some patients and providers may opt do a quick incision without anesthesia.

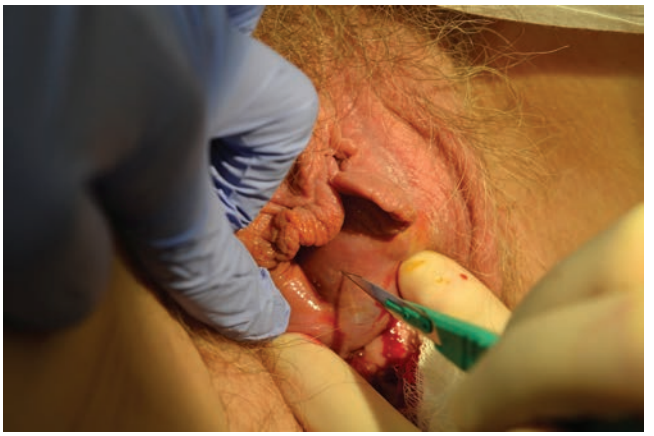

Figure 15.11 Make a stab incision with a no. 11 or 15 scalpel blade to create an opening into the cyst just inside the hymenal ring.

Insert the Word catheter (Figure 15.13). After the tip is inserted through the incision, the bulb is inflated with 3–5 cc of water or lubricating gel, and the free end of the catheter is tucked into the vagina (Figure 15.14). Use water or gel rather than air to prevent premature deflation of the balloon. Leave the catheter in place for 4–6 weeks to permit complete epithelialization of the new tract. The patient may take daily baths or showers and gently cleanse the area with soap and water. If the catheter falls out, it can be put back in if noticed immediately.

Follow-Up

Instruct the patient to return in 4 weeks for a follow-up examination or sooner if she experiences discomfort, swelling, or other symptoms of infection. Patients may use a nonsteroidal anti-inflammatory pain reliever such as ibuprofen (400–800 mg taken every 6 hours) for discomfort in the immediate

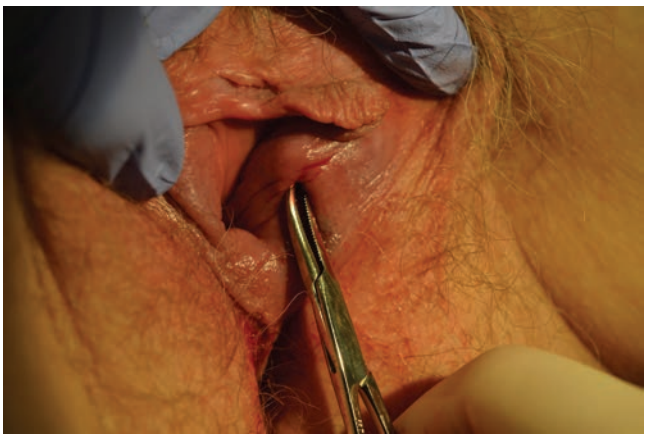

Figure 15.12 Break up loculations with a hemostat or probe.

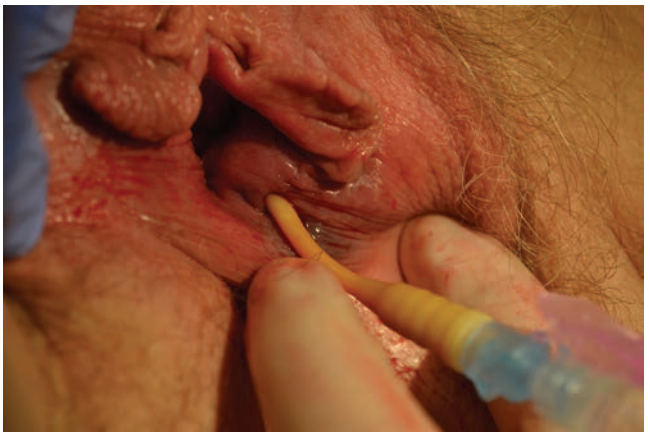

Figure 15.13 Insert the Word catheter tip through the incision and inflate the bulb with 3–5 cc of water or lubricating gel.

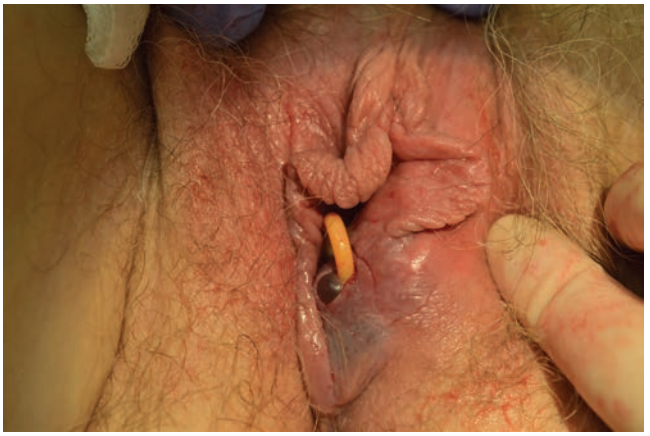

Figure 15.14 After the bulb is inflated, tuck the free end of the catheter into the vagina.

postoperative period, and they should refrain from intercourse during the healing time to prevent displacement of the catheter. The catheter is removed by deflating the balloon and, over time, the resulting orifice will decrease in size and become unnoticeable (3).

Marsupialization

Marsupialization may be used to treat an enlarged or painful Bartholin's cyst or abscess. It is used preferentially for recurrent Bartholin's cysts or abscesses after previous Word catheter treatment. The main advantage of marsupialization over Word catheter placement is less associated postoperative discomfort.

Procedure

Marsupialization is more commonly performed in the outpatient surgical suite, often with regional anesthesia utilizing pudendal block, spinal block, or general endotracheal anesthesia depending on the anxiety of the patient (37,38). When performed in the office, a field block with local lidocaine injection similar to that used for fistulation is effective. Place the patient

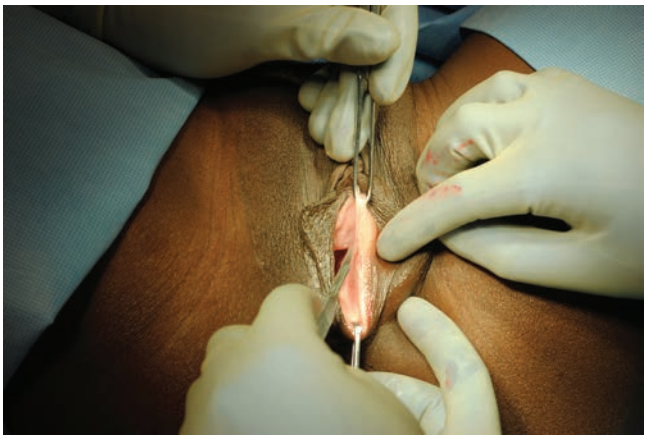

Figure 15.15 To start a marsupialization, apply a field block and make a fusiform (elliptical) incision adjacent to the hymenal ring.

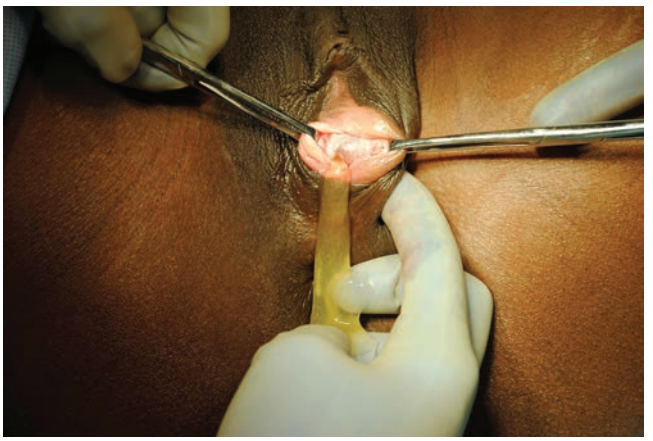

Figure 15.16 Non-purulent drainage from an incised cyst.

in the dorsal lithotomy position, preferably using candy cane stirrups for adequate exposure. Prepare the vaginal and vulvar areas and make a fusiform incision using a no. 15 blade adjacent to and immediately outside of the hymenal ring (Figure 15.15). Do not make the incision on the outer labium minus or labium majus. The incision should measure about 2 cm long and should be deep enough to enter the cyst. Remove an oval wedge of vulvar skin and the underlying cyst wall. The cyst or abscess will drain once it has been unroofed (Figure 15.16). Grasp the cyst wall and adjacent vestibular tissue with Allis clamps and break up loculations inside the cyst if present (Figure 15.17). Irrigate the area with sterile water or saline. The lining of the cyst is everted and sutured to the adjacent vestibular skin using interrupted 2-0 or 3-0 absorbable (Vicryl®) sutures (Figure 15.18). The new tract will slowly shrink over time and epithelialize, forming a new, larger duct orifice. If bleeding occurs, use suture placement or direct pressure for hemostasis of the skin edge.

Follow-Up

For marsupialization, have the patient take hot sitz baths starting on postoperative day 2 or 3. Advise use of oral pain medication such as ibuprofen, acetaminophen, or an appropriate

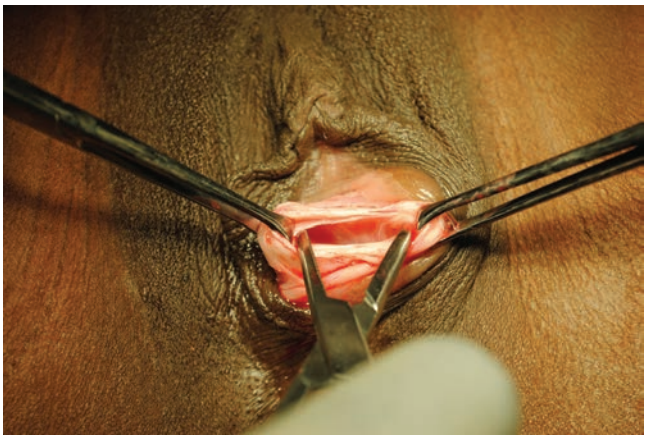

Figure 15.17 Grasp the cyst wall with Allis clamps and break any loculations inside the cyst.

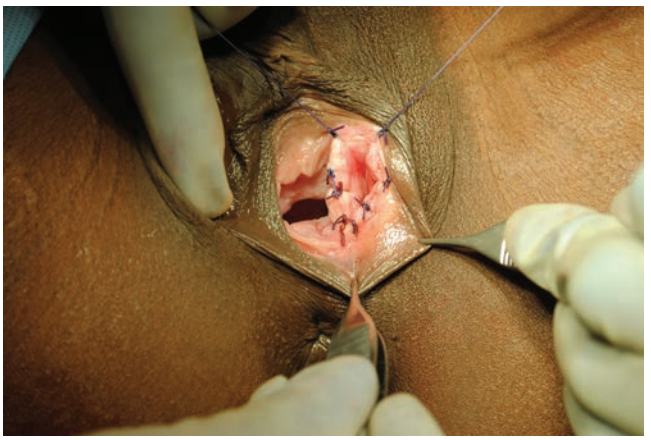

Figure 15.18 Suture the lining of the cyst wall to the adjacent vestibular skin using interrupted absorbable sutures.

narcotic if pain is severe. Antibiotics are not routinely prescribed for Bartholin's gland cysts or abscesses unless there is evidence of cellulitis. Antibiotic administration has not been shown to prevent recurrence (39). Have the patient return to the clinic 4 weeks postoperatively to ensure adequate healing, at which point she may resume sexual intercourse. Complications may include poor healing, recurrent cyst/abscess, scarring, bleeding, and infection/septic shock (with incision of abscess). Rare case reports exist of necrotizing fasciitis after abscess drainage (27).

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Condyloma

James Cook, James Ferguson, and E. J. Mayeaux, Jr.

INTRODUCTION

Condyloma, from the Greek for "knuckle," refers to papular genital wart-like growths. Condyloma lata refers to those lesions associated with secondary syphilis. Condyloma acuminatum (single genital wart) and condylomata acuminata (multiple genital warts) (1) are caused by human papilloma virus (HPV) and are often referred to simply as condyloma, or genital warts. Genital warts are far from a new condition. Greek physicians and writers have been documenting genital warts since the ancient world. The fifth-century Byzantine physician, Aetius of Amida, described two different types of genital warts and referenced the Greek authors Philoumenos from the third century and Aspasia from the second century CE (2).

ETIOLOGY

Genital warts are productive vegetative manifestations of an epithelial infection by HPV. HPV infects the basal layer of epithelial cells, where it usually exists for approximately 3 months in a subclinical state. The virus replicates in dividing epithelial cells, eventually producing exophytic clinical lesions known as genital warts. Viral DNA replication and assembly occur in the superficial epithelial cells. These cells are eventually filled and exfoliated with infectious HPV particles (3). Improved research techniques, including deeper metagenomic sequencing, have shown that prior condyloma specimens that were thought to be "HPV negative" are actually HPV infected. In one study, HPV was found in 37 of 40 prior negative samples, and the researchers were able to identify 75 different HPV types, of which 43 were novel putative types (4).

More than 100 distinct HPV subtypes have been described and 40 types of HPV have been found in genital warts (5,6). Patients with genital warts can be infected simultaneously with multiple HPV types. Low-risk (low-oncogenic) HPV infections, such as HPV types 6 and 11, cause at least 90% of genital warts and, rarely, recurrent respiratory papillomatosis (7). Higher-risk HPV types 16, 18, 31, 33, and 35 are also occasionally found as coinfections in genital warts, and can be associated with high-grade squamous intraepithelial lesions.

INCIDENCE

Most sexually active persons become infected with at least one strain of HPV sometime in their lifetime (8). Around 404,000 new cases of genital warts were diagnosed in the USA in 2013 (9). Young adults aged 15–24 years account for approximately half of new HPV infections each year (10). Using data from self-collected cervicovaginal specimens from 4150 females in four consecutive U.S. National Health and Nutrition Examination Surveys (2003–2006), HPV was found in 42.5% of U.S. females aged 14–59 years. The highest rate of infection is among young females aged 20–24 years (11). Patients on immunosuppressive drugs and patients with defects in cell-mediated immunity, including HIV, are especially susceptible to developing HPV infections. U.S. Centers for Disease Control and Prevention (CDC) collected data from sexually transmitted disease (STD) clinics and private practitioners' offices estimated the incidence as more than 6 million new patients a year in the USA (in 2008) and an estimated prevalence of more than 20 million (12,13). Following sexual contact with a HPV-infected individual, the risk of contracting the virus is thought to be approximately 75%, resulting in a 50% lifetime risk of acquiring condyloma for individuals who are sexually active with no additional risk factors (13).

Globally, HPV infection is the most common STD (14). The annual global incidence of condyloma ranged from 160 to 289 per 100,000 and prevalence estimates ranged between 0.13% and 0.20% (15). Genital warts have affected as many as 30 million individuals worldwide. A study in Finland in the mid-1980s found that the annual incidence of cytologic cervical HPV infection was 7% (16). A study of Finnish males determined that 6.5% had evidence of HPV in exfoliative cells obtained from the urethra and genital epithelium (17). Australian researchers have determined that genital warts have become relatively rare in young Australian women and heterosexual men after widespread use of quadrivalent HPV vaccines, but remain common in men who have sex with men and older women who were not vaccinated or were incompletely vaccinated. They reported that the proportion with genital warts decreased in women aged <21 years, from 18.4% in 2004/2005 to 1.1% in 2013/2014 (18).

Genital warts are rare in the general pediatric population. In more than half of children with genital warts, the lesions are a manifestation either of viral inoculation at or near birth or of incidental spread of cutaneous warts, often caused by non-genital HPV types. In many countries, the diagnosis of genital warts in a child requires that the clinician report possible abuse in order to begin an evaluation process that may or may not confirm sexual abuse (19,20).

An increased prevalence of HPV infection during pregnancy has been reported by several investigators, with the prevalence increasing as the gestational age increases and declining in the postpartum period. HPV is believed to be vertically transmitted, and maternal history of genital warts was found to be the strongest risk factor for neonatal juvenile-onset respiratory papillomatosis in a retrospective cohort study. However, this Danish registry study showed no protective benefit of cesarean delivery on the rate of neonatal juvenile-onset respiratory papillomatosis (21). Other authors have concluded that cesarean delivery decreases but does not completely prevent

HPV transmission and the development of laryngeal papillomas in the infant (22–25). The seventh and most recent version of the Guidelines for Perinatal Care, published jointly by the American College of Obstetricians and Gynecologists and the American College of Pediatrics, recommends against cesarean section for the sole purpose of protecting the infant, concluding that that the risk to the infant is very small with vaginal delivery (26). Cesarean delivery may still be indicated if the lesions are significant enough to obstruct delivery or the risk of lacerations is too great. The risk of perinatal HPV transmission to the oropharyngeal mucosa of the neonate is low for mothers with latent infections or genital warts.

ECONOMIC BURDEN

A review of treatment practices in the UK, the USA, and France shows that patients often prefer immediate treatment, even though—whether treated or untreated—more than 90% of patients have resolution within 2 years (27). The direct cost of condyloma is difficult to define, which makes comparing the expenses of the different treatment modalities challenging. Even within the same country and at the same time, different patients will have different expenses related to the price of medications and provider visits. Despite these limitations, a direct comparison is useful to help with treatment planning. An analysis of recent studies, published in 2016, showed average medical costs per course of treatment in 2013 British pounds to be as low as £14.68 for podophyllotoxin and as high as £362.71 for surgical excision (28). Please see Table 16.1 for a comparison of treatment technique costs, clearance rates, and recurrence rates.

Raymakers et al. (29) used available datasets for comparison to provide evidence of the financial burden of condyloma treatment. For instance, in the UK, a comparison (in 2009 U.S. dollars) shows that, in 2003, the direct cost of cervical cancer was $85.1 million, while the direct cost of genital warts was $40.7 million (29,30). In a similar comparison using 2009 U.S. dollars, the direct cost of cervical cancer in the USA for the year 2000 was $436 million (31), with genital warts costing $250 million (32), again demonstrating a rough 2:1 ratio of direct costs between cervical cancer and condyloma. Notably, whether the treatment chosen is ambulatory, at home, or in the hospital reflects on the overall cost as well. An Italian study (using 2011 Euros) found that the average cost of diagnosis and treatment for Italian men and woman combined was €111.39 ± 76.72 in the sexually transmitted infection clinic, €160.88 ± 95.69 when treated at home, and €2825.94 when hospital care was involved (33). Typically, the cost of care is reduced when a female-only cohort is studied.

Table 16.1 Clearance Rate and Recurrence Rate by Treatment Method[a]

Treatment	Clearance rate (%)	Recurrence rate (%)	Cost (2013 British pounds)
Cryotherapy	79–88	21–39	266.86
Laser ablation	23–52	≤77	341.75
Excisional procedures	35–72	25–40	162.71
Podophyllotoxin 0.5%	45–77	≤38	14.68
Imiquimod 5%	40–70	9–19	194.40
Imiquimod 3.5%	28	15	–
Sinecatechins	54–65	6–9	–
Trichloroacetic acid	56–81	36	249.86

[a] Clearance and recurrence rates from individual trials—there is not a comprehensive head-to-head study. The costs are reported in 2013 British pounds and represent the average total cost per course of treatment. From references (28,42–45,47,53,55).

DIAGNOSIS

The diagnosis of condyloma can typically be made by visual inspection. Typical condylomata are discrete, cauliflower-like papules that involve multiple sites on genital surfaces (Figures 16.1 through 16.4). They vary in size and can form large, exophytic masses (Figures 16.5 and 16.6) (34). With female patients, they may be found on the vulva, vagina, urethra, cervix, perirectal epithelium, anus, and rectum (35). A thorough assessment of the entire vulva and perianal area, as well as speculum examination for vaginal/cervical inspection, is indicated when lesions are present. In patients with extensive disease, atypical findings, or who are immunocompromised, anoscopy as well as colposcopy may be useful adjunct procedures. HPV tests are not recommended for the diagnosis of genital warts. The routine application of 3%–5% acetic acid with magnified visual observation for white areas in order to detect genital mucosa

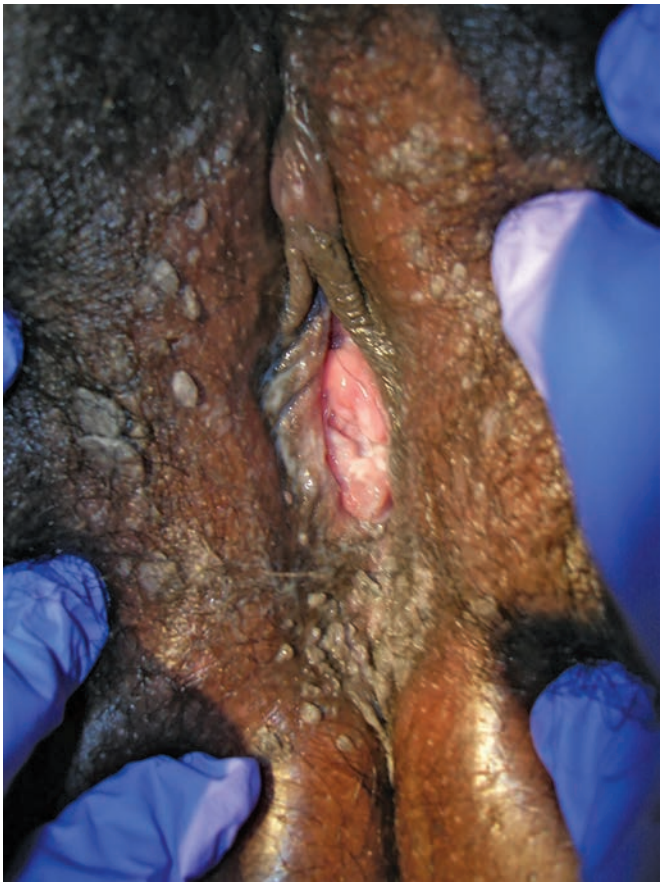

Figure 16.1 This patient presents with numerous small cauliflower-shaped condylomata throughout the labia minora, labia majora, and posterior fourchette.

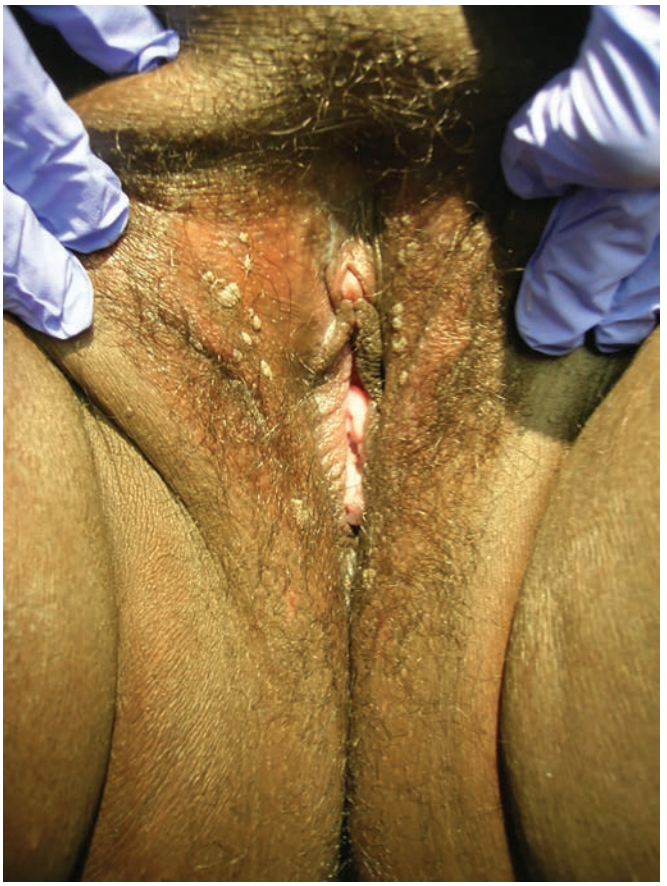

Figure 16.2 The distribution of this patient's condylomata is mainly on the labia majora.

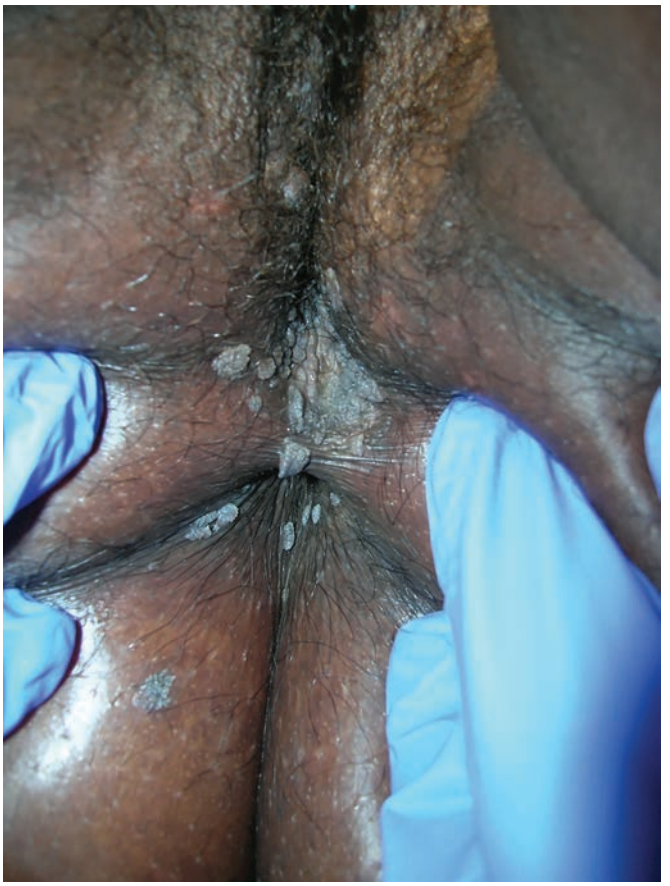

Figure 16.3 These condylomata in the posterior fourchette and perianal area are more flat. Note the isolated lesion further out on the buttocks.

infected with HPV is not routinely recommended because the results do not influence clinical management (35).

Differential Diagnosis

Other verrucous lesions of the vulva and anus can be mistaken for condylomata acuminata (36). While condyloma are the most common papular lesion of the genitals, condyloma lata should be considered in patients who are known to have had primary syphilis or to be at risk for syphilis. Condylomata acuminata can usually be distinguished from condylomata lata due to the condylomata acuminata typically having a cauliflower-like, dry, and bulky appearance, while condylomata lata are typically smooth, moist, and flat or dome-shaped (37). Other sexually transmitted infections such as herpes simplex, molluscum contagiosum, chancroid, and giant condylomata of Buschke and Lowenstein may also be confused with genital warts.

Benign lesions in the anogenital region may also be confused with genital warts, including hemorrhoids, vestibular papillomatosis, mucosal polyps, and Fordyce spots (visible genital sebaceous glands). It is important to distinguish these benign conditions from condylomata since treating benign lesions as if they were genital warts may result in unnecessary procedures, expenses, and chronic pain. Precancerous and cancerous lesions of the anogenital area are often papular in morphology and may be confused with condylomata (Figure 16.7). They often do not respond completely to wart treatments, so when treatment failure occurs, a biopsy is indicated. Precancerous and cancerous lesions may also coexist with genital warts.

Failure to diagnosis genital papules correctly can result in considerable morbidity. Confusing other STDs for genital warts will lead to inappropriate and ineffective therapy. Confusing benign papules with genital warts will result in unnecessary treatment and likely psychosocial distress. Missing a dysplastic or cancerous diagnosis is likely to delay appropriate therapy and may lead to additional morbidity or mortality.

Biopsy

Biopsy is indicated if the lesion is atypical, such as when the warts are pigmented, indurated, fixed, bleeding, or ulcerated. Additionally, biopsy might be indicated if: (i) the diagnosis is uncertain; (ii) the lesions do not respond to standard therapy; or (iii) the disease worsens during therapy (35). Currently, the CDC recommends that these criteria for biopsy should be especially considered in a patients who are immunocompromised or HIV positive. The routine biopsy of all lesions has been advocated for in the past, with routine biopsy of those who are HIV infected being argued for by others (38). On histological examination, condylomata acuminata are described as having branching, tree-like patterns in the squamous epithelium, with pyknotic, deeply blue nuclei surrounded by a halo and clear

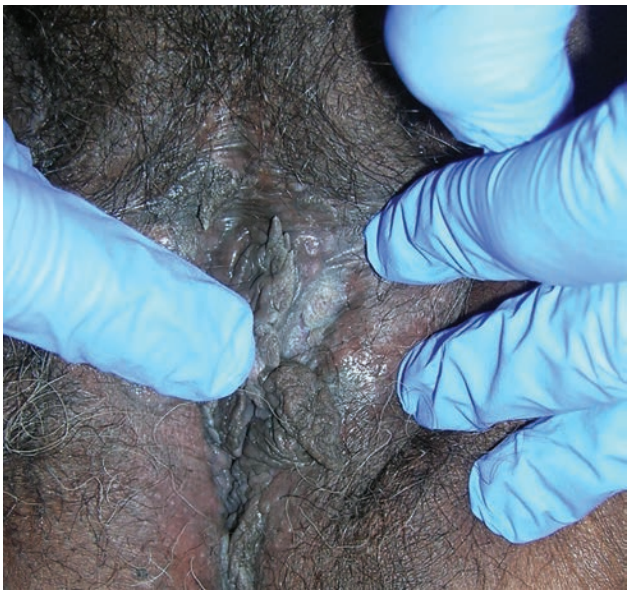

Figure 16.4 This image shows multiple typical genital warts on the labia majora, labia minora, and the clitoral hood.

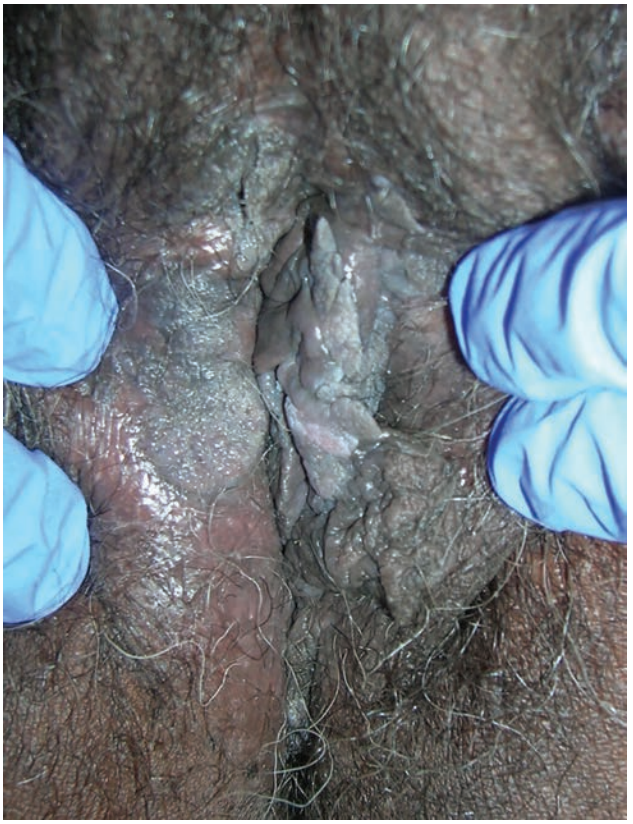

Figure 16.5 This image is the same patient as in Figure 16.4. Note that on her right side she has a flat lesion that has a different morphology than her other lesions. A biopsy should be considered in patients with atypical lesions.

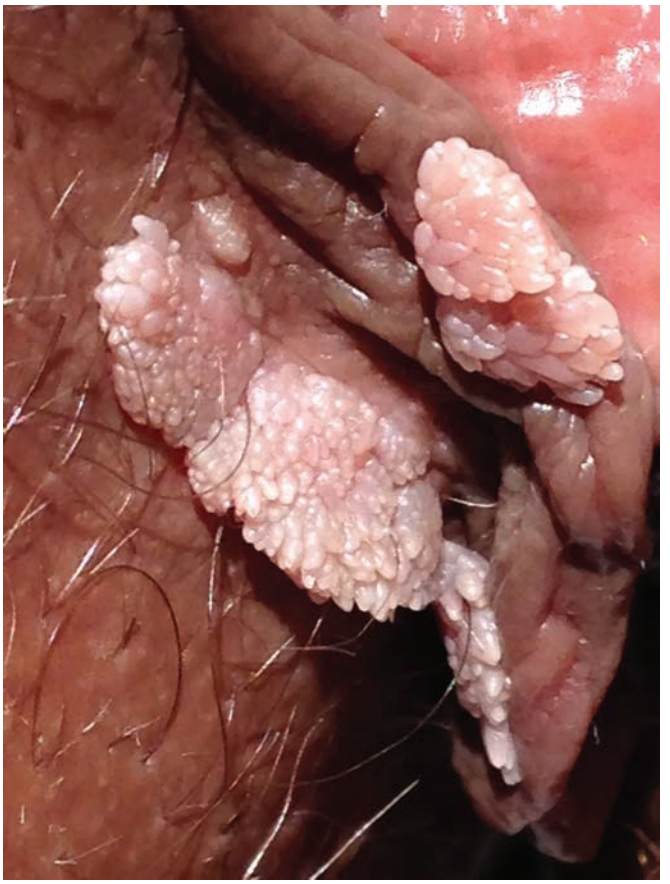

Figure 16.6 These lesions represent larger, more exophytic masses. Note that the lesions have multiple projections but a common base.

cytoplasm with a paucity of keratohyaline granules (koilocytes) present (36).

TREATMENT

Many HPV infections resolve without intervention and many are asymptomatic or unrecognized (35). There is no single best treatment for condylomata acuminata (35). Eradication or reduction of symptoms is the primary goal of treating warts. Treatment is generally reserved for patients with visible warts, and treatment is not recommended for subclinical disease in the absence of coexistent dysplasia (35). The general treatment strategy is to eliminate visible lesions until the host's immune system can control disease expression. There is currently no evidence demonstrating that treatment eliminates HPV infection or decreases infectivity. In fact, warts may recur after treatment because of the activation of latent virus present in healthy skin adjacent to the lesion.

Patient factors that influence treatment choice include the size, morphology, number, and anatomic site of the lesions. Cost, availability, adverse effects, patient preferences, previous therapy, and provider experience affect the treatment choice as well. Most treatments involve directly ablating or excising lesions. Some treatments require multiple rounds of therapy over several weeks or months. If substantial improvements

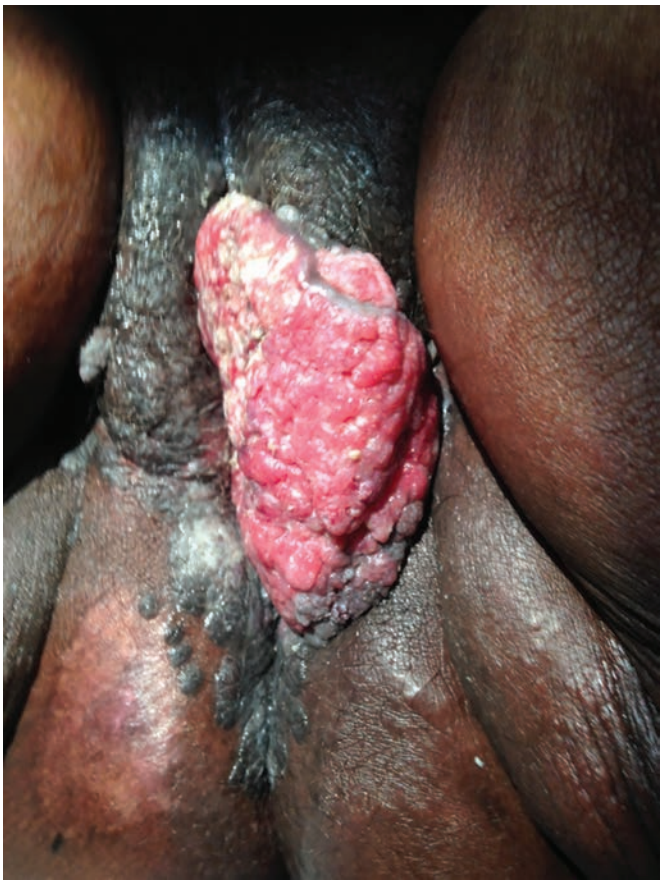

Figure 16.7 This patient was referred to clinic for treatment of a condyloma. Biopsy of the lesion demonstrated high-grade squamous intraepithelial lesions (vulvar intraepithelial neoplasia [VIN] 2).

have not occurred after three rounds of treatments or complete clearance has not occurred after six treatments, a different treatment modality should be considered. Patients who are immunosuppressed usually require more aggressive management. Regardless of the mode of therapy chosen, recurrence rates are high for any patient with condylomata acuminata, resulting in a high level of frustration for both the patient and the clinician.

Pregnant women with condyloma require special consideration. Higher HPV infection rates have been reported in pregnant women. Rapid growth during pregnancy may be observed, possibly due to suppression of immunity during pregnancy and hormonal changes (39). Small asymptomatic lesions need not be treated, but larger lesions can be treated with keratolytics or cryotherapy (35,40). Occasionally, condylomata in pregnant women become large and macerated, requiring surgical excision after the first trimester. Interferon, podophyllin, and 5-fluorouracil are contraindicated in pregnancy.

The treatment of condyloma can be divided into several categories: at home versus in clinic versus in the operating room; topical versus surgical; and patient versus provider administered—see Table 16.1 for a comparison of treatment success and recurrence rates. The effectiveness of therapies is defined by the initial clearance of the lesions and the rate of recurrence. The overall rate of effectiveness varies across the treatment options. The efficacy of most therapies is disappointing, with recurrence ranging from 30% to 70% at 6 months (41).

Table 16.2 U.S. CDC-Recommended Therapy for Anogenital Warts by Body Area

External anogenital warts	• Imiquimod 3.75% or 5% cream • Podofilox 0.5% solution or gel • Sinecatechins 15% ointment • Cryotherapy with liquid nitrogen or cryoprobe • Surgical removal • TCA or BCA 80%–90% solution
Cervical warts	• Cryotherapy with liquid nitrogen • Surgical removal • TCA or BCA 80%–90% solution For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade SIL must be performed before treatment
Intra-anal warts	• Cryotherapy with liquid nitrogen • Surgical removal • TCA or BCA 80%–90% solution
Vaginal warts	• Cryotherapy with liquid nitrogen (not a cryoprobe due to the risk for vaginal perforation and fistula formation) • Surgical removal • TCA/BCA 80%–90% solution
Urethral meatus warts	• Cryotherapy with liquid nitrogen or surgical removal

Source: Adapted from Sykes NL, Jr. *Int J Dermatol* 1995; 34(5): 297–302.

Abbreviation: BCA: bichloroacetic acid; SIL: squamous intraepithelial lesion; TCA: trichloracteic acid.

The CDC-recommended methods for the treatment of anogenital warts are shown in Table 16.2 (35). The World Health Organization (WHO) guidelines for the management of sexually transmitted infections also include podophyllin 10%–25% in a compound tincture of benzoin as a first-line therapy (42).

SURGICAL THERAPIES

Cryotherapy

Cryotherapy is an office therapy applied by the practitioner. It involves the use of nitrous oxide, carbon dioxide, or liquid nitrogen to induce dermal and vascular injury to condylomata, which leads to epidermal and dermal cellular necrosis. The clearance rates for cryotherapy range from 79% to 88% within three treatments. Recurrence rates range from 21% to 39% (43). Since the treatment is superficial and remains localized, it is considered safe to use in pregnancy.

Liquid nitrogen treatment involves choosing either a refillable applicator that sprays liquid nitrogen directly on the lesion or the use of a cotton-tipped swab that is dipped into liquid nitrogen. Apply the liquid nitrogen until the lesion turns white, which is when it is frozen. The border of the frozen area should extend 2–3 mm around past the lesion. The wart is then allowed to thaw and may then be refrozen again. The areas can be retreated every 2–3 weeks for up to 4 months. For external warts only, cervical cryotherapy units with dermatologic probes may also be used. Like on the cervix, a water-soluble lubricant should be used on the tip to act as a thermocouple. Some clinicians find that for small condyloma, the use of a disposable otoscope specula placed over the lesion can help reduce the lateral spread of dermal injury.

Side effects are local pain, blister formation, local ulceration, and, with aggressive therapy, scarring. Since it may require multiple treatments, some patients may not be adherent

to the full course of therapy. Cryotherapy is considered a first-line therapy for its high effectiveness, low recurrence, high tolerability, and safety in pregnancy.

Laser Ablation

Laser treatment of condylomata utilizes infrared light energy to create thermal injury and vaporization of the lesion. Laser therapy uses carbon dioxide (CO_2) lasers almost exclusively. Several other variants may be used in the future. The clearance rate for a CO_2 laser is 23%–52%, with recurrence rates up to 77% (44). Depending on the bulk of condyloma and the patient's preference, the treatments can be done in the office with local anesthesia or in the operating room under general anesthesia. With the use of local anesthesia, laser therapy is safe during pregnancy. Expertise and training in the safe use of laser treatment is required by the clinician before offering this treatment, reducing its overall availability.

One of the primary drawbacks to laser therapy is the cost of the device itself and a relatively high level of training needed. Another limitation of this treatment includes the risk of inhalation of vaporized HPV during the procedure. This has been mitigated by the use of vacuum suction during therapy and sub-micron masks worn during the procedure. The side effects of the procedure are limited to the effects of local thermal destruction and scarring. The laser can be beneficial to the immunocompromised patient as well as pregnant patients not responding to trichloroacetic acid (TCA) or cryotherapy.

Excisional Procedures (Shave and the Loop Electrosurgical Excision Procedure)

Excisional procedures all share the same technique of surgical removal of the condyloma and the underlying affected epidermis. The two most common techniques are the loop electrosurgical excision procedure (LEEP) and sharp (knife, scissor, shave, or curettage) excisions. The overall clearance rates range from 35% to 72%, with recurrence rates of 25%–40% (45).

LEEP has the advantages of decreased blood loss and ease of application for large lesions. There is a possible risk of aerosolization of the HPV, and this procedure requires the same precautions as laser therapy. Sharp excision has benefits of improved cosmesis, immediate effect of treatment, and, if the lesion concerns dysplasia, the option for pathology confirmation. The disadvantages include the need for anesthesia, substantial clinical training, additional equipment, sometimes a longer office visit, and the increased amount of bleeding that can occur. The side effects are similar to any surgical procedure and include bleeding, infection, and scarring.

Topical Therapies

Topical agents have the advantage of not requiring anesthesia, are generally well tolerated, and some can be administered in the privacy of the home. The main disadvantage is the possible need for multiple treatments that can take weeks to months for resolution.

Podophyllin and Podophyllotoxin

Podophyllin is derived from the roots of the Mayapple plant (*Podophyllum peltatum*) (46). It binds to the cellular microtubules to induce necrosis by inhibiting mitosis. Two formulations are available: podophyllin, the unpurified form, is normally suspended in a 10%–25% tincture of benzoin solution; podofilox (or podophyllotoxin) is the purified extract. Both forms are considered teratogenic, and all patients of reproductive age should be counselled of these risks. Podophyllin has fallen into disfavor and is considered a second- or third-line treatment option in the USA. The reasons for this include it being less effective, it must be administered in the office, it has potential systemic toxicity, and there have been reports of drug-related deaths.

Podophyllotoxin comes in a 0.5% solution, gel, or cream and a 0.15% cream. Clearance rates for the 0.5% preparation range from 45% to 77%, with recurrence rates as low as 38%. The 0.15% cream has shown similar effectiveness rates when used to treat vulvar lesions (47). The high effectiveness, low cost, tolerability, and ease of home application all make podophyllotoxin one of the first-line treatment options.

The course of treatment is twice-daily application to lesions of no more than 10 cm^2 surface area or 0.5 mL solution for 3 days followed by 4 days of rest. The medication should not be placed on vaginal or mucosal areas because of the risk of absorption and irritation. When possible, the CDC recommends that a health care provider apply the initial treatment in order to demonstrate proper application technique and identify which warts should be treated (35). The medication should be rinsed off 1–4 hours after application. The treatment may be repeated weekly up to a maximum of 4 weeks. Side effects are well tolerated but include temporary burning, itching, swelling, tenderness, and erythema.

Imiquimod

Imiquimod is a topical, at home, patient-applied medication that is thought to act as an immunomodulatory, stimulating an inflammatory and cytolytic response, and it comes in a 5% and 3.5% cream. It requires an intact immune system to be most effective. The 5% cream is applied three times a week with at least 1 day in between each application for up to 16 weeks. It is normally applied at night and then washed off 6–10 hours later. For the 5% cream, the clearance rate is 40%–70%, with a recurrence rate of 9%–19% (42). The 3.5% cream is applied once daily and washed off 6–10 hours later for up to 8 weeks. The 3.5% cream clearance rate is 28% and the recurrence rate is 15%. The nightly application has been shown to have a higher compliance rate at the cost of a lower clearance rate (45).

The side effects of both doses are itching, burning, redness, and ulceration of lesions. With the 3.5% preparation, the side effects are less intense. There have been reports of hypopigmentation and worsened inflammatory or autoimmune skin diseases such as psoriasis, vitiligo, and lichenoid dermatoses (48–51). Imiquimod has been studied in rats and rabbits and shown no teratogenic effects. Limited studies in pregnant women have shown no fetal abnormalities. With other effective treatments available during pregnancy, imiquimod should be avoided in pregnant patients until further studies can be completed (42,52).

Sinecatechins

Sinecatechin ointment is a topical, patient-administered therapy that is derived from green tea. It is composed of catechins and other extracts of *Camellia sinensis*. Although its exact mechanism of action is unknown, it is thought to have immune-enhancing actions (53). This effect is similar to that found in

many other studies regarding the properties of green tea. No studies have looked at sinecatechin effectiveness in immunocompromised patients.

The ointment comes in a 10% (Europe) or 15% (USA) preparation that is applied three times a day by the patient for up to 16 weeks. It should not be washed off after use, and genital, anal, and oral sexual contact should be avoided while the ointment is on the skin (35). Clearance rates range from 54% to 65%, with recurrence rates of 6%–9% (53). The side effects are similar to other topical preparations of redness, burning, irritation, itching, and pain. The safety of sinecatechins in pregnancy has not been established and therefore its use is contraindicated.

Trichloracetic Acid

TCA and bichloroacetic acid (BCA) are topical, provider-applied, destructive solutions. When suspended in alcohol in a 50%–90% preparation, these agents chemically coagulate proteins and cauterize and erode the lesion when it comes into contact with the condyloma. It is directly applied to the lesion, normally with a toothpick or fine-tipped swab. To prevent unintended spread to healthy tissue, petroleum jelly can be applied circumferentially to normal skin around the lesions prior to treatment. Once applied, it quickly dries, leaving a white, lichenous-appearing area. During this time, the patient will experience a burning sensation for several minutes. If pain is too intense because an excess amount of acid has been applied or if the acid has spread beyond the intended location, the area can be covered with sodium bicarbonate, washed with liquid soap preparations, or be powdered with talc to neutralize the acid (35). The number of lesions treated is based on how well the patient tolerates the discomfort of administration. Treatment is every 1–2 weeks as needed for up to 4 months.

TCA has a clearance rate range of 56%–81% (54–56), with a recurrence rate of 36% (55). Common side effects are the discomfort of application, ulceration of lesions, and possible scar formation. A related risk is the accidental destruction of surrounding healthy tissue due to incidental spread of the solution. Application during pregnancy is considered safe. TCA is a first-line therapy due to its low morbidity, ease of treatment, high clearance rates, safety in pregnancy, and low cost.

Treatment in Immunocompromised Patients

Treatment of the immunocompromised patient can be difficult since the immune cellular response has been reduced or eliminated. Most of the therapies utilized are based on the destruction of the lesion followed by the elimination of the remaining virus by the host. The other challenge to the treatment of condylomata is the unseen subclinical infection. This accounts for the higher rates of recurrence after initial successful treatment. Another problem encountered is the increased rate of lesion growth that can occur with uninhibited viral replication. This leads to a larger burden of condyloma to be treated.

When choosing a treatment plan, the clinician must counsel the patient about the potential need for multiple treatments and the increased rate of recurrence. The most effective treatments are those that directly destroy the lesions. TCA and cryotherapy are two initial options that are well tolerated and can be performed in the office. They are limited by the overall bulk and diameter of the lesions. For most patients, the use of a laser proves to be the most successful approach, especially with extensive lesions. As a last resort, excisional techniques may be required. The benefits of destruction of the viral base of the lesion should be weighed against the increasing risk of scarring and problems with healing. Another concern is the increased potential for conversion of HPV-related lesions to squamous cell carcinoma. A low threshold should be present for biopsying atypical or treatment-resistant lesions prior to treatments beginning.

Synergistic Approaches

The use of synergistic therapy has normally been reserved for those with recurrent lesions or with a very high burden of condyloma. There are no current guidelines on how best to utilize combined treatments. Many are still experimental and are presented in case reports. One use of synergy is the attempt to reduce the size of lesions prior their excision. Imiquimod has shown promise for shrinking these lesions and decreasing the amount of tissue necessary for removal. Inversely, some are using imiquimod to treat subclinical lesions after surgical excision (57). Another approach involves the intralesion injection of α-interferon followed by cryotherapy. The downsides of this treatment are the cost and the potential systemic side effects of the interferon.

PREVENTION

Safe-Sex Practices

Abstaining from all sexual activity is the most reliable method for preventing genital HPV infection. Persons can decrease their chances of HPV infection by limiting their number of sex partners and consistent and correct use of condoms (35). Although studies vary in quality and results, condom use has been found to decrease HPV acquisition among men and women and is recommended by the WHO (42,58,59). Although these interventions might not fully protect against HPV, they can decrease the chances of HPV acquisition and transmission (35,42).

Vaccination

Both the four-valent and the nine-valent HPV vaccines (Gardasil®, Merck, Whitehouse Station, NJ, USA) prevent against infection by HPV types 6 and 11, which cause the majority of genital warts. They are administered as a three-dose series of IM injections, with the second and third doses given 2 and 6 months after the first dose, respectively, over a 6-month period. For girls and boys in the USA, either vaccine is recommended routinely at ages 11–12 years and can be administered beginning at 9 years of age (60). It may also be routinely administered to girls and women aged 13–26 years and boys aged 13–21 years who have not completed the vaccine series (60). For previously unvaccinated, immunocompromised males (including those with HIV infection) and men who have sex with men, vaccination is recommended through age 26 years (60). Post-vaccination monitoring studies in the USA have demonstrated reductions in genital warts (35). The three-dose quadrivalent HPV vaccine resulted in almost complete disappearance of incident condyloma in Australian-born women aged 21 years or younger within 3 years of introduction of the national HPV vaccination program (61). A meta-analysis found significant reductions in anogenital warts of 61% (relative risk [RR]: 0.39; 95% confidence interval [CI]: 0.22–0.71) in girls aged 13–19 years, boys younger than 20 years of age (RR: 0.66; 95% CI: 0.47–0.91), and in women aged 20–39 years (RR: 0.68; 95% CI: 0.51–0.89) (62).

For the prevention of cervical cancer, the WHO recommends girls aged 9–13 years (prior to becoming sexually active) as the primary target group for HPV vaccination. Vaccination of older adolescent females or young women is recommended only if this is feasible, affordable, cost effective, and does not divert resources from vaccinating the primary target population. HPV vaccination of males is not recommended as a priority, especially in resource-constrained settings. The WHO now recommends a two-dose schedule with a 6-month interval between doses for females younger than 15 years. A three-dose schedule (at 0, 1–2, and 6 months) is recommended for females aged 15 years and older, and for those who are known to be immunocompromised and/or HIV infected (63). Pre- and postlicensure safety evaluations have found the vaccine to be safe and well tolerated (64). Garland et al. studied pregnancy and infant outcomes in women who received the prophylactic quadrivalent HPV vaccine before becoming pregnant and observed no significant differences between live birth, fetal loss, or spontaneous abortion (65).

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Vulvar seborrheic keratosis

Jason C. Reutter

CLINICAL FEATURES

Seborrheic keratoses are benign epidermal growths that are found on hair-bearing skin. They are usually found in patients over 40 years of age and predominantly in the head and neck or trunk regions or extremities. Familial forms, possibly autosomal dominantly transmitted, are described, and eruptive forms of seborrheic keratosis constitute the paraneoplastic syndrome of Leser–Trelat, associated with internal malignancies. The lesions are typically well demarcated and raised with variable coloration, from pink to yellowish to brown or black. The lesions may begin as macules, but later develop a rough, velvety to papillomatous appearance. Scale is typically present and the lesions typically have a greasy, "stuck on" appearance (Figure 17.1). Occasionally, the lesions may become irritated and painful or pruritic and erythematous in coloration. Vulvar seborrheic keratoses are exclusive to hair-bearing surfaces, are not found on mucosal surfaces, and are usually solitary.

ETIOLOGY

There exists controversy as to whether seborrheic keratoses are related to human papilloma virus (HPV) or not. Vulvar seborrheic keratosis are not considered to be caused by HPV by some authorities (1). There is tremendous variability in the finding of HPV in non-genital seborrheic keratoses by polymerase chain reaction. While most studies show either complete absence or near absence of HPV (2–7), other studies have shown its presence in the vast majority of lesions (8,9). The incidence of HPV infection in vulvar seborrheic keratoses of women of all ages ranges from 42% to 70% (5,6,10). However, the current author has performed HPV polymerase chain reaction on vulvar seborrheic keratoses from women over 50 years of age, who were thought to represent a subset of women with theoretically lower risk of possible recent HPV exposure. In that study, the incidence was much lower (14%) (11). Giant genital seborrheic keratoses have been reported (12–15), but were challenged as representing condylomata accuminata (16), and some feel that all seborrheic keratosis are condylomata (17). This may serve to demonstrate a theoretical overlap with condyloma accuminatum and seborrheic keratosis, or at least serve to demonstrate an inconsistent ability to distinguish between them. Therefore, the relationship between vulvar seborrheic keratosis and HPV remains uncertain. The genital skin may serve as a reservoir for dormant HPV, and vulvar seborrheic keratosis may be incidental bystanders or may represent a latent form of condyloma, an observation based partly on the morphological overlap of the two entities, as discussed below in further detail.

Fibroblast growth factor receptor 3 mutations have been reported in some non-genital seborrheic keratosis (18), as have mutations is *PIK3CA* (19). Less common genetic events include *HRAS*- and *KRAS*-mutated lesions (20), suggesting these mutation may be a step in their pathogenesis or a mechanism for their familial tendencies.

DERMOSCOPY

Dermoscopy may be helpful in the evaluation of seborrheic keratosis. Comedo-like openings and milia-like cysts are distinguishing features, as well as fissures, hairpin vessels, and moth-eaten borders (Figure 17.2) (21).

HISTOLOGY

The histology of seborrheic keratoses in general is characterized by variable degrees of epidermal acanthosis, which usually is exophytic and characterized by a "flat bottom." Rarely, an endophytic pattern is present. Quite often, seborrheic

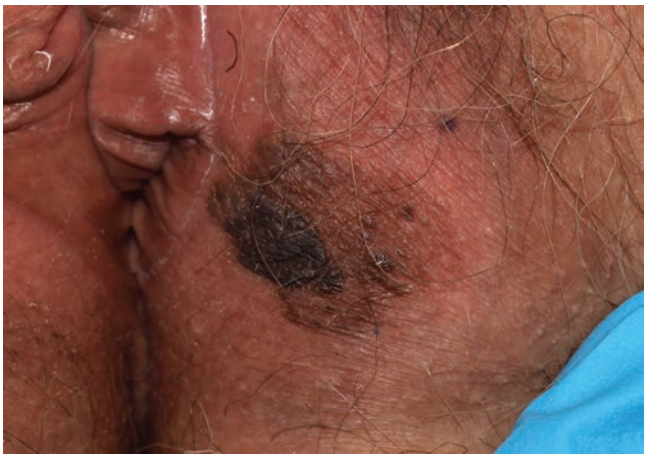

Figure 17.1 Clinical appearance of vulvar seborrheic keratosis. (Photo courtesy Libby Edwards, MD.)

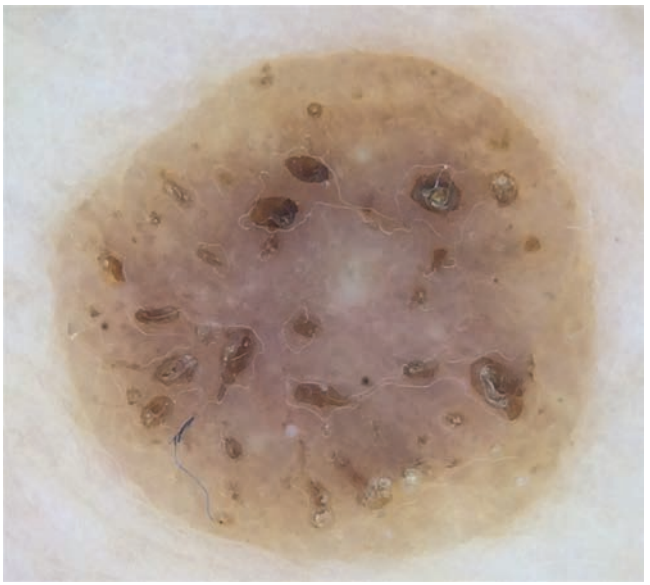

Figure 17.2 Dermoscopy of seborrheic keratosis. (Photo courtesy of Erica Kelly, PA-C.)

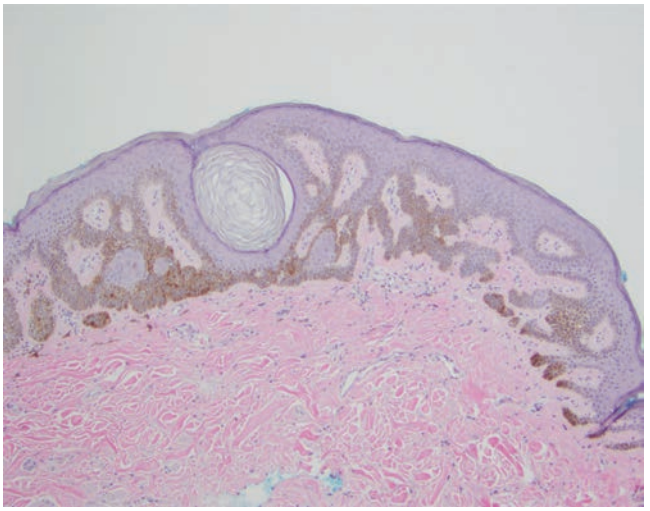

Figure 17.3 Classic seborrheic keratosis with pigmented and reticulated rete ridges and a central horn cyst (100×). This was from an 84-year-old female and the lesion was negative for HPV by polymerase chain reaction.

keratoses will have horn cysts present and other forms of hyperkeratosis. The base of the lesion often has reticulation of the rete ridges or hyperpigmentation (Figure 17.3). The constituent cells are monotonous without significant atypia, except in cases of irritation, where nuclear enlargement may be present. However, nuclei rarely overlap. Also, in irritation, enlargement of the cytoplasm may be present, and the cells have a whorled appearance in the form of squamous eddies. A monotonous basaloid cytomorphology may be present, the cells have a high nuclear:cytoplasmic ratio, and the cells appear "clonal" (Figure 17.4).

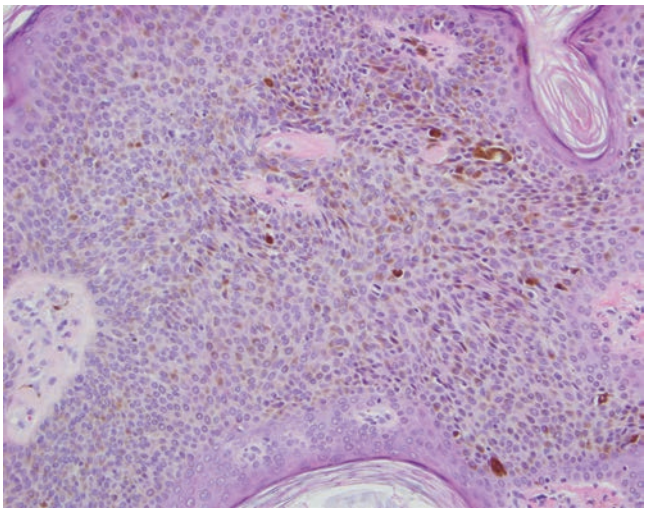

Figure 17.4 Clonal basaloid cells are present in this vulvar seborrheic keratosis, which are monotonous, do not overlap, and do not show significant mitotic activity (200×). The patient was 60 years old and the lesion was negative for HPV by polymerase chain reaction.

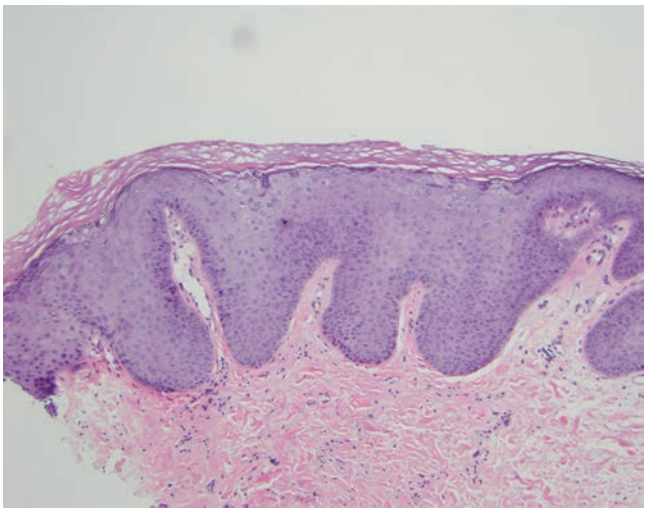

Figure 17.5 A classic condyloma with HPV koilocytic changes (100×). The patient was 70 years old.

DIFFERENTIAL DIAGNOSIS

The most common consideration as a differential diagnosis from a histological perspective is condyloma accuminatum. Condylomata are acanthotic and have koilocytes (Figure 17.5), but may also have horn cysts (Figure 17.6). Papillomatous change is variably present. Koilocytosis may not be as prominent as in other HPV-related lesions and so a careful evaluation for this change can be beneficial. Multiple tissue sections in a paraffin-embedded block may be necessary in order to find subtle histological changes (22). The presence of parakeratosis may be a useful

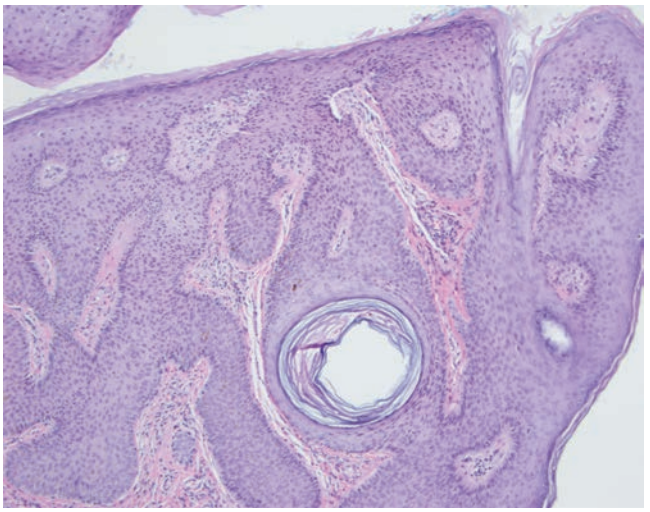

Figure 17.6 Condyloma may display horn cysts (100×). The patient was 51 years old and had conspicuous koilocytosis and the lesion was HPV positive by polymerase chain reaction.

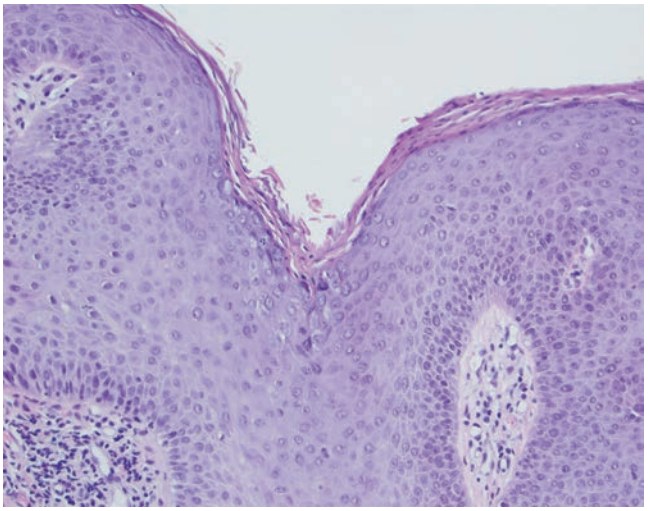

Figure 17.7 In the same patient, cryptic invaginations contain parakeratosis (200×).

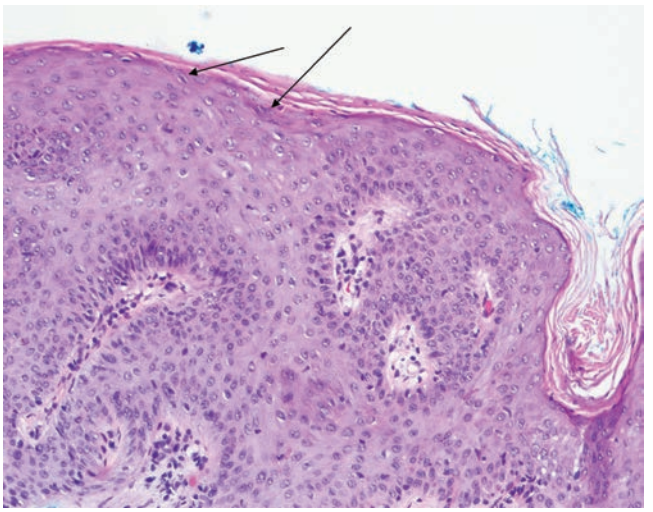

Figure 17.8 This ambiguous lesion has features of condylomata and seborrheic keratosis (200×). Koilocytes are demonstrated at the arrow.

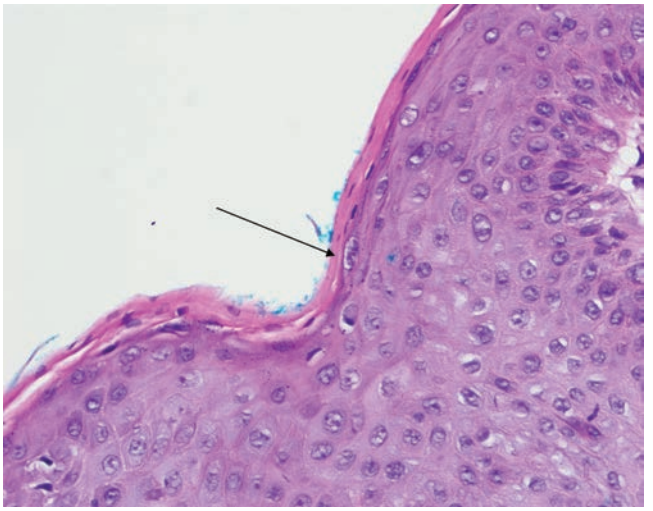

Figure 17.9 Higher power of the lesion in Figure 17.8, reveals areas suspicious for koilocytes, marked by arrows, in the cryptic invaginations (400×).

clue to identifying condylomata and may overlie focal koilocytic changes (Figures 17.7 through 17.9). Condylomata, unlike seborrheic keratosis, will involve the mucosa and are more likely to present as multiple lesions. When viewed with dermoscopy, condylomata have nonspecific findings, but finger-like, mosaic patterns and knob-like patterns have been observed (23).

High-grade squamous intraepithelial lesions (HSIL), also known as usual-type vulvar intraepithelial neoplasia or vulvar intraepithelial neoplasia 3, may occasionally bring about difficulty in terms of the histologic evaluation, especially for clonal seborrheic keratosis with basaloid features (Figure 17.10). The presence of mitotic figures throughout the full thickness of the epidermis, overlapping and pleomorphic nuclei, and multinucleated keratinocytes favor HSIL (Figure 17.11). Block-like positivity of p16, an immunohistochemical marker that is upregulated by oncogenic HPV (Figure 17.12), favors HSILs (24) over benign lesions, and Bcl-2 positivity favors seborrheic keratosis (25).

Epidermal nevi will have identical histological changes, and only clinical features such as a congenital onset can help differentiate the two. On the other hand, malignant melanoma, nevi, squamous cell carcinoma, and basal cell carcinoma may have overlapping clinical appearances, but are easily discerned by histology. The absence of scale in nevi and melanoma may be of assistance for the clinician in the evaluation of these lesions (26).

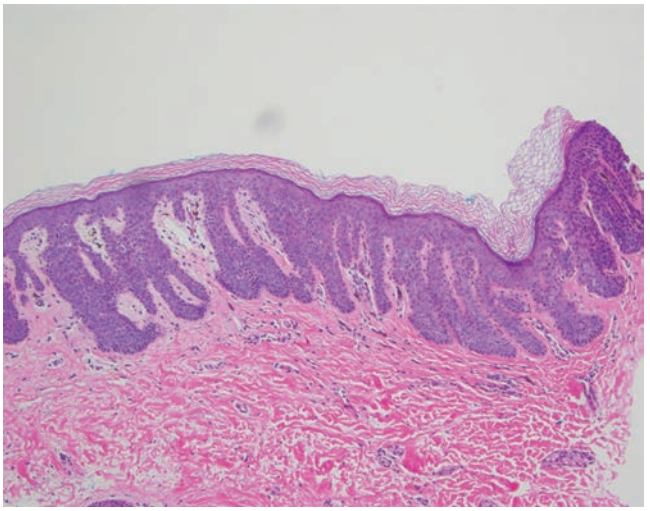

Figure 17.10 This lesion on low power is consistent with a seborrheic keratosis upon a cursory glance (100×).

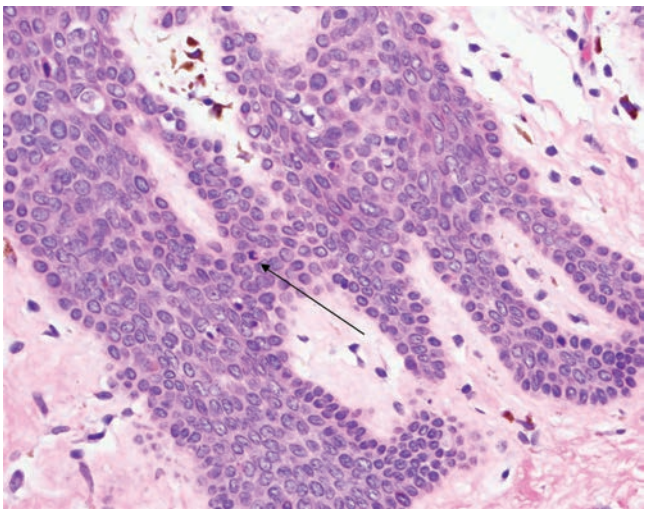

Figure 17.11 High-power inspection of the same lesion reveals mitotic figures, such as that at the arrow, throughout the thickness, raising the suspicion of HSIL (400×).

THERAPY

No treatment is necessary for these lesions. However, shave removal or liquid nitrogen therapy may be utilized if the lesion is irritating to the patient or causes cosmetic concerns. Because approximately 6% of cutaneous lesions that are clinically thought to be seborrheic keratosis are malignant tumors (27) and 0.5% of lesions are actually melanomas (27,28), one may consider accordingly adjusting their threshold in sampling these lesions (26).

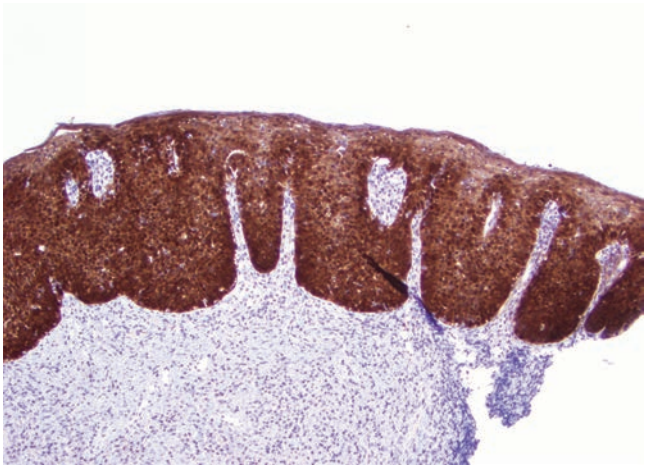

Figure 17.12 A p16 performed on the same lesion as in Figures 17.10 and 17.11 is useful in revealing block-like reactivity, defined as strong and continuous staining in at least the lower third of the epithelium (100×). This confirms HSIL.

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Vulvar edema diagnosis

Katherine Gilmore and Jane Hussey

INTRODUCTION

This chapter is written as a practical guide on how to reach a diagnosis when presented with a case of vulvar edema and provides the basic tools needed to appropriately assess and manage this presentation. General practitioners, gynecologists, dermatologists and physicians working in sexual health should find this a useful aid when presented with a case of vulvar edema. The chapter deals with isolated vulvar edema rather than generalized lower limb edema, which should always be excluded.

There are many causes of vulvar edema and a diagnosis can be challenging to make. An understanding of the disease process and possible causes, along with good history taking and examination, will aid you in gathering further information to support or refute a diagnosis. Prompt diagnosis and management is important to reduce the long-term morbidity of chronic vulvar edema (1).

Diagnosing and managing vulvar edema can require a variety of skills, and different specialists play key roles in evaluating and treating such patients. A multidisciplinary approach may be required and/or patients may need to be referred to other specialists for their care once a diagnosis has been made (2).

PATHOPHYSIOLOGY

Edema is defined as an abnormal fluid collection in the tissues and it can occur at different bodily sites. It may be more pronounced in the vulva due to the nature of the loose, distensible tissue. Vulvar edema, in particular, can be caused by an inflammatory process or by obstruction to the drainage of fluid (3). Any chronic inflammatory disease of the vulva can also cause lymphatic damage through scarring, which then leads to secondary lymphedema of the vulva (4). There are also other causes and disease processes that lead to or mimic vulvar edema, such as a localized vulvar mass (e.g., lipoma or Bartholin's cyst) (3).

HISTORY

A good history will inform your examination and investigation rationale and is an opportunity for you to explore in more detail the patient's symptoms and their thoughts about what might be going on (and, at times, a "hidden agenda").

The questions that you ask will inevitably be guided by the patient's presenting complaint, but it may be useful to have some specific questions in mind to help you to form differential diagnoses. Always consider other health problems that the patient may have and whether the woman is sexually active.

Five useful initial questions to reach a diagnosis are:

1. How long have you had the problem?
2. Is it there all of time or intermittent?
3. Do you have to see any other doctors for health care problems?
4. Do you have any itching or pain to the vulvar area?
5. Do you have any symptoms anywhere else?

Other generalized important questions not to forget are:

1. Is there a risk of pregnancy?
2. Is there a history of trauma?
3. Has there been sudden weight loss suggesting a possible malignant process?
4. Is there urinary frequency/incontinence associated with a pelvic mass?
5. Is there a travel history (particularly to tropical countries)?

CAUSES

Table 18.1 (3–17) lists the causes of vulvar edema. In some cases, the diagnosis is apparent very quickly; however, in other cases, a detailed history, including past medical history, family history, and a review of systems is required. Diagnoses often missed are rarer presentations of common conditions such as vaginal *Candida* or herpes infection. Vulvar edema of all causes can become secondarily infected, resulting in intermittent exacerbations of vulvar swelling often associated with increases in pain/discomfort. It can be difficult to determine whether recurrent vulvar skin infection is the primary cause of the edema or if there is another cause of the edema with superimposed infection (the chicken and egg scenario).

EXAMINATION

Sometimes vulvar edema is found on examination without the patient being aware—they may often present "feeling sore" rather than complaining of swelling. Begin by examining the vulva itself. Sometimes the diagnosis is immediately visible, such as genital herpes with secondary bacterial infection, but sometimes the vulva just appears "swollen." Table 18.2 (18–24) outlines potential clinical findings on genital examination and their interpretation. If the diagnosis is not immediately obvious, extend your local examination to include the perianal area and speculum examination of the vagina and cervix (if the vulvar edema and discomfort does not prevent this). You may then need to assess other systems and this can be guided by history, but if there are no clues or the initial provisional diagnosis is not confirmed, a full examination is needed. Table 18.3 (3,12,25–37) outlines specific examination findings and their interpretation.

Table 18.1 Causes of Vulvar Edema

Infection	Herpes simplex virus (3)
	Candida (5)
	Trichomonas vaginalis (6)
	Cellulitis/secondary bacterial infection[a]
	Other rarer infections:
	Filariasis (4)
	Granuloma inguinale (7)
	Epstein–Barr virus (8)
	Parvovirus (9)
	Lymphogranuloma venereum (3)
	Chancroid (3)
	Tuberculosis (10)
Autoimmune	Crohn's disease (11)
	Sarcoidosis (12)
Dermatological	Semen allergy (13)
	Stevens–Johnson syndrome/toxic epidermal necrolysis (3)
	Hidradenitis suppurativa (3)
	Vulvar dermatoses (7)
	Contact or allergic dermatitis (14)
Trauma	Secondary to vaginal delivery/instrumental delivery
	Vulvar hematoma
	Tourniquet syndrome (15)
Venous/lymphatic obstruction	Varicosities (especially in pregnancy)
	Pelvic mass
Localized vulvar mass (with associated edema)	Vulvar malignancy (4)
	Lipoma
	Bartholin's cyst
	Lymphangioma (16,17)
	Lymphoma
	Arteriovenous malformation
Dependent edema	Prolonged sitting (3)
Iatrogenic	Topical treatments/irritant or allergic response
	Following vulvar surgery or radiotherapy (3)

[a] This can occur with any breach in the vulvar epithelium—ulcers of all causes (including syphilis, herpes, and malignancy) and fissures (due to contact dermatitis, lichen sclerosis, atopy, eczema, and many other dermatological conditions).

INVESTIGATIONS

Investigations should be guided by history and examination findings. More detailed investigations are listed later in this chapter. Table 18.4 (33,38,39) shows the initial investigations that can be performed in all cases and that, combined with history and examination, may then lead to further investigations before a diagnosis is reached.

A diagnosis might be reached through history alone or by clinical findings and diagnostic investigations. It may be necessary to revisit the diagnosis if initial treatment fails to ensure that you are not missing the more rare but important diagnoses, such as vulvar Crohn's disease (Figure 18.1).

KEY HISTORY, INVESTIGATIVE, AND EXAMINATION FINDINGS FOR SPECIFIC/COMMON DIAGNOSES

Infections

Any infection of the vulva, be it yeast, bacterial, viral, or parasitic, can present with vulvar edema. Secondary infection may also occur in the form of cellulitis (Figure 18.2), particularly if the condition has been associated with pruritus and the epithelium is breached from scratching. Table 18.5 (7,36,40–51) has some useful further questions to ask when considering infection as a cause of edema.

Table 18.2 Examination, Genital

Finding	Clinical interpretation
Skin tags	Lymphangioma circumscriptum seen with Crohn's disease (18)
Ulceration	Seen with genital herpes, syphilis, Crohn's disease, drugs (Nicorandil) (19), *Trichomonas* (20), Behçet's, LGV, Lipschütz (caused by Epstein–Barr virus, influenza, and CMV) (21), severe vaginal *Candida*, and malignancy. Can occur both to vulva and/or vagina and cervix
Fissures	Seen with vaginal *Candida*, contact/irritant vulvitis, eczema, psoriasis, lichen sclerosis, lichen planus, genital herpes (22), and Crohn's vulvitis (knife-like fissures) (23)
Inflammation	Secondary bacterial infection and *Candida*
Pelvic mass	Pregnancy, malignancy, and inflammatory bowel disease
Perianal signs	Tags, edema, and sinus tracts seen with Crohn's disease. Hypopigmention seen with lichen sclerosis and vitiligo (linked with other autoimmune conditions)
Discharge	Seen with vaginal *Candida* (not always), *Trichomonas*, and internal genital herpes
Absence of edema	Intermittent cause such as genital herpes and semen allergy (13)
Specific dermatosis	Typical features of specific genital dermatosis may be present (e.g., lichen sclerosis), with secondary edema often resulting from secondary infection
Inguinal lymphadenopathy	Seen with secondary bacterial infection of all causes, genital herpes, and malignancy (24)
Varicosities	Consider pelvic mass including pregnancy or arteriovenous malformation

Abbreviation: CMV: cytomegalovirus; LGV: lymphogranuloma venereum.

Herpes

Herpes simplex virus typically presents with intermittent ulceration and this can be preceded by prodromal symptoms of altered sensation. Herpes can also be asymptomatic. A rarer presentation is intermittent vulvar edema, lasting about a week, which can be associated with pain or altered sensation preceding and/or during the swelling episode. This presentation of herpes can take a long time to be diagnosed. Careful examination can sometimes but not always reveal a small fissure and a swab from this can be sent for herpes polymerase chain reaction (PCR) testing. A trial of herpes-suppressive treatment can make the diagnosis if the intermittent swelling and pain resolve (47).

Vaginal *Candida*

Common symptoms of itch and discharge if present will usually result in a prompt diagnosis and treatment. Vaginal *Candida* will often result in some degree of vulvar edema and vulvar fissures, which can be mistaken for genital herpes (52). If symptoms return quickly after treatment, consider requesting a swab for fungal culture and sensitivities to diagnose rarer strains that may be resistant to standard azole treatment. Some rarer strains, such as *Candida parapsiliosis*, can present more

Table 18.3 Examination, General

System	Examination finding	Interpretation
Skin	Erythema nodosum (bruised appearance typically to shins)	Consider vulvar Crohn's disease, vulvar cellulitis due to streptococcal infection, pregnancy, some malignancies (non-Hodgkin's lymphoma), and recent penicillin use (25)
	Erythema multiforme (archery target-like lesions)	Consider genital herpes, can occur with recurrent atypical episodes where ulceration is not present (26). There are many other causes, including Epstein–Barr virus, various bacterial infections, and drugs (including some antibiotics)
	Eczema, psoriasis, seborrheic dermatitis	All can be present genitally and result in fissures and secondary bacterial infection with edema (12) Examine scalp (seborrheic dermatitis and psoriasis), natal cleft (psoriasis), flexures (eczema)/extensors (psoriasis), and nails (pitting seen in psoriasis)
	Vitiligo	Associated with other autoimmune conditions (27) such as Crohn's disease and sarcoid and dermatological conditions such as lichen sclerosis (28) and lichen planus (29) (predisposing to vulvar malignancy or secondary bacterial infection from fissures)
	Pyoderma granulosum	Consider inflammatory bowel conditions such as Crohn's disease (30)
Oral cavity	Ulceration	Consider Crohn's disease, herpes simplex virus, and Stevens–Johnson syndrome (31)
	Wickham striae (white lace pattern on inside cheek)	Seen in oral lichen planus (32). Consider genital lichen planus with secondary infection and edema, or other associated autoimmune condition such as Crohn's disease
	Lip and face edema	Seen in orofacial granulomatosis, a presentation of Crohn's disease, and strongly linked with vulvar Crohn's edema (33)
Joints	Arthritis	Seen in extragenital Crohn's (34), rheumatoid arthritis (linked with other autoimmune conditions), and sarcoid (35)
Body mass index		Overweight and obesity linked with type 2 diabetes (and vaginal *Candida*), hidradenitis suppurativa (3), and urinary dysfunction (and need for incontinence wear) (36) Underweight can be a sign of malabsorption and inflammatory bowel disease or coeliac disease (linked with other autoimmune conditions) (37)

unusually without itch and discharge at all and just with edema (53). Therefore, do not let the absence of itch and discharge stop the undertaking of an investigation for *Candida*.

Trichomonas vaginalis

Current standard culture for *Trichomonas* has poor sensitivity (54). *Trichomonas* can be asymptomatic, or typical symptoms are of vaginal discharge and soreness. More unusual presentations include ulceration and edema (55). Referring to a service with access to microscopy on site can help make a diagnosis as *Trichomonas* can be seen under light microscopy. Alternatively, consider a *Trichomonas* PCR test if locally available. Presumptive treatment with metronidazole could be used if *Trichomonas* is suspected, but current sexual contacts will also need treating (56).

Syphilis

Do not forget to consider the less common infections by performing a full infection screen. In a study looking at pregnant Mozambican women, syphilis screening by venereal disease research laboratory (VRDL) was undertaken in women with vulvar edema compared with unselected normal antenatal clinic attenders. Screening was positive in 61.9% of edema cases compared to 5.0% in the referent group (57).

Common Skin Conditions

A variety of dermatological conditions can affect the vulva. Symptoms and signs can include pruritus, pain or irritation, and changes in skin color and texture. Causes include vulvar dermatoses, contact dermatitis, hormone deficiency, and systematic skin disorders (58). Vulvar edema may occur in acute inflammatory conditions such as eczema. The edema usually settles with treatment of the primary problem. Table 18.6 (59) outlines some useful questions when considering a dermatological cause.

Hidradenitis Suppurativa

Hidradenitis suppurativa is a chronic inflammatory disease caused by hair follicle obstruction. It may be associated with frequent episodes of inflammation of the apocrine glands, acute edema, and secondary infection. It can cause painful lesions or abscesses in the axillae, groin, vulva, or anal regions, and these areas should be carefully examined to support a diagnosis and to instigate a referral to dermatology for treatment (60).

Allergy/Contact Dermatitis

Be aware of allergens or irritants that may cause an inflammatory edema. A review of common contact irritants should include laundry detergents, fabric softeners, dyes in clothing, washing products (bubble bath and scented shower gels), nail polish, toilet paper/wet wipe use, vaginal/vulvar moisturizers, sexual lubricants, condoms, creams/ointments (prescribed and over the counter), sanitary wear, and incontinence pads (59).

The edema may occur directly through an inflammatory response to a substance in the form of an allergic reaction or irritant contact dermatitis and/or may be caused by or exacerbated by itching. This may then breach the epithelium, introducing secondary infection.

Please refer to Chapter 29 further information on allergic contact dermatitis.

Steven–Johnson Syndrome/Toxic Epidermal Necrolysis

Steven–Johnson syndrome (SJS) and toxic epidermal necrolysis are acute, severe mucocutaneous reactions in which there is sheet-like skin and mucosal loss. They are variants of the same condition distinguished by the surface area of skin involved and they can be life threatening. They are thought to arise from a disorder of the immune system (61). Medication is the most common cause and is thought to trigger an immune reaction, although genetic factors are associated with a predisposition to SJS (62). Other causes include infection and malignancy (24).

Table 18.4 Initial Investigations and their Interpretation in Vulvar Edema

Blood tests	Full blood count—all cases	Low hemoglobin—can be seen in malabsorption and chronic disease Raised platelets—seen in inflammatory states such as inflammatory bowel disease Raised white cell count—seen in secondary bacterial infection
	Random glucose—all cases	Raised in diabetes
	Serology—all cases	Syphilis, Epstein–Barr virus, and HIV
	Inflammatory markers (ESR and CRP)—all cases	Raised with infection and inflammatory conditions
	Serum ACE level and prolactin—all cases where clinical diagnosis not apparent	Raised in sarcoid (not specific and also seen with hyperthyroidism, diabetes, and chronic renal disease). Prolactin level raised in sarcoid, but not specific (33)
	Renal function, liver function, and bone profile—all cases where clinical diagnosis not apparent	Raised calcium in sarcoid (33). Bone and liver abnormalities in malignancy
Genital swabs	Herpes polymerase chain reaction	From any ulcers or fissures
	Bacterial culture and sensitivity	Any ulcers or fissures or discharge
	High vaginal swab for fungal type and sensitivities	All cases
	High vaginal swab for *Trichomonas vaginalis* culture or polymerase chain reaction (if available)	All cases
	Chlamydia and gonorrhea polymerase chain reaction	All sexually active cases
Imaging	Chest X-ray	Hilar lymphadenopathy seen in sarcoid (33)
	Ultrasound pelvis	Pregnancy and pelvic mass—causing lymphatic obstruction
	Magnetic resonance imaging pelvis	Fistulae in Crohn's disease, pelvic mass, and congenital gynecological tract abnormality
Stool sample	Fecal calprotectin	Raised in inflammatory bowel and bowel malignancy (38)
Urine sample	Pregnancy test	All cases of fertile age
	Urinalysis	Glucose—suggests diabetes
Biopsy	Vulvar	Granulomas suggest Crohn's disease or sarcoid. May also show malignancy (from ulcers), dysplasia, or specific genital dermatosis
	Bowel via colonoscopy	Granulomas suggest Crohn's disease, but also more rarely sarcoid (39)
	Skin	Can confirm clinical findings histologically of erythema nodosum and erythema multiforme
	Oral ulceration	Granulomas suggest Crohn's disease
Ophthalmic opinion	Slit lamp examination	Arrange if diagnosis not clear even if there are no eye symptoms or signs. Can help diagnose Crohn's and sarcoid (uveitis) (33)
Dermatology opinion	Patch testing	Medicaments—if edema occurring after topical medicinal preparations Other allergens—if no clear cause (bleaches and perfumes in sanitary/incontinence wear and nail polish) (British Contact Dermatitis Society's standard series)
	Dermatological signs	Arrange for confirmation/to make diagnosis and onward management
Sexual health opinion[a]	Infection treatment/further investigation	Sexually transmitted infection and non-sexually transmitted infection causes. Some services have on-site microscopy to assist in diagnosis of infective causes
Gynecology opinion[a]	Gynecological symptoms	If abnormal bleeding, pregnant, or pelvic mass, must have gynecological assessment
Gastroenterological opinion	Bowel symptoms or findings suggesting vulvar Crohn's disease	Any bowel symptoms with vulvar edema should see gastroenterologist. However, Crohn's disease should be considered in absence of bowel symptoms
Immunology opinion	If suspecting semen allergy	Further assessment and management

[a] All women presenting with vulvar edema should have either a sexual health or gynecological assessment if they have presented to other services initially.

Abbreviation: ACE: angiotensin converting enzyme; CRP: c-reactive protein; ESR: erythrocyte sediment rate.

Clinical features include fever, sore throat, headache, and malaise followed by ulcers or lesions in the mucous membranes (such as the mouth, lips, genitals, and eyes).

It is a dermatological emergency and must be promptly recognized so that the patient can be hospitalized for fluid/nutritional replacement and temperature regulation. It is important to review medication history, including any new medications that may be a trigger, so that these can be stopped.

Semen Allergy

Symptoms of semen allergy may include redness, swelling, pain, itching, and pain in the vagina or vulva after exposure to specific protein components in seminal fluid. This can be partner specific and diagnosis is based on clinical history. Immunology referral can allow further investigation and management. The gold standard for diagnosing seminal plasma hypersensitivity is the prevention of symptoms with the use of

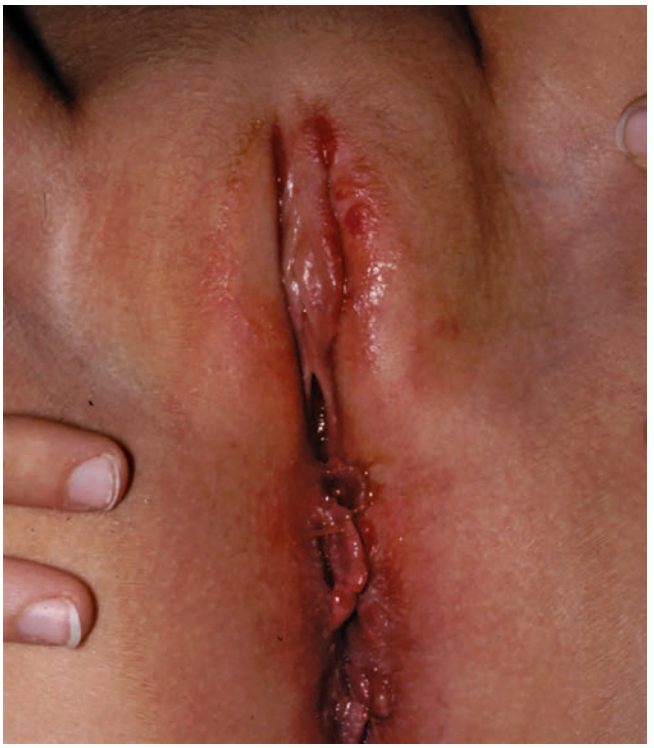

Figure 18.1 Crohn's disease. (From Micali G, Donofrio P, Nasca MR, Veraldi S. *Vulval Dermatologic Diagnosis: Diagnosis by Clinical Presenting Sign*. Boca Raton, FL: CRC Press, 2015, with permission.)

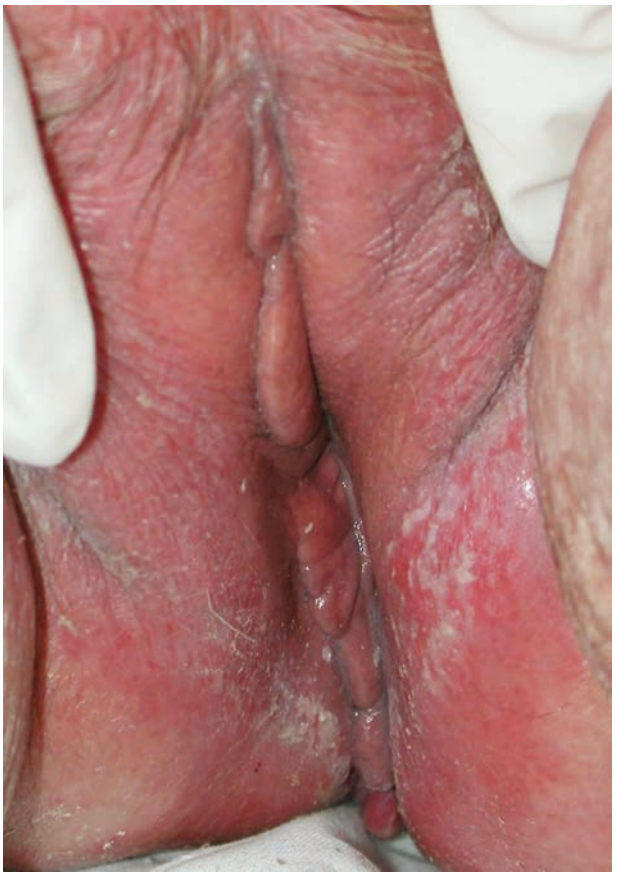

Figure 18.2 Vulvar cellulitis. (From Micali G, Donofrio P, Nasca MR, Veraldi S. *Vulval Dermatologic Diagnosis: Diagnosis by Clinical Presenting Sign*. Boca Raton, FL: CRC Press, 2015, with permission.)

a condom (63). Desensitization is available through immunology for couples wishing to conceive, for example, or with severe allergy and risk of anaphylaxis (64).

Autoimmune Conditions

Common autoimmune conditions include hypothyroidism, hyperthyroidism, vitiligo, lichen sclerosis, lichen planus, rheumatoid arthritis, pernicious anemia, alopecia areata, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, coeliac disease, type 1 diabetes, and Addison's disease. There are many other autoimmune conditions and this is not a definitive list.

Any autoimmune condition increases the risk of others, such as vulvar Crohn's disease and sarcoid. Systemic problems presenting with vulvar edema may have a range of other symptoms (skin, bowel, and eye symptoms) in addition to associated autoimmune conditions.

Family history is vital. Often a patient will have a family history of multiple autoimmune conditions, which the patient themselves will not perceive as linked.

The two main autoimmune conditions resulting in vulvar edema are Crohn's disease and sarcoid. However, remember that lichen sclerosis, lichen planus, and vaginal *Candida* (more common with diabetes) can all cause fissures and secondary infection resulting in edema. Table 18.7 (65) outlines some useful questions when considering an autoimmune cause.

Crohn's Disease

Crohn's disease is a chronic granulomatous inflammatory bowel disorder. There are many extraintestinal manifestations, including uveitis, arthritis, and erythema nodosum, as well as vulvar involvement, which may be asymptomatic. Two diagnostic characteristics have been described (66) that may help the early diagnosis of metastatic Crohn's disease on the vulva. It should be considered as to whether the patient has perianal lesions in the form of skin tags, anal fissures, ulcers, fistulas, perianal abscesses, or anorectal strictures with associated painless vulvar swelling. Vulvar Crohn's disease can predate any bowel symptoms by 10 years. As Crohn's disease is often associated with bowel symptoms, their absence can result in a late diagnosis of vulvar Crohn's disease (2).

Sarcoid

Sarcoid is due to an abnormal inflammatory collection of inflammatory cells (granulomas), typically affecting the lungs, but can occur in any and multiple organs. It may result due to a response to an infection. Presentations can be with shortness of breath, cough, tiredness, arthritis, lymphadenopathy, eye and neurological problems, skin involvement including erythema nodosum, vulvar itch, and edema. It is a diagnosis of exclusion, and chest X-ray, serum angiotensin converting enzyme (ACE) level, bone profile, prolactin, slit lamp examination, and biopsy of any involved tissues can help make the diagnosis. Treatment involves treating symptoms with anti-inflammatories, steroids, or immunomodulators (depending on the severity of symptoms) (35).

Table 18.5 History of Infectious Causes

Problem	Example questions	Implications of response
Vaginal discharge	Have you noticed any change in vaginal discharge?Does it have an odor?	The absence of vaginal discharge does not exclude infection as a cause. *Trichomonas* can present with an odorous discharge (40) (as can more common infections such as bacterial vaginosis) (41) Vaginal *Candida* will typically present with a thick, itchy discharge (36)
Fissures/ulcers	Have you noticed any small cuts or sores to your vulva?	Both can be seen with genital herpes and vaginal *Candida*, where scratching can mimic ulceration. Fissures and ulcers of any cause can become secondarily infected, causing edema Vulvar Crohn's disease can present with fissures, ulcers, and edema all independently (42)
Pain	Do you have any: Pain with sex? Pelvic or lower abdominal pain? Tingling or shooting pain to the vulva or around the legs?	Any cause of vulvar edema can lead to superficial dyspareunia Vaginitis due to *Candida*, atrophy, secondary bacterial infection, or *Trichomonas* can result in vaginal pain, which gets worse throughout vaginal sex Pain and swelling when having sex without a condom, but not with a condom, may suggest semen allergy Abdominal/pelvic masses can result in both vulvar edema, spontaneous pain, and deep dyspareunia Tingling/shooting pains that are intermittent and may precede edema can suggest genital herpes (43)
Urinary symptoms	Do you have any pain urinating? Are you having to urinate more frequently?	Symptoms resulting from vulvar inflammation can mimic a urinary tract infection. Vulvar edema can also predispose to increased risk of urinary tract infections Sexually transmitted infections such as *Trichomonas* can cause dysuria and edema independently (7,44)
Sexual history	Have you got a current partner? Have you had any recent changes in partners? Does your partner have any symptoms?	Recent change in sexual partner can increase risk of having a sexually transmitted infection (45); however, even in long-term relationships, testing for sexually transmitted infections should be considered due to infidelity in one in five marriages (46). Presence of symptoms in a partner can indicate an infective cause such as *Candida* (typically settles spontaneously within 3 days of sexual contact) or other infection (trichomonas—penile rash, dysuria, and urethral discharge (47)—or genital herpes—ulcers and discharge (48))
Contraceptive method	What contraceptive method do you use?	Use of the combined oral contraceptive pill has been associated with increased risk of vaginal *Candida* (36). Depo Provera can have an extreme drying effect, leading to secondary bacterial infection and edema (36)
Medications	Are you taking any medicines?	Use of steroids, immunosuppressants, and antibiotics will increase risk of vaginal *Candida*. Steroids and immunosuppressants can increase frequency of genital herpes (49)
Other medical problems	Do you have to see any health care provider about other health problems?	Diabetes will increase risk of vaginal *Candida* (50) and frequent genital herpes (51)

Table 18.6 History of Dermatological Causes

Problem	Example questions	Implications of response
Onset	Are symptoms intermittent or constant? Is there a pattern to the swelling?	Any relationship to the menstrual cycle might raise the possibility of allergy to sanitary products. Dermatitis can be intermittent
Trigger	Have you used any recent topical treatments? Has there been any change in washing powders or hygiene products? Have you used any new nail polish? Has there been any change in any products used in the genital area, such as lubricants?	Cryotherapy, topical creams for warts or thrush, or new oral medications and exposure to new allergens can result in dermatitis
Associated symptoms	Are you itchy around your vulva?	Sudden-onset itch might indicate contact dermatitis
Menopausal status	Have you gone through the menopause, and if so, how long ago? Are you using any hormone-replacement therapy or topical estrogen?	Postmenopausal women may have atrophy and secondary infection. Some women can have allergies to some topical estrogen preparations
Past medical history	Do have any skin problems or have you had any in the past? Do you have any other health problems?	Genital dermatological problems such as eczema and psoriasis can affect the vulva in addition to extragenitally Other autoimmune conditions (e.g., thyroid disorder) can be linked to lichen sclerosis and lichen planus Asthma, hay fever, and drug allergies can increase the risk of genital eczema (59), semen allergy, and allergic vulvitis
Family history	Do you have any skin problems, allergies, or health problems in your family?	Atopy, autoimmune conditions, or psoriasis present in family members can increase the patient's risk of having similar problems (59)

Table 18.7 History of Autoimmune Causes of Vulvar Edema

Problem	Example question	Clinical interpretation
Medical history	Do you have any other medical problems?	Presence of other autoimmune conditions increases risk more The patient may already be known to have Crohn's disease or sarcoid and think (or have been told by health care providers) that her vulvar edema is not related
Family history	Does anyone in your family have medical problems?	Sometimes you will need to list examples of some autoimmune conditions specifically. Family history of autoimmune conditions will increase patients' risk
Skin	Do you have any rashes?	Erythema nodosum is linked to Crohn's disease
Eyes	Do you have any eye problems?	Uveitis is linked to both sarcoid and Crohn's disease. Dry eyes is linked to sarcoid
Bowels	Do you have any bowel problems?	Crohn's disease can cause loose stool, rectal bleeding, abdominal and rectal pain, and mucous. Remember that there are many causes of these symptoms and, if present, seek advice from a gastroenterologist
Joints	Do you have any joint problems?	Crohn's disease can cause arthritis, typically peripheral arthritis, in which the large joints are affected (65)
Oral	Do you suffer from mouth ulcers? Do you ever get mouth swelling?	Recurrent mouth ulcers and intermittent lip and facial swelling can be seen in Crohn's disease

FURTHER MANAGEMENT

Your management plan will be guided by your diagnosis or working diagnosis; however, do not forget the psychological impact that the condition may have, particularly on sexual function, if there has been associated pain or discomfort. You may need to involve the pain team and/or make a referral for psychosexual counseling.

MANAGEMENT IF NO CAUSE IS FOUND

Vulvar edema, depending on its pathophysiology, has been treated with steroids, furosemide, albumin, and continuous epidural analgesia (67,68). In a case report of massive vulvar edema confined to the labia minora in a lady presenting in her 35th week of pregnancy, simplicity of management was highlighted. The swelling was drained by using a sterile 22-gauge hypodermic needle to make four punctures on each labia. The swelling resolved immediately and did not recur (69).

Prevent recurrent secondary infection by good vulvar skin care (washing with soap substitutes and avoidance of allergens) (70) and treating any symptoms or signs of secondary infection early. For those with frequently recurrent secondary infection, prophylactic antibiotics may be used. Also consider a trial of suppressive genital herpes treatment if edema is intermittent.

Ensure full multispecialty opinion and expert advice (e.g., a regional or national genital edema service) has been sought. The patient should be kept under review and any new symptoms investigated (71).

SUMMARY

Vulvar edema is associated with a variety of conditions and it can be difficult to determine its cause. This guide should help you to determine the origin of the edema and give you practical suggestions to investigate, diagnose, and manage the condition. It is important to consider causes such as Crohn's disease and other rare diagnoses such as arteriovenous (AV) malformations and malignancy so that these can be treated promptly and appropriately.

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Vulvar/vaginal atrophy
A review

Rossella E. Nappi and Barbara Gardella

INTRODUCTION

Life expectancy has significantly increased around the world, and by the year 2025 there will be 1.1 billion women older than the age of 50 years with specific needs in order to enter an active and healthy aging (1). Fifty years of age is a turning point in women's lives because natural menopause—the permanent cessation of menstrual cycles following the loss of ovarian follicular activity—usually occurs between 48 and 52 years of age (2). Therefore, most women will spend at least a third of their lives in the postmenopausal period, a hypoestrogenic state that may bring about significant changes in the female body. Although menopausal syndrome is a multidimensional phenomenon in which biological variables are modulated by intrapersonal and interpersonal factors and are influenced by the sociocultural environment and the health care system, there is a consensus that the fall in ovarian estrogen production is associated with the occurrence of early symptoms and long-term consequences (3). Among the multitude of symptoms that women may suffer in an individual pattern in terms of type, severity and duration, those associated with vulvar and vaginal atrophy (VVA) have a significant impact on quality of life and sexual health (4).

The term "VVA" describes anatomic and physiologic changes in the vulvar and vaginal tissues that are directly related to the reduced circulating estrogen levels associated with menopause and aging. Atrophic vaginitis connotes a state of inflammation or infection that may be present in some women with VVA (5–7). It may also occur as a consequence of other hypoestrogenic states, but this is less common (8). Typical symptoms associated with VVA are dryness, itching, irritation, burning, and dyspareunia, which may negatively influence well-being and partnership. Even urinary symptoms are eventually associated with VVA, such as increased frequency, urgency, dysuria, and recurrent urinary tract infections (rUTIs), as well as urinary incontinence resulting mainly from pelvic floor relaxation (9–11). At variance with hot-flushes that usually resolve over time, VVA has a chronic, progressive nature, and the temporal pattern of symptoms and their clinical relevance are variable (12,13). Indeed, the presence and severity of symptoms, from mild discomfort to great impairment, depend on age, time, and type of menopause, parity and vaginal delivery, frequency of coital activity, cigarette smoking, and certain medical conditions/medications (14–18). Breast cancer survivors are a special group of women who may suffer from VVA and require individualized care (19). Even ethnicity and attitudes towards menopause influence the occurrence and severity of urogenital symptoms (20). Interestingly, VVA has recently been included in a much broader definition of the genitourinary syndrome of menopause (GSM), which was proposed following a consensus conference held in May 2013 (21). The GSM is a more descriptive term than VVA and does not imply pathology. It has the aim of encompassing genital, sexual, and urinary symptoms and describes clinical signs associated with changes in estrogen and other sex steroids at the level of the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra, and bladder (22). Even though it may also include changes due to the effects of aging and other processes on the bladder and pelvic floor, this new definition has the advantage of removing the stigma associated with the atrophy of a private and intimate organ such as the vagina (23), facilitating postmenopausal women in seeking medical advice on urogenital health. There is hope that a more socially acceptable term can be useful to overcoming the medical challenge of VVA or atrophic vaginitis. Indeed, in spite of its commonness at the time of menopause and of its clear link with hypoestrogenism, VVA is under-reported by women, under-recognized by health care practitioners (HCPs), and, therefore, under-treated (24).

VVA AS A CHRONIC CONDITION AFTER MENOPAUSE

After menopause, objective signs of VVA are usually present upon physical examination as some of the main consequences of reduced estrogen levels (5,6,11). Estrogen stimulation is vital to maintaining normal structure and function of the vagina and the lower urogenital tract. Estrogen receptors (both α and β) are widely present in the vagina, vulva, muscles of the pelvic floor, endopelvic fascia, urethra, and bladder trigone during reproductive life, decline with menopause, and may be restored by estrogen treatment. Early data show that untreated postmenopausal women displaying less than 50 pg/mL of estradiol suffer more from symptoms associated with VVA (25). The absence of estrogen stimulation contributes to the loss of mucosal elasticity by inducing the fusion and hyalinization of collagen fibers and the fragmentation of elastin fibers. Even mucosal hydration is reduced in the dermal layer with a reduction of intercellular acid mucopolysaccharide and hyaluronic acid. The vagina loses its rugae, the epithelial folds that allow for distensibility, and there is a shortening and narrowing of the vaginal canal. The mucosa of the vagina, introitus, and labia minora becomes thin and pale and the significant reduction of vascular support induces a decrease in the volume of vaginal transudate and other secretions. Over time, there is a progressive dominance of parabasal cells with fewer intermediate and superficial cells as a marker of a deprived estrogen vaginal squamous epithelium, which becomes friable with petechiae, ulcerations, and eventually bleeding after minimal trauma. With thinning of the vaginal epithelium, there is also a significant reduction of glycogen and, therefore, of the population of lactobacilli, causing

an increase in vaginal pH (between 5.0 and 7.5), and a decrease of vaginal hydrogen peroxide that allows the growth of other pathogenic bacteria, including staphylococci, group B streptococci, and coliforms. Similar anatomical and functional changes in the vulva occur, as well as in the pelvic floor and within the urinary tract, resulting in an impairment of the neurovascular and neuromuscular substrates of the pelvic area. In particular, the vulvar introitus retracts and hymeneal carunculae involute and lose elasticity, leading to significant entry dyspareunia. The urethral meatus appears prominent relative to the introitus, and thinning of the urinary epithelium and weakening of the surrounding tissue may promote reduced urethral closure pressure, reduced sensory threshold in the bladder, and, in some cases, increased risk of rUTIs (5,16,18,26–29). Even androgen receptors are highly expressed in vulvar and vaginal tissues, especially within the vaginal epithelium and also in the lamina propria, with a lower expression in the muscularis layer and blood vessel walls. Aromatase activity and androgen-forming enzymes are also present, implying that testosterone (T) or other precursors of estrogen and androgen production, such as dehydroepiandrosterone (DHEA) and its sulfate DHEAS, may significantly contribute to the functional anatomy of the genital area (30–32). As such, postmenopausal women may suffer from chronic symptoms that cannot regress unless adequately treated. Recent surveys indicate that approximately 50% of postmenopausal women experience vaginal discomfort attributable to VVA (4,24), and the most common symptom is vaginal dryness, with a prevalence ranging from about 3% at premenopause to 47% at 3 years postmenopause (33). Two very recent online surveys (REVIVE-EU and REVIVE-US) from large cohorts of postmenopausal women between 45 and 75 years who were diagnosed with VVA or reported a clinical picture that was consistent with VVA symptomatology showed that vaginal dryness was reported less frequently in Europe than in the U.S. population (47% vs. 55%) (34). In another international survey (VIVA), 45% of postmenopausal women (N = 3520; age range 55–65 years) reported vaginal discomfort, and 83% of them had experienced vaginal dryness as the most relevant symptom, followed by pain during intercourse (42%) (35). It must be mentioned that a true epidemiology of VVA is difficult to determine because most of the data rely on self-reported symptoms, and the severity of symptoms (from mild to severe) is rather subjective (36). In a very recent study (AGATA) conducted in Italy, there was no strict association between signs and symptoms, apart from subjective and objective vaginal dryness (37). It is likely that some women may not report symptoms because they are self-treating, feel that the symptoms are not important enough, abstain from sexual activity because of no partner/a partner with health/sexual problems, or are embarrassed to discuss such an intimate topic (38). As such, HCPs should be proactive in order to help postmenopausal women to disclose the symptoms related to VVA and to seek adequate treatment when vaginal discomfort is clinically relevant. Women are poorly aware that VVA is a chronic condition with a significant impact on sexual health and quality of life and that effective and safe treatments may be available (4). VVA can lead to symptoms not only in response to sexual activity (low lubrication, pain, poor desire and arousal, and impaired sexual pleasure and orgasm), but also during simple activities such as walking or exercising (itching, burning, discharge, unattractive odor, and discomfort). Dyspareunia may be accompanied by postcoital bleeding and secondary vaginismus with pelvic floor hypertonicity triggered by avoidance, anxiety, and loss of sexual desire because of the anticipation of coital pain (5,28). A woman with VVA may also experience bleeding with minimal trauma, such as during a medical examination or when practicing physical activities. Therefore, it is very important to include VVA in the menopause agenda by encouraging an open and sensible conversation on the topic of urogenital health and performing a gynecological pelvic examination, if indicated. According to very recent guidelines for the appropriate management of VVA in clinical practice, it is essential to overcome the vaginal "taboo" in order to optimize elderly women's health care (7,39,40).

VVA IMPACT ON SEXUAL HEALTH

Sexual health is an essential right of human beings (41) and staying sexually active later in life is a key element of successful aging (42). Indeed, the experience of sexual dysfunction is more likely among women and men with poor physical and emotional health and it is highly associated with satisfaction in sexual relationships and overall well-being (43,44). In spite of the frequency of sexual intercourse declining with age (45), a considerable proportion of postmenopausal women are still sexually active (46). Moreover, the majority of postmenopausal European women (71%) reported it was important to them to maintain an active sex life (47).

It is interesting to point out that not all women exhibiting signs of VVA are highly symptomatic from a sexual standpoint. In the Hormone Therapy (HT) Trials of the Women's Health Initiative (WHI), VVA at baseline correlated with sexual inactivity, but among those women (69%) having physical evidence of VVA upon clinical examination, only 10% reported moderate to severe symptoms (48). Sexual dysfunction almost doubles with advanced menopause status (49), and in the Study of Women's Health Across the Nation (SWAN), women reporting vaginal dryness were more likely also to report dyspareunia and lower arousal (50). The Melbourne Women's Midlife Health Project found a significant decrease of women's desire, arousal, orgasm, and frequency of sexual activity and a significant increase in vaginal dryness, poor lubrication, and dyspareunia throughout the menopausal transition, with a rate of sexual dysfunction that ranged from 42% to 88% (33,51). A cross-sectional, population-based study of 1480 sexually active U.S. postmenopausal women (aged 40–65 years) reported that 55% of sexually active women experienced female sexual dysfunction (FSD) and 57% experienced VVA (52). Interestingly, those women with positive scores for FSD were almost four-times more likely to experience VVA in comparison with those women not reporting sexual symptoms. A similar prevalence of FSD (56.8%), mostly related to poor vaginal lubrication, was found in middle-aged Latin American women (age range: 40–59 years), with a wide range of variability depending on different populations (53).

Women's reactions to their VVA varied according to personality, and those discussing VVA symptoms with their HCPs felt that their concerns were dismissed as a normal part of aging without receiving any counseling about treatment options (54). However, the discussion of symptoms with HCPs seems to be the most critical factor for the diagnosis and treatment of VVA (55).

The Global Survey of Sexual Attitudes and Practices, which was administered to 6725 women from 11 countries (56), has shown that women from different cultural backgrounds differ substantially in their experiences, concerns, and reports of vaginal dryness/sexual pain, as well as in their familiarity with personal lubricants as a treatment. In the "women's voices

in the menopause" international survey (57), VVA was deemed to impact quality of life by a higher proportion of women in Finland and Sweden (≥60%) in comparison with women in the UK, the USA, and Canada (≤50%). Among women with vaginal discomfort, 40% declared that VVA had negative consequences on sex life. In spite of this, 63% of women who had experienced VVA had never been treated, while 67% of those who had been treated reported positive effects, including improvements in everyday life (28%), sex life returning to normal (27%), and better quality of life (26%). In the VIVA online survey (35) conducted in Europe and North America in order to further explore women's knowledge regarding vaginal health, 75% of postmenopausal women declared that VVA would have a negative impact on various aspects of life in general, 65% considered that it would have negative consequences on a woman's sex life, 40% thought that it would have negative consequences on marriage or relationships, 36% felt that it would lower quality of life, 31% stated that it would make them feel old, 26% thought that it would have negative consequences on self-esteem, and 13% felt that it would be detrimental to a woman's social life. The areas of a woman's life thought most likely to be negatively impacted by VVA were sexual intimacy (64%), having a loving relationship with a partner (32%), overall quality of life (32%), feeling healthy (21%), and feeling attractive (21%). The REVIVE online survey (58) conducted in 3046 postmenopausal women with VVA symptoms in the USA confirmed the negative impact on enjoyment of sex (59%). Also, the European REVIVE online survey (55) conducted in 3768 postmenopausal women with VVA symptoms found a significant impact of the condition on the ability to be intimate (62%), to enjoy sexual intercourse (72%), and to feel sexual spontaneity (66%).

All of these data indicate that symptoms of VVA are strongly associated with FSD because painful sex (dyspareunia, secondary vaginismus, and non-coital pain) may prevent women from desiring sex, initiating sex, or responding sexually to their partner (52). It is also true that the sexual performance of the partner may affect the clinical relevance of FSD and vice versa (59,60). The Clarifying Vaginal Atrophy's Impact on Sex and Relationships (CLOSER) survey (61) was the first multinational (involving the UK, Finland, Norway, Sweden, Denmark, Italy, France, Canada, and the USA) research study in postmenopausal women coping with VVA in which an equal number of men whose female partners suffer from VVA (4100 females and 4100 males) shared their feelings and the impact of this condition on intimacy. The CLOSER survey revealed that 28% of women did not tell their partners when they first encountered vaginal discomfort, mainly because they felt "it was just a natural part of growing older" (52%) or due to "embarrassment" (21%). Eighty-two percent of male respondents wanted their partner to share their experiences with VVA; males were also more comfortable discussing VVA than females (68% vs. 58%, respectively). Having sex less often (women: 58%; men: 61%), less satisfying sex (women: 49%; men: 28%), and putting off having sex (women: 35%; men: 14%) were the main effects of VVA on the sexual aspect of a couple's relationship. Intimacy avoidance was attributed to painful sex (women: 55%; men: 61%) and women's reduced sexual desire (women: 46%; men: 43%). Interestingly, significant differences were evident in Northern and Southern Europe (62). For example, Southern European women were generally more worried about the long-term effects of vaginal discomfort on their relationship with their partner and were more likely to avoid intimacy because of vaginal discomfort. Accordingly, Southern European women were more likely to report benefits in terms of their relationship with their partner after treatment for VVA. Sociocultural peculiarities were also evident in the UK (63) and North American (64) samples.

Collectively, the CLOSER survey indicates that the evaluation of men's attitudes regarding VVA affecting their postmenopausal partners may lead to better understanding of the impact of VVA on sexual intimacy and may help couples to address the consequences of vaginal discomfort with their HCPs. This will not only enhance the physical quality of life experienced by postmenopausal women, but will also help to restore their self-esteem and their sexual and emotional well-being by removing barriers to intimacy between women and their partners.

VVA DIAGNOSIS

During menopausal consultation, women are often uncomfortable reporting intimate symptoms spontaneously and they assume that VVA is a natural part of aging (4,65). However, postmenopausal women like to be asked about VVA, and very simple questions may help HCPs to "break the ice" in order to discuss vaginal and sexual health (66). Unfortunately, HCPs tend not to take a proactive approach to urogenital health management in the middle and later life age groups, mainly because of inadequate training, constraints of time, personal attitudes, and beliefs that sex is not a priority for older patients (67). Whenever postmenopausal women report urogenital symptoms (Table 19.1) in clinical practice, an accurate pelvic examination should be performed in order to recognize the signs of VVA (Table 19.2). Dyspareunia is generally less reported later in life mainly because older women are less likely to still have a spousal or other intimate relationship and sexually related personal distress declines with age. Tissues may be easily traumatized and irritated and a gentle approach is mandatory in the most severe cases (6,68). It has been comprehensively described that the inspection should include the tissues of the vulva, vestibule, vagina, and urethra and clinical scales may be used in the attempt to quantify VVA (69,70). Organ prolapse and the muscle tone of the pelvic floor should also be noted, as well as other disorders that can cause symptoms similar to those of VVA (71,72). Although VVA is typically a clinical diagnosis, other laboratory tests may be used to support the evidence, such as an evaluation of vaginal pH and the vaginal maturation index, which describes the relative proportion of parabasal, intermediate, and superficial vaginal epithelial cells. A more alkaline pH (>5) leads to a shift in the vaginal flora towards more coliforms and, together with the other atrophic changes, is responsible for increased susceptibility to and frequency of infections and odor, as well as traumatic bleeding associated with sexual intercourse or secondary to speculum insertion during routine gynecological examination. A dominance of parabasal cells, calculated on specimens obtained directly from the lateral upper vaginal walls, indicates hypoestrogenism and atrophy. Thus, the shift to a higher number of superficial cells is a primary end-point of any treatments prescribed to relieve the symptoms of VVA (73). Finally, other tools may be used to quantify the degree of VVA. The Wood's light lamp, a device that emits ultraviolet light, may detect changes in the color according to the thickness of vaginal mucosa (74). The CytoCam, a real-time system for the observation of the human microcirculation, has recently been used to measure vaginal wall thickness and to assess the effects of treatments (75).

Table 19.1 Most Common Symptoms associated with VVA in Menopause

- Dryness (vaginal, vulvar, and genital skin)
- Decreased lubrication with sexual intercourse
- Discomfort with sexual activity
- Irritation/burning/itching
- Vulvovaginal infections
- Dysuria
- Urinary frequency
- Urinary urgency

The potential burden of VVA should be considered not only in sexually active postmenopausal women, but also in women who abstain from sexual activity, because they may suffer even more of the long-term consequence of estrogen deprivation, especially vaginal and introital stenosis, fusion of the labia minora to the labia majora, and other urogenital conditions (16,72,76). Special care should be devoted to women with breast cancer and other gynecological malignancies who are at very high risk of VVA and associated symptoms as a consequence of endocrine chemotherapy, surgery, and/or radiation (77). Finally, severe VVA may be a barrier to adequately assessing both cytologic and colposcopic findings for the prevention of cervical cancer, and it is a very common reason of urgent referral in order to exclude endometrial cancer and other malignancies after an episode of postmenopausal bleeding (78,79). Vaginal occlusion is uncommon (80) but may cause vaginal synechiae and hematocolpos, impeding the early diagnosis of cancer (81).

VVA TREATMENT OPTIONS

The therapeutic management of VVA in the menopause is multifaceted and should include non-hormonal and hormonal preparations according to very recent guidelines (7,39,40). An open dialogue between women and their doctors is needed in order to individualize the most suitable strategy for VVA according to their personal risk–benefit profile, women's preferences, and their expectations. The principles of treatment in women with clinical diagnosis of VVA are: (i) restoration of urogenital physiology; and (ii) alleviation of symptoms. Given the progression of VVA over time, it is mandatory to start an effective treatment as soon as the symptoms become bothering for the woman in order to avoid severe impairment of urogenital tissues with aging. Indeed, it has been shown that more than half of those women who had experienced VVA reported having symptoms for 3 years or longer because they did not feel comfortable discussing VVA with their HCPs (35). By delaying the treatments, unfortunately VVA symptoms may be magnified due to psychosocial factors, such as low self-esteem and poor relationships (82), and may become refractory to treatment.

Table 19.2 Most Common Signs associated with VVA in Menopause

- Decreased moisture
- Decreased elasticity
- Labial resorption
- Pallor/erythema
- Loss of vaginal rugae
- Tissue fragility/fissures/petechiae
- Discharge
- Odor/infections

There is a general agreement that systemic hormone-replacement therapy (HRT) may be prescribed at the lowest effective dose in the absence of contraindications. Indeed, HRT is efficacious in relieving most of the symptoms of VVA because VVA is an integral part of the climacteric syndrome (83). However, when VVA is the sole consequence of menopause, HRT is not indicated and local estrogen therapy (LET) is the first-line treatment for the maintenance of urogynecological and sexual health (84). Moreover, around 10%–25% of women using systemic HRT will still experience VVA symptoms and, therefore, its combination with LET may be useful in order to relieve vaginal dryness, dyspareunia, and other urogenital symptoms, after appropriate counselling (7). Low-dose intravaginal estrogen (conjugate equine estrogens, estradiol, estriol, and promestriene) preparations in various formulations (creams, rings, tablets, suppositories, and gels) are available, with some differences between countries. They have been shown, when used as directed, to be safe and effective, without causing significant proliferation of the endometrium or increases in serum estrogen levels beyond the normal postmenopausal range (85). LET provides vaginal estrogen while minimizing systemic exposure, and results in increased blood flow, increased epithelial thickness, and increased secretions, as well as reduced pH. These physiological improvements represent a reversal of atrophy and lead to a positive clinical outcome for most postmenopausal women. In older women, LET has been shown to improve urinary urge incontinence and overactive bladder symptoms and to reduce the episodes of rUTIs. Generally, there is no need for administering progestogen because low-dose LET has not been associated with increased risk of endometrial hyperplasia (86,87). Given the comparable efficiency of the different low-dose, locally administered estrogen products, the best guide to selecting the type of treatment is the level of effectiveness and safety for the individual patient. In addition, it is important that patients accept and adhere to their treatment in order to fully realize its benefits, and therefore, they have to like the treatment of choice (88). The intravaginal use of DHEA (6.5 mg) has significant positive effects in the treatment of sexual symptoms associated with VVA, and it has the advantage of not significantly increasing plasma levels of sex hormones (89). Every woman with VVA may also be helped by prescribing non-hormonal treatments, such as commercial vaginal moisturizers and lubricants. The characteristics of non-hormonal products are extremely important for efficacy and tolerability in women of any age wishing to relieve vaginal dryness, and those products that are optimally balanced in terms of both osmolality and pH and are physiologically most similar to natural vaginal secretions should be preferred (90). Lubricants are usually used on demand to relieve vaginal dryness during intercourse and therefore do not provide a long-term solution. On the other hand, women use moisturizers on a more regular basis, and these local products may induce some positive modification of genital tissues according to their composition (reduction of pH, maturation of the vaginal epithelium, and improvement of natural moisture). Although over-the-counter treatments may work for women with mild symptoms, they are often inadequate for women with moderate to severe symptoms (7,39,40). However, non-hormonal options are primarily indicated for women wishing to avoid hormonal therapy or for high-risk individuals with a history of hormone-sensitive malignancy, such as breast or endometrial cancer. In case of severe symptoms of VVA, it may be appropriate to discuss the relative risk of using LET with the oncology team as

well as with the patient. Whereas there is very little concern that the use of LET may compromise the effects of tamoxifen in women taking tamoxifen following breast cancer, the situation is different in women treated with aromatase inhibitors, which still represent a contraindication to LET use (91).

In general, physical therapy, including pelvic floor exercises, medical devices, laser technology, and other activities with the aim of learning new areas of sexual expertise, are useful alone or in association with other treatments in order to improve urogenital health (22,92). It is also important to mention that regular sexual activity, when it is possible, facilitates active blood flow to the vagina and increases vaginal lubrication. Psychoeducational programs and cognitive reconstruction have been shown to be highly effective in menopause, namely after gynecological and breast cancers, and such techniques are both for the individual woman and also for the couple (66,91). Indeed, recent data indicate that evaluation of men's attitudes regarding VVA affecting their postmenopausal partners may lead to better understanding of the impact of VVA on sexual intimacy and may help couples to address the consequences of vaginal discomfort with their HCPs (4).

Systemic plant-derived and herbal remedies are very popular alternatives to medical treatments, but their real effectiveness in improving VVA is not proven in well-controlled studies, even though a combination of vaginal phytoestrogens and lactobacilli has proven effective in women with contraindications to hormone therapy (93).

Finally, ospemifene, a selective estrogen receptor modulator (SERM) with unique estrogen-like effects in the vaginal epithelium, is the first oral treatment that has been approved for moderate to severe symptoms associated with VVA (94). At the dose of 60 mg, ospemifene has been shown to reduce symptoms of both dyspareunia and vaginal dryness significantly compared with placebo in randomized phase III studies. The long-term safety of ospemifene up to 1 year has also been shown, with no significant estrogenic or clinically relevant adverse effects reported on endometrial tissue in women with an intact uterus. Given its pharmacological characteristics, ospemifene may be suitable in cured breast cancer survivors (95). Other SERMs may become available in the near future (96).

CONCLUSION

VVA is a chronic, age-dependent condition resulting mainly from estrogen deficiency, and its associated symptoms have a major impact on women and their partners. Early recognition and effective treatment of VVA is necessary in order to enhance sexual health and quality of life and should be part of an overall strategy to meet the challenges of successful aging.

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Female-specific pruritus

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INTRODUCTION

Advances in the understanding of both the pathophysiology and treatment of pruritus have rapidly progressed in the past few decades. Such advances have expanded to the realm of female-specific disorders, bringing increased awareness of the distress that women endure. Yet, due to numerous factors including fear, cultural taboo, or embarrassment, patients are still reluctant to see their physician.

Vulvar pruritus may stem from numerous etiologies. In addition, pruritic conditions may exhibit a predilection for particular anatomical sites. The most common pruritic disorders of the vulva are listed in Table 20.1. This chapter will discuss the most common pruritic conditions commonly encountered in different age groups: prepubertal, reproductive age, and postmenopausal. While some conditions will be encountered in some or all of the different age groups, we have highlighted the principal age-specific pruritic disorders in order to avoid repetition. In addition to pruritus, many patients will also suffer from psychological distress, and physicians must bear this in mind when determining the optimal "patient-oriented" management plan.

PREPUBERTAL

While vulvar pruritus is an exceptionally common ailment across all age groups in the female population, very little has been specifically reported on it in children. Many of the etiologies of vulvar pruritus in the general female population are not observed in the prepubertal age group. However, there are causes of vulvar pruritus that are unique to prepubescents. These differences can be attributed to the divergence of anatomy, physiology, hygiene, and sexual practices between pre- and post-pubertal females (1). Table 20.2 highlights the pathophysiology of itch among the different age groups (2).

In the years before the onset of puberty, the epithelia of the vulva and vagina maintain a low level of estrogen. As a result, the vaginal mucosa is thin and atrophic (1). Moreover, a distinctly neutral pH is not conducive to colonization with *Lactobacillus* bacteria (3). These factors, together with the lack of protective labial fat pads and pubic hair, as well as an increased proximity of the anus (and thus fecal matter) to the vaginal opening, might create an environment that is primed for pathogenic invasion (1).

The main pruritic dermatologic pathologies that affect prepubertal females include atopic dermatitis (AD), irritant contact dermatitis (ICD), psoriasis, and lichen sclerosus (LS) (2).

Atopic Dermatitis and Irritant Contact Dermatitis

The most prevalent causes of prepubertal vulvar pruritus are AD and ICD, which often present as erythematous patches and plaques and may be aggravated by the overuse of topical antifungals and copious washing of the area. Clinically, the labia majora may appear ridged and scaly; the labia minora may be erythematous and desquamated. Patients often report severe pruritus, and preventing children from scratching is extremely difficult (2). Pruritus is exacerbated by extremes in temperature and by any vehicle that causes drying of the skin. The mechanical trauma induced by scratching or rubbing can be severe. Excoriations lead to secondary infections and the skin may become hardened or lichenified. The most important treatment for ICD is the avoidance of irritants (e.g., urine, feces, harsh soaps, fabric softeners, and chlorinated water). Wet clothing (e.g., swimsuits) should be removed as quickly as possible, and limited washing of irritated areas with plain water is advised (1). Medical management of both AD and ICD includes the administration of topical steroids. Other therapies include topical pramoxine combined with hydrocortisone, topical tacrolimus, or topical silvadene. Subsequent secondary infections may be treated with the use of topical antimicrobials or oral antibiotics for more serious cases (1,2).

Psoriasis

Vulvar psoriasis may first appear as an unremitting diaper rash in infants, and then develop into pruritic, non-scaly, well-demarcated, symmetrical red plaques that extend to the perianal area, but spare the mucosal surface of the vagina itself (4,5). The diagnosis of psoriasis that is limited to the vulva is often challenging, but can be aided by the observation of other psoriatic signs, including nail changes, joint abnormalities, and cradle cap, as well as scalp and postauricular rashes (3). Furthermore, a family history of psoriasis can also aid the diagnostician (6). The treatment of vulvar psoriasis includes mid- to high-potency topical steroids or topical tacrolimus (3).

Lichen sclerosus

A total of 7%–15% of all cases of LS occur in prepubertal females (generally 4–5 years of age) (3). The most common location for LS lesions in females is the anogenital region (1). LS can be defined as a chronic, autoimmune, inflammatory skin disease of unknown etiology that affects mucocutaneous tissue. It follows a relapsing and remitting course. Grossly, LS appears as white-colored, hypopigmented plaques distributed in a "figure of eight" pattern, with characteristics of both atrophy and subcutaneous hemorrhage presenting on the vulvar and perianal skin. Lesions presenting on other parts of the body are visible as white, asymptomatic "confetti" spots. Pruritus of the vulvar lesions often occurs in conjunction with soreness, dysuria, and constipation (3). Scarring of the vulvar region may occur over time, often culminating in the loss of genital architecture such

Table 20.1 Common Dermatological Causes of Vulvar Pruritus

Interface dermatitis • Lichen sclerosus • Lichen planus	Carcinoma • VIN • Paget's disease • Vulvar carcinoma
Lichen simplex chronicus	Atrophic vulvovaginitis
Contact dermatitis • Irritant • Allergic	Infections • Candidiasis • STI • Tinea cruris • Molluscum contagiosum
Psoriasis	Infestations • Scabies • Pediculosis pubis • Pinworms
Atopic dermatitis	Immunobullous disease
Seborrheic dermatitis	Drug eruption
Neuropathic • Sacral spinal disease • Post-herpetic • Diabetes	

Abbreviation: VIN: vulvar intraepithelial neoplasia; STI: sexually transmitted infection.

as the labia minora and clitoris (4). Excoriations, bruising, and cracking of the skin are often observed secondary to chronic scratching. As a result, the lesions of LS can be misdiagnosed as sexual abuse (1). The treatment of LS includes high-potency topical steroids and topical calcineurin inhibitors (3). Interestingly, some studies have found that the onset of puberty can culminate in the spontaneous resolution of LS (1).

Infective Vulvovaginitis

Group A streptococcal vulvovaginitis, a condition rarely seen in adults, is the most common culprit of infective vulvovaginitis in prepubertal females (5). These infections may be acute or subacute. The acute infections tend to be more severe, featuring painful, red, weeping plaques, as well as a thin, grayish–white vaginal discharge (3,4). Subacute infections generally present as red, pruritic patches and plaques. Diagnosis is accomplished via lesion culture and treatment involves oral antibiotics (e.g., penicillin, amoxicillin, or cephalexin). Infective vulvovaginitis is less commonly caused by *Staphylococcus aureus*, *Haemophilus influenzae* (due to routine vaccination), and *Shigella* (3).

Non-bacterial causes of infective vulvovaginitis include scabies, public lice, and pinworm infestations, and are summarized in Table 20.3 (7–11). Patients suffering from these conditions often report intense pruritus and may also present with an eczematous rash.

Fungal infections, including candidal vulvovaginitis, are rarely seen in children, as the unestrogenized vagina is a poor reservoir for chronic fungal growth (6). If present, sexually transmitted infections such as gonorrhea and chlamydia warrant careful investigation into sexual abuse (1).

Poor hygiene and vaginal foreign bodies are important differential diagnoses of vulvar pruritus in prepubescent patients (3). All patients with vulvar pruritus should be counseled regarding personal hygiene, dressing habits, and the avoidance of irritants. Young patients in particular are prone to poor hygienic habits, including incorrect cleansing of the vulva after urination or bowel movements. For example, fecal matter may be inadvertently passed onto the vulva by improperly wiping from back to front. Furthermore, tightly worn non-cotton pants or undergarments limit the movement of air and

Table 20.2 Pathogenesis of Vulvar Pruritus in Prepubertal, Reproductive-Age, and Postmenopausal Females

	Prepubertal females	Reproductive-age females	Postmenopausal females
Estrogen levels	Low—facilitates vulvovaginal bacterial colonization	High—facilitates vulvovaginal fungal colonization	Low—facilitates vulvovaginal bacterial colonization
Vulvovaginal pH	>4.5	≤4.5	>4.5
Lactobacillus colonization	Absent	Present	Absent
Vulvovaginal mucosa and epithelium	Thin and atrophic Lack of protective labial fat pads and pubic hair	Rich in glycogen	Thin and atrophic Decreased collagen Impaired wound healing

Table 20.3 Common Parasitic Infestations associated with Genital Pruritus

Infestation	Scabies	Pediculosis pubis	Pinworm
Cause	*Sarcoptes scabiei*	*Pthirus pubis*	*Enterobius vermicularis*
Clinical features	Itch ++ Burrows less commonly identified on the vulva	Itch ++ Identification of lice *Maculae ceruleae* at feeding site (notably the mons pubis)	Itch ++ (perianal and genitals) May be asymptomatic Presence of eggs under fingernails
Pruritus pathophysiology	Increased nocturnal activity Immune activation (Th2) with release of pruritogenic cytokines Activation of protease-activated receptor-2	Immune system activation Hypersensitization to louse saliva	Increased nocturnal activity Immune activation (Th2) with release of pruritogenic cytokines
Treatment	Topical permethrin 5% Oral ivermectin in treatment-resistant cases and crusted scabies	Topical permethrin 1% Pyrethrin with piperonyl butoxide	Antihelminthic therapy

stimulate perspiration, thus promoting a wet and warm habitat that is conducive to the growth of bacteria and fungi (1).

While many of the dermatoses that contribute to vulvar pruritus in prepubertal children are known, there is still much to be investigated within this field. Pruritic conditions in this age group can significantly impact the quality of life of both children and their parents, and insight into the causes and treatments of these pathologies can aide in the avoidance of associated morbidities.

REPRODUCTIVE AGE

The onset of puberty triggers significant changes in the cutaneous environment of the vulvar region. The driving force behind these changes is increased production of estrogen, which acts on vulvar keratinocytes to induce a number of environmental alterations. At puberty, the previously neutral pH of the vulvovaginal area becomes acidic (pH 4), which facilitates regional colonization with lactobacilli (12). In addition, menarche induces cyclical variations in hormone levels, with corresponding effects on epithelial cell proliferation. A diverse array of pathologies can cause pruritus in these patients. Common causes include vulvovaginal candidiasis (VVC), contact dermatitis, lichen simplex chronicus (LSC), and psoriasis (13).

Vulvovaginal Candidiasis

Pruritus is the predominant symptom of VVC, a condition in which excessive growth of yeast occurs in the vaginal region. Itch in VVC can be severe, and may occur with concomitant burning, soreness, dysuria, and dyspareunia. VVC is most commonly caused by overgrowth of the species *Candida albicans*, which colonizes the lower genital tract of up to 20% of healthy women of reproductive age (14). The incidence of VVC is highest in this age group due to increased levels of estrogen, which enhances the ability of *Candida* to adhere to the vaginal epithelium (15). VVC is often exacerbated in the premenstrual phase of the menstrual cycle, when estrogen levels are highest. Moreover, VVC occurs with greater frequency with estrogen-containing oral contraceptive use, pregnancy, and hormone-replacement therapy. Additional risk factors include the use of antibiotics, diabetes, and HIV/AIDS.

Clinically, VVC often presents with vulvovaginal erythema and edema. Vulvar excoriations and fissures may also be visible. If present, discharge is usually odorless, and may be thin and watery or thick and white (cottage cheese-like). Diagnosis is achieved through a wet mount revealing characteristic budding, pseudohyphae, and hyphae. Additionally, pH is typically normal; however, the pH of diabetic patients may be elevated in intertriginous areas, which may facilitate *Candida* overgrowth (16). Treatment of VVC consists of topical or oral azole preparations. Although both routes of administration are effective, many women prefer the convenience of oral therapy (17).

A subset of patients experience recurrent VVC, defined as four or more episodes of symptomatic infection within 1 year. In such cases, vaginal cultures should be taken to confirm the diagnosis and identify the pathogenic species. Management of recurrent cases is difficult, and the reduction of risk factors should be emphasized (18).

Allergic and Irritant Contact Dermatitis

Itch may also be present in ICD; however, burning and stinging sensations are often the predominant symptoms. Repeated exposure results in the development of vulvar erythema and edema. Common causes of ICD in the vulvar region may include harsh soaps, lubricants, certain sanitary pads, urine, and some topical medications (19).

Table 20.4 Common Agents associated with Irritant and Allergic Contact Dermatitis

Irritant contact dermatitis	Allergic contact dermatitis
Potential medications • Antifungal therapies (e.g., imidazole) • 5-fluorouracil cream • Capsaicin cream • Certain topical lotions, gels, and creams	Potential medications • Neomycin • Sodium metabisulfie (constituent of topical antifungal medication) • Benzocaine • Chlorhexidine • Ethylene diamine • Lanolin
Hygiene • Certain antiseptic wipes • Certain sanitary pads and tampons • Certain douches • Certain kinds of synthetic underwear	Hygiene • Very rarely sanitary pads
Moisture (if left on skin) • Urine • Feces • Sweat • Vaginal discharge • Semen • Lubricants and spermicides	Cosmetics • Certain kinds of perfumes • Certain nail polishes
Bathing and washing • Harsh soaps and cleansers and antiseptic washes • Certain detergents • Overzealous cleaning • Rough wash cloths	Other • Thiuram (constituent of rubber condoms) • Dyes (black hair dyes; also in underwear)
Friction • Skin folds • Exercise • Sexual intercourse	

Diagnosis should be based on a constellation of suggestive findings from the patient-provided history and clinical presentation. Patch testing may be useful in instances where a particular agent is suspected, but is not needed in the majority of cases. Management involves discontinuation of the offending agent, with the addition of topical steroids in cases of marked inflammation.

Pruritus is a common feature of allergic contact dermatitis (ACD). In ACD, burning often accompanies itch, but is less pronounced than the pruritus. Erythema and edema of the vulvar region may be present. Symptoms initially present 48–72 hours after allergen exposure, but can develop within hours of contact once sensitization has occurred (20). Care should be taken to elucidate the use of new products or medications, as these often serve as the cause of ACD. Commonly implicated agents include neomycin, benzocaine, and sodium metabisulfite. Table 20.4 highlights the main causes of both ICD and ACD.

Lichen Simplex Chronicus

Pruritus is the inciting factor in the development of LSC (Figure 20.1), a condition that arises secondary to chronic scratching or frictional irritation. Patients often describe a

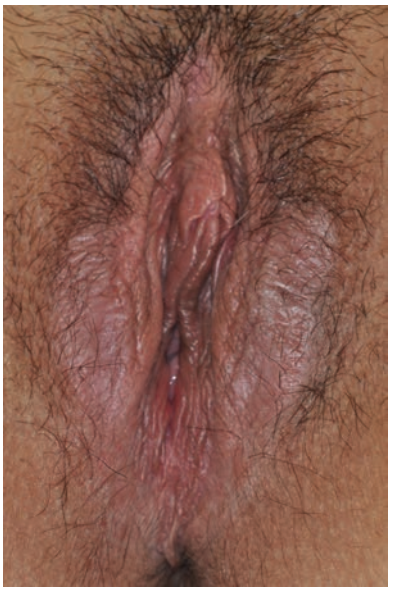

Figure 20.1 Lichen simplex chronicus. Thickened plaques with accentuated skin markings. (Courtesy of Lynette J. Margesson, MD.)

pleasurable sensation from scratching. LSC may develop in the vulvar region in response to a number of pruritic pathologies. Implicated causes range from inflammatory conditions, including ACD, to neuropathic conditions, including spinal nerve compression. In some cases, psychological factors may also be involved. Clinically, vulvar LSC is characterized by well-defined, hyperpigmented, lichenified plaques, often located on the hood of the clitoris, labia majora, and the posterior commissure (20). Excoriations may also be present, and secondary infection may occur.

Treatment should be tailored according to underlying etiology. In cases of inflammatory origin, topical steroids or topical calcineurin inhibitors may be beneficial (20,21). In cases of unclear etiology, a neuropathic cause should always be considered. Lumbosacral spinal imaging studies, including magnetic resonance imaging or X-ray, may be useful in ruling out sacral nerve compression as a cause of LSC (22). If a neuropathic cause is identified, treatment with neuromodulatory agents such as gabapentin and pregabalin may prove useful (3). Neural hypersensitivity may develop over time, which may perpetuate pruritus. Therefore, topical preparations that reduce neural signaling, such as pramoxine or a compounded formulation of topical ketamine, amitriptyline, and lidocaine, may help reduce the pruritus. The importance of scratching cessation must be emphasized as an integral part of LSC management.

Psoriasis

Patients who suffer from psoriasis (Figure 20.2) may experience pruritus in the vulvar region. In such patients, well-defined, salmon-colored plaques may be present on the keratinized surfaces of the mons pubis or labia majora. Additionally, inverse psoriasis may be present in the intertriginous folds, characterized by smooth red plaques. In a subset of patients with psoriasis, vulvar pruritus may occur in the absence of skin manifestations. The presence of vulvar psoriasis may

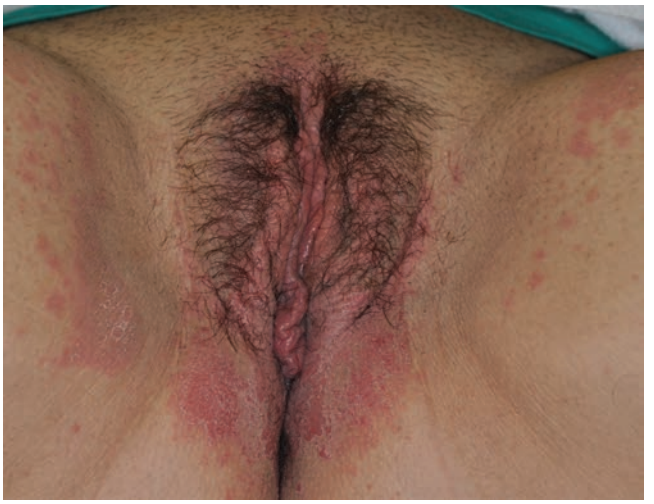

Figure 20.2 Psoriasis. Erythematous plaques with silvery scale on a background of irritant contact dermatitis. (Courtesy of Lynette J. Margesson, MD.)

have a significant impact on quality of life and sexual health. Involvement of the vulvar region may cause dyspareunia, as well as post-coital exacerbation due to köebnerization (23). Treatment should consist of low- to mid-potency topical steroids, with potency escalation as clinically indicated. Topical vitamin D analogues, coal-tar preparations, and calcineurin inhibitors are alternative therapies (3,24). However, data on genital psoriasis and the treatment thereof are scant. Therefore, further research in this field is warranted.

POSTMENOPAUSAL

Estrogen could be vital in maintaining the integrity of vulvar structures. After menopause, systemic levels of estrogen decrease, causing disruption of epidermal skin barrier function. In addition, vaginal pH increases, creating an environment that is conducive to serine protease activity, which may trigger itch through the activation of protease-activated receptor-2 (PAR-2).

The most common pruritic vulvar diseases in the postmenopausal age group include LS, lichen planus (LP), LSC, ICD, and atrophic vulvovaginitis.

Lichen Sclerosus

LS (Figure 20.3) was first described in 1887 (25). Previous terminology included LS et atrophicus, vulvar dystrophy, and white-spot disease; however, LS is now the accepted nomenclature that encompasses both genital and extragenital pathology.

Between 1 in 300 and 1 in 1000 women may be affected with LS (26). Goldstein et al. reported a prevalence of 1.7% in a cohort of 1675 consecutive patients who presented to a general gynecology clinic within a 3-year period. A total of 54% of the LS patients in this study were postmenopausal (27). There is a bimodal distribution with peaks in prepubertal and postmenopausal women.

The exact etiology of LS is unclear; however, it is widely believed to be an autoimmune disorder that occurs in genetically predisposed individuals. This theory is corroborated by the association between LS and other autoimmune diseases (e.g.,

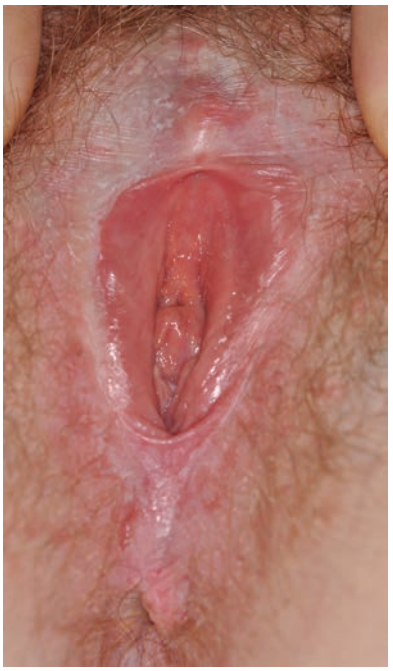

Figure 20.3 Lichen sclerosus. Shiny, atrophic plaques with loss of vaginal architecture. (Courtesy of Lynette J. Margesson, MD.)

autoimmune thyroiditis, alopecia areata, vitiligo, and LP). In addition, IgG autoantibodies targeting the extracellular matrix 1 protein have been discovered in 74% of women with anogenital LS (28). Basement membrane zone antibodies (BP 180 and BP 230) were previously identified in 33% of vulvar LS cases (29); however, a recent study identified these antibodies in only 3.4% of vulvar LS patients (30). Ongoing research is warranted in order to elucidate this further. Factors that may induce this autoimmunity include trauma and irritants. The role of infection as a precipitating factor remains controversial (25). Hormonal involvement may also play a role in the underlying pathophysiology.

The most common presenting symptoms are pruritus and pain. Other symptoms include dyspareunia, dysuria, and sexual dysfunction. Patients may be asymptomatic, which makes diagnosis challenging. On examination, there are porcelain-white or waxy papules and plaques, along with areas of sclerosus and atrophy. Other clinical features include edema, excoriations, lichenification, fissures, purpura, and scarring. Erosions and ulcerations generally occur if there is irritation, infection, or carcinoma. There is the characteristic "figure of eight" or "hourglass" pattern, with involvement of the clitoris, clitoral hood, labia majora, labia minora, interlabial sulci, perineum, and perianal. Involvement of the genitocrural folds, thighs, and buttocks may also occur. There is no vaginal involvement.

Extragenital LS may involve the neck, shoulders, axillae, trunk, breasts and submammary area, periumbilical region, flexor aspects of the wrists, buttocks, and thighs. Rarely, the scalp and acral areas may be involved. Extragenital LS may also be present in up to 15%–20% of genital LS cases (31). However, only around 6% of extragenital LS occurs as isolated cases (26). The diagnosis can be made clinically, although a biopsy is warranted if there is clinical ambiguity. Skin biopsy in children should be avoided.

Treatment consists of both topical and systemic therapy. High-potency topical steroids are effective in the majority of cases. Calcineurin inhibitors are a useful alternative. Systemic therapies include Psoralen and UV A light (PUVA), ultraviolet B light (UVB), methotrexate, and hydroxychloroquine.

Up to 3%–5% of anogenital LS cases can progress to squamous cell carcinoma. Consequently, long-term follow-up is required. There have been no reported cases of malignant transformation in extragenital LS.

Lichen Planus

LP (Figure 20.4) is an autoimmune mucocutaneous disorder that mainly affects postmenopausal women. LP may affect the genitalia and may occur alongside extragenital involvement affecting the scalp, nails, and mucous membranes (oral, esophageal, urinary tract, and anus). The constellation of erosive LP involving the vulva, vagina, and gingiva is termed Hewitt–Pelisse syndrome (vulvovaginal–gingival syndrome) (32). This can clinically mimic mucous membrane pemphigoid. In addition, an association with hepatitis C infection has been reported (33).

LP is characteristically itchy. Other symptoms include pain, dyspareunia, and dysuria; however, patients may be asymptomatic. On examination, there may be purple, polygonal papules, plaques, and bullae that may be erosive or hypertrophic. White, lacy reticular lines (Wickham's striae) may cover these lesions and may also be present on the oral mucosa. There are three types of LP: erosive, classical, and hypertrophic. Erosive LP is the most common variant. It usually involves the introitus and is characterized by painful erythematous patches and erosions. Diagnostic criteria were recently published for erosive LP (34). Vulvovaginal LP is present in around 20%–25% of patients with oral LP (35). Diagnosis is usually made clinically; however, histology is warranted in the context of clinical ambiguity.

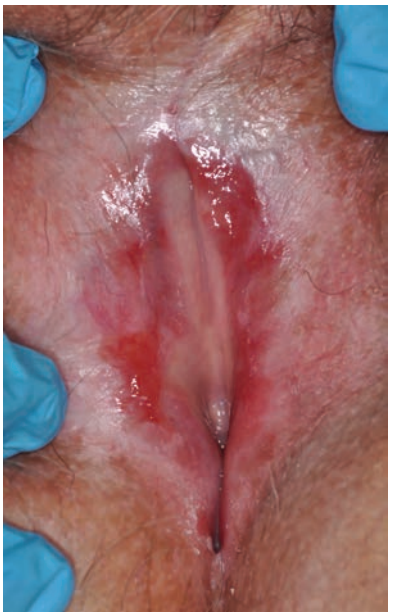

Figure 20.4 Lichen planus. There is evidence of erosive lichen planus. The patient suffered from intense pruritus. (Courtesy of Lynette J. Margesson, MD.)

Table 20.5 Comparison of the Interface Dermatoses (Lichen Sclerosus and Lichen Planus)

	Lichen sclerosus	Lichen planus
Epidemiology	Between 1 in 300 and 1 in 1000 women	Ten-times less common than lichen sclerosus
Location	No vaginal involvement	Vaginal involvement
Principal symptoms	Itch +++ Burning sensation	Itch +++ Burning sensation
Associated features	Autoimmune disorders Extragenital lesions	Wickham's striae Extragenital lesions
Scarring	Scarring present	Scarring present

First-line treatment for vulvovaginal LP consists of topical steroid therapy; however, systemic or intralesional steroids may be needed for resistant or severe cases. Steroid-sparing agents include methotrexate, mycophenolate mofetil, hydroxychloroquine, and acitretin.

Complications of LP include the development of squamous cell carcinoma, psychosocial issues, and vulvar hyperalgesia.

Table 20.5 highlights some comparisons between LP and LS (4,36,37).

Irritant Contact Dermatitis

ICD (Figure 20.5) may also be present. Urinary incontinence, urge, or overflow are common in the postmenopausal age group. In addition, decreased mobility and obesity impair the ability to ensure that the genital area is dry and clean (38). Alkaline urine, along with the existing alkaline vulvar environment, creates a propensity for itch induction through serine protease-mediated activation of PAR-2 (39). Furthermore, there is vulvar skin atrophy, causing increased sensitization (3).

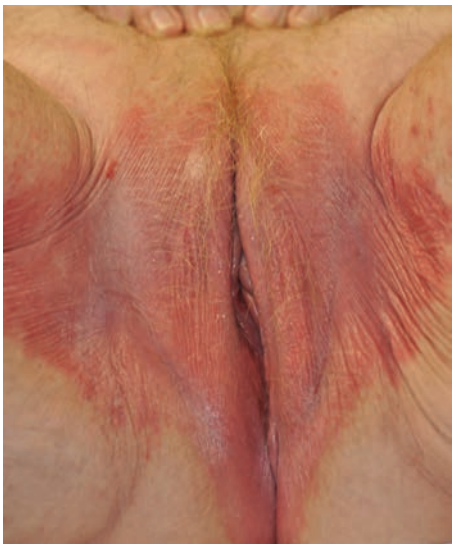

Figure 20.5 Contact dermatitis from incontinence cleansers. On examination, there are symmetric, well-defined erythematous plaques. (Courtesy of Lynette J. Margesson, MD.)

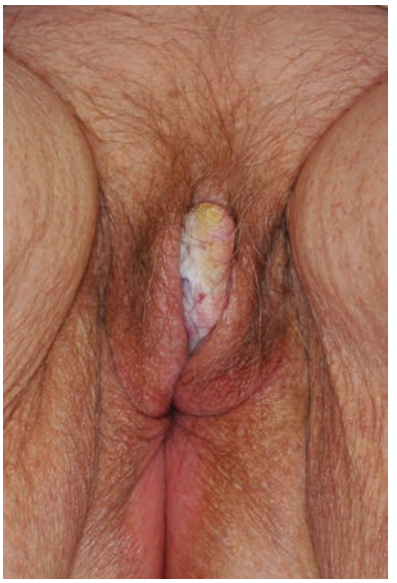

Figure 20.6 Squamous cell carcinoma of the vulva. This patient presented with symptoms that were suggestive of lichen simplex chronicus, highlighting that genital examination is mandatory. (Courtesy of Lynette J. Margesson, MD.)

Carcinoma

Vulvar carcinoma is an important consideration in a patient presenting with vulvar pruritus, particularly in refractory cases. Examination may reveal an irregular mass, non-healing ulcerations, erosions, bleeding, and pain. Physicians should have a low threshold for biopsy where there is clinical suspicion of malignancy.

Vulvar carcinoma can be classified into vulvar intraepithelial carcinoma and invasive carcinoma (squamous cell carcinoma; Figure 20.6) and is covered in more detail in a separate chapter.

Atrophic Vulvovaginitis

Atrophic vulvovaginitis, is a condition that is characterized by atrophic genital structures. It is commonly encountered in postmenopausal women due to decreased estrogen levels. Atrophic vulvovaginitis may rarely be observed in premenopausal women, due to use of progesterone pills, postpartum state, or lactation, as well as any cause of hyperprolactinemia, all of which may contribute to the presentation of atrophic vulvovaginitis.

Atrophic vulvovaginitis may manifest as vulvar dryness, itch, pain, and dyspareunia. Other symptoms include abnormal discharge and urinary tract infections. Decreased estrogen levels alter the microbial flora—from lactobacilli in premenopausal women to Gram-negative organisms in postmenopausal women—increasing the risk of developing urinary tract infections (40,41). On examination, the vulva will be pale and thin, with atrophy of the labia and clitoris. Irritation can be caused with only minimal stretching of the vulva. Petechiae may be present (42,43).

Diagnosis is entirely clinical. Biopsy may be performed if there is diagnostic uncertainty.

The mainstay of treatment is estrogen, either as a cream, ring, or pessary. Oral estrogen may also be used. There is an increased risk of estrogen-dependent tumors (e.g., breast and ovarian cancer), along with thromboembolic disease, migraines, depression, and metabolic and liver impairment with estrogen therapy. Gentle skin care utilizing moisturizers and non-soap cleansers should also be encouraged.

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Vulvar lichen sclerosus

Jill M. Krapf and Andrew T. Goldstein

INTRODUCTION

Lichen sclerosus (LS) is a chronic inflammatory mucocutaneous disorder that shows a predilection for the anogenital area. A French author named Hallopeau first described this condition as an atrophic variant of lichen planus in 1887, referring to it as "lichen plan scléreux" (1). In 1976, the newly formed International Society for the Study of Vulvar Diseases, renamed as the International Society for the Study of Vulvovaginal Diseases (ISSVD), formally adopted the term "lichen sclerosus" to refer to this condition (2).

Vulvar LS is a potentially debilitating and chronically relapsing disease that may lead to destructive scarring, impairment in sexual function, and the potential for malignant transformation. Early diagnosis, prompt treatment, and appropriate follow-up are extremely important in order to limit these negative sequelae (3). LS may be encountered by a variety of medical providers, including gynecologists, dermatologists, dermatopathologists, general practitioners, pediatricians, nurse practitioners, physician assistants, and certified nurse midwives. A solid knowledge of this disease is essential to ensuring proper diagnosis and treatment. This chapter will provide a clinical review of vulvar LS, focusing on diagnosis, treatment options, and clinical follow-up.

EPIDEMIOLOGY

The exact prevalence of LS is largely unknown and difficult to determine. Patients may present to various clinical specialties, physicians do not always recognize the condition, and patients may not report symptoms due to embarrassment or lack of symptoms (3). In a community-based dermatology practice, Wallace (4) calculated a prevalence of 0.1%–0.3% (cited by (3), p. 28). Both males and females may be affected and display anogenital disease, with a higher incidence in women. Although the disease may occur at any age, there is typically a bimodal onset in prepubertal girls and peri- or post-menopausal women. However, it is important to consider that a substantial number of women with LS (up to 40%) will display onset of symptoms and cutaneous changes of vulvar LS during their reproductive years (5,6).

The estimated prevalence in premenarchal girls is 0.1%, with a mean age of presentation at 5 years (5,7). Of 1675 women presenting to a general gynecology practice in the USA, 1.7% were found to have biopsy-proven vulvar LS. Of these patients, 54% were postmenopausal and about a third of patients were asymptomatic at the time of diagnosis, but already displayed scarring of the clitoral prepuce or resorption of the labia minora (8). In an elderly population of postmenopausal nursing home residents (average age of 82 years), 1 in 30 women were found to have vulvar LS (9).

Although the mean age of symptom onset is 45–55 years, mean age at diagnosis has been found to be 60 years, suggesting a significant delay in diagnosis of this condition (5,6). Extragenital LS lesions occur in about 11% of women with vulvar LS (5).

PATHOGENESIS

The exact pathogenesis of LS is unclear, with potential factors including genetic predisposition, autoimmune disorder, local immune response, sex hormone factors, and specific infections.

Genetics

Familial predisposition has been reported in LS; however, an inheritance pattern for this condition has not been clearly established. In a study of 1052 women with vulvar LS, a positive family history was found in 12% of cases, suggesting a genetic contribution (10). Studies have found a significant association of LS with human leukocyte antigen (HLA) class II antigens, which are expressed on immunocompetent cells that recognize foreign antigens (2). Specifically, women with LS demonstrated a statistically significant difference in expression of HLA-DQ7, -DQ8, and -DQ9 compared with controls, indicating an association with the disease (10,11). There have been no associations reported with HLA class I antigens, which are expressed on the surfaces of all nucleated cells and platelets (2). Genetic studies have also identified an association with interleukin (IL)-1, a cytokine involved in regulating the inflammatory response (12).

Autoimmune Disease and Local Immune Response

Many experts consider LS to be an autoimmune disorder. This is supported by an association with certain HLA haplotypes as discussed above, as well as the disease displaying characteristics of other autoimmune conditions: higher prevalence in females, an association with other autoimmune diseases, and the presence of autoimmune antibodies (13,14). The most frequent autoimmune diseases associated with LS include autoimmune thyroiditis, alopecia areata, vitiligo, pernicious anemia, and lichen planus (2,14,15). Other conditions have also been reported in association with LS, such as diabetes, cicatricial pemphigoid, primary biliary cirrhosis, systemic lupus erythematosus, lupus panniculitis, and polymyalgia rheumatic (15). Oyama et al. (16) identified circulating IgG autoantibodies to a specific skin antigen, extracellular matrix protein 1 (ECM1), in the sera of 74% of patients with vulvar LS, compared with 7% in controls. The authors theorized that in LS, acquired autoantibodies disrupt the function of ECM1, contributing to disease

pathology (16). In comparing expression patterns of ECM proteins and related growth factors in LS compared to healthy skin, Gambichler et al. (17) found that expression of ECM1 and connective tissue growth factor (CTGF) is altered in LS, with up-regulation of CTGF possibly inducing the accumulation of ECM proteins and maintaining fibrosis in chronic LS.

It is thought that absence of the suppressive function of regulatory T cells plays an important role in inducing autoimmunity (18). Almost 50% of vulvar biopsies of LS were found to contain T cells with a rearranged receptor gene (19). In a small subset of LS patients, systemic T-cell immune deficiencies were identified, leading to dysregulation that could allow for malignant transformation (20,21).

Sex Hormones

Estrogen and androgen deficiency has been explored as a potential cause of LS, related to a defect in the enzyme 5α-reductase (22). This may explain the lack of efficacy of hormonal therapies in LS (2). In an analysis of 110 samples, estrogen-related receptor-α (ERR-α), a regulator of cell energy metabolism and inflammatory processes, was found to be reduced in almost 80% of patients with childhood-onset LS and 51% of patients with adult-onset LS. Absence or a substantial reduction in ERR-α was found in all 50 samples of vulvar squamous cell carcinoma (SCC), indicating that estrogen receptor expression may play a role in the pathogenesis of LS and related vulvar SCC (23).

A retrospective case–control study of 40 premenopausal women with early-onset LS compared potential risk factors with a matched control group of 110 unaffected women. Oral contraceptive (OCP) use was found to be significantly different between the groups, with 100% of the LS patients compared to 66% of the control group taking such medications. Interestingly, OCPs with antiandrogenic activity were used by 70% of the LS patients compared to 48% of controls, suggesting that the antiandrogenic properties of OCPs may contribute to the development of early-onset LS in susceptible women (24). Studies have not shown significant clinical changes related to the menstrual cycle, and the effects of pregnancy on LS symptomatology have been conflicting (11,25).

Infection

Infectious causes, such as human papilloma virus (HPV), acid-fast bacteria, and spirochete *Borrelia burgdorferi*, have been investigated, but no clear relationship has been identified (14,26).

CLINICAL PRESENTATION

Symptoms

Vulvar itching, especially at night, is the most common presenting symptom of LS. There is no correlation between the degree of pruritus and superficial extent of vulvar lesions present (2). It is also important to note that LS may be entirely asymptomatic and found incidentally on gynecologic examination (8).

With disease progression, scratching and sclerotic changes lead to erosions and fissures, which may result in pain with urination, defecation, and intercourse. Fissures in the perianal area may result in painful defecation, constipation, and stool retention (14). Seventy-nine percent of women with LS report chronic vulvar pain (27).

Vulvar LS can cause different forms of sexual dysfunction, with introital dyspareunia, decreased orgasm, and decreased coital frequency (28). In a study of 45 women with vulvar LS, the most common sexual complaints included vulvar pain, introital dyspareunia, and reduced frequency of sexual intercourse (25). Progressive scarring may lead to narrowing of the vulvar vestibule and vaginal introitus, resulting in loss of tissue elasticity and easy tearing at the base of the fourchette during intercourse (2). A questionnaire of 215 women with vulvar LS revealed that of all quality of life domains, sexual function was the most impacted. Compared to controls, LS patients scored significantly lower in sexual desire, arousal, lubrication, orgasm, satisfaction, and higher in pain, causing significant sexual distress (29). Even after adequate treatment confirmed by improvements in biopsy specimens, women with vulvar LS continued to have significant sexual dysfunction, as assessed by the Female Sexual Distress Scale (28).

Findings/Signs

Vulvar LS most commonly affects the medial labia majora, interlabial creases, labia minora, clitoral hood, clitoris, and posterior fourchette. Perianal LS occurs in up to 60% of women, with skin changes involving the genitocrural creases, perineum, and perianal area. This pattern of involvement has characteristically been described as a figure of eight or hourglass configuration (14). Although LS does not typically affect the vaginal mucosa, two case reports have demonstrated vaginal involvement, possibly related to vaginal prolapse (30,31).

Lesions often appear as ivory-white atrophic patches and plaques with a waxy texture or epidermal wrinkling, characteristically described as a "cigarette paper" appearance (Figure 21.1). Fissures, erosions, ulceration, and purpura (Figure 21.2) may also be seen (14). Fissuring often occurs in the perineum, interlabial sulci, and anterior vestibule,

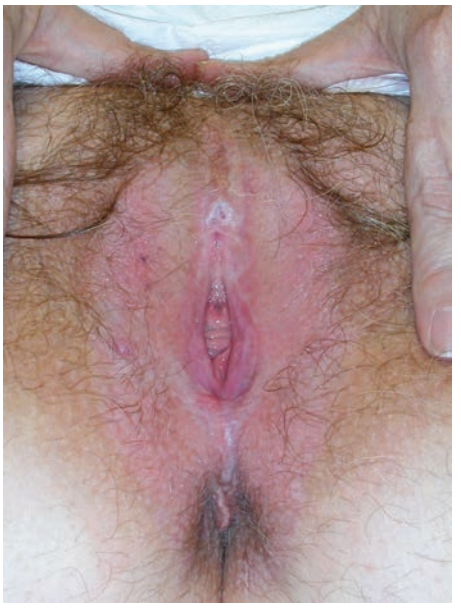

Figure 21.1 Ivory-white atrophic patches and plaques with a waxy texture are characteristic of vulvar lichen sclerosus, often described as a "cigarette paper" appearance.

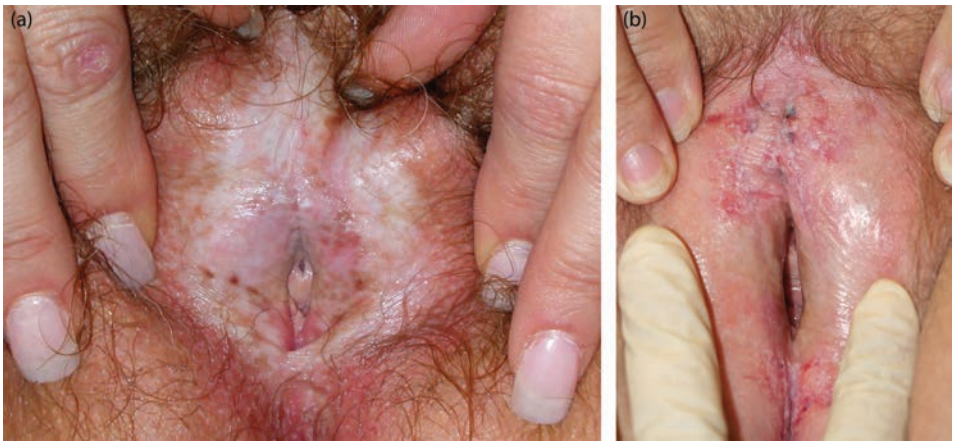

Figure 21.2 Erosions (a), ulcerations (b), and purpura (a,b) may be seen with more severe vulvar lichen sclerosus.

between the clitoris and the urethral meatus (Figure 21.3). Repeat scratching may lead to thickened skin, or lichenification (Figure 21.4), with ecchymoses and hemorrhage. With disease progression, the labia minora may adhere to surrounding structures (2).

Severe chronic inflammation leads to agglutination, labial resorption, phimosis of the clitoris, and narrowing of the introitus (Figure 21.5). The labia minora may be decreased in size or completely absent. Agglutination of the clitoral hood can result in clitoral phimosis (Figure 21.6). In these cases, the clitoris may not be visible, but is still palpable and neurologically intact. Accumulation of keratin debris may result in the formation of a smegmatic pseudocyst or a smegmatic pseudocyst abscess, leading to pain in this area. Scarring of the introitus may lead to narrowing between the urethral meatus and frenulum of the clitoris, as well as at the posterior fourchette (Figure 21.7). In severe cases, the introitus can be almost completely sealed.

Extragenital or cutaneous LS most often occurs on the neck, upper back, breasts, axillae, abdomen, and thighs. The lesions appear as white, waxy, wrinkled papules and plagues with follicular plugging and are typically asymptomatic (14).

Diagnostic Evaluation

Vulvar LS is usually a clinical diagnosis; however, identification may be difficult, especially in early stages of the disease (32). Vulvar LS may resemble a number of other vulvar dermatoses, including lichen planus, psoriasis, vitiligo, lichen simplex chronicus, mucous membrane pemphigoid, vulvar intraepithelial neoplasia (VIN), and SCC (2,32). It may be difficult to

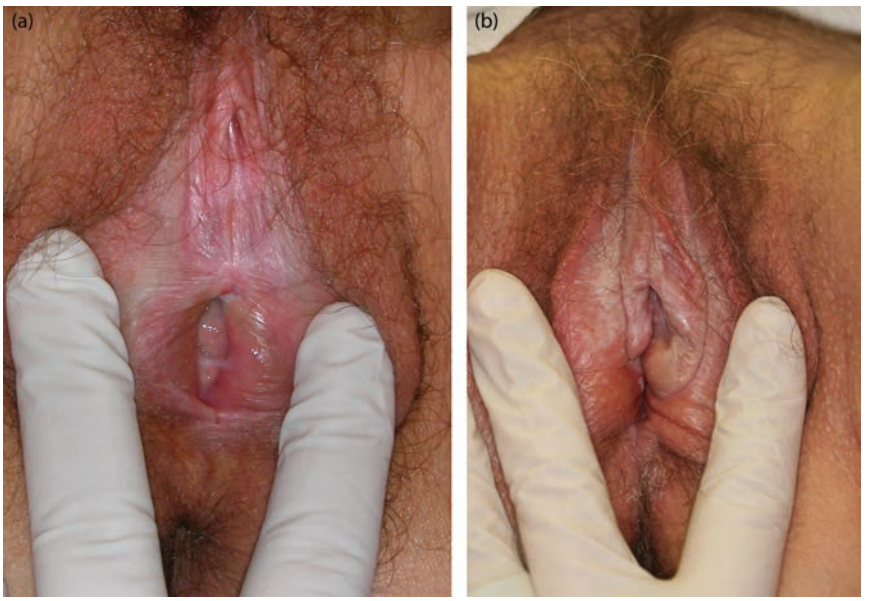

Figure 21.3 Fissures often occur in the anterior vestibule and posterior forchette (a), as well as in the interlabial sulci (b).

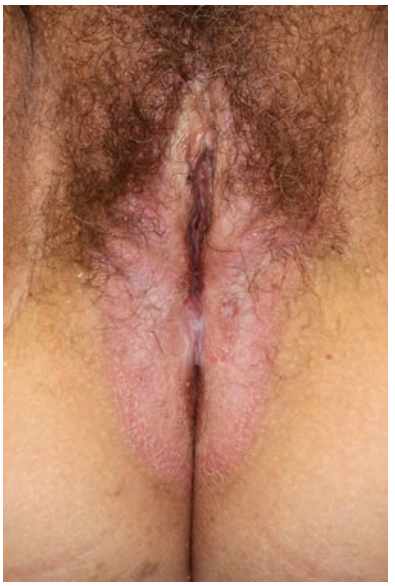

Figure 21.4 Lichenification may occur with repeated scratching.

distinguish LS from lichen planus, as the two conditions may both be present. Unlike lichen planus, LS only very rarely involves the vaginal mucosa (2).

Günthert et al. (33) explored a clinical scoring system for the diagnosis and management of vulvar LS in a case–control study. The authors included four symptoms (pruritus, burning, soreness, and dyspareunia) and six physical examination findings (erosions, hyperkeratosis, fissures, agglutination, stenosis, and atrophy) in order to determine a clinical score. Compared to controls, final composite scores were shown to be statistically valid for ruling in vulvar LS (33).

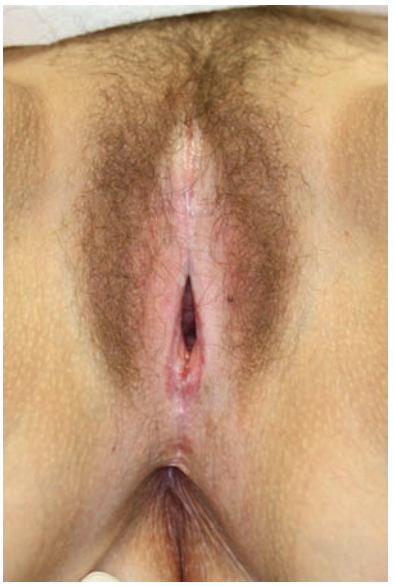

Figure 21.5 Agglutination, labial resorption, phimosis of the clitoris, and narrowing of the introitus may occur with disease progression.

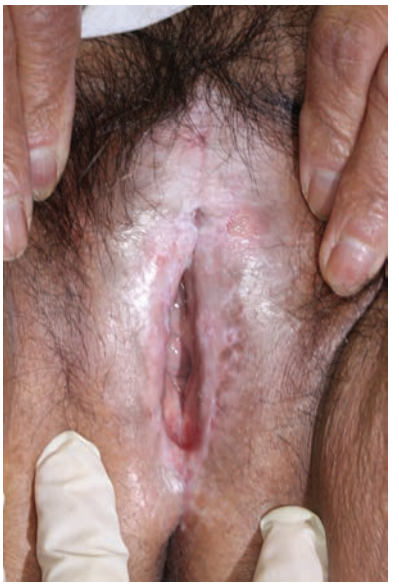

Figure 21.6 Agglutination of the clitoral hood may lead to clitoral phimosis, a condition in which the clitoral hood is difficult to retract and exposure to the glans clitoris is limited.

There is debate as to the necessity of histopathologic confirmation of the diagnosis of LS. This is because the pathology of LS is often difficult to interpret and there is no overall correlation between histologic appearance and duration of disease (32,34). Biopsy may not be needed in typical presentations; however, with atypical features, diagnostic uncertainty, concern about VIN or carcinoma, or failed response to treatment, histological examination is advisable (14,35). While classic histologic findings confirm the diagnosis of LS, a nonspecific

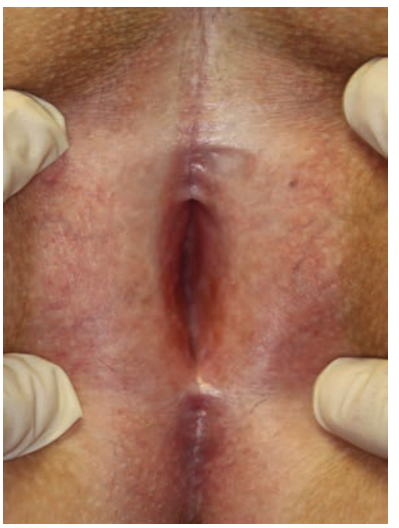

Figure 21.7 Scarring may lead to narrowing of the introitus.

biopsy should not rule out clinically suspected disease (32). Prior treatment with corticosteroids can also eliminate the classic pathognomonic histopathologic changes of LS. A vulvar biopsy is typically performed with local anesthesia using a 4-mm Keyes punch under sterile conditions (36). The biopsy site heals best if re-approximated with an absorbable suture. A relationship with an experienced dermatopathologist may aid in the accuracy of biopsy results.

Histopathology

The classic histological features of uncomplicated LS include atrophic epidermis, edematous superficial dermal area, or hyalanized subepithelium with dilated vessels and red blood cell extravasation, as well as a lymphocytic infiltrate in the dermal layer (Figure 21.8) (37). Histologic features of early-stage disease are often subtle, and may be mistaken for lichen planus (20). Often, histologic characteristics of superimposed lichen simplex chronicus, such as hyperkeratosis and epidermal hyperplasia, are also present (38). When LS is associated with differentiated VIN or carcinoma, a thicker epidermis with atypia of basal keratinocytes and loss of dermal hyaline or edematous changes may be present (37,39).

TREATMENT

There is no cure for LS; however, a number of successful treatment modalities have been explored for this condition. The goals of treatment include alleviating symptoms, preventing anatomic changes, and possibly preventing malignant transformation. A recent prospective cohort study of 507 women with LS showed that patients who were compliant with long-term topical corticosteroid (TSC) treatment had a significantly lower risk of malignant transformation compared to women who were partially compliant with treatment (40). This study, if confirmed by other prospective studies, may end the controversy that currently exists as to whether all women with vulvar LS, even those who are asymptomatic, must be treated. Generally, treatment is offered to even asymptomatic patients exhibiting clinically active signs of disease.

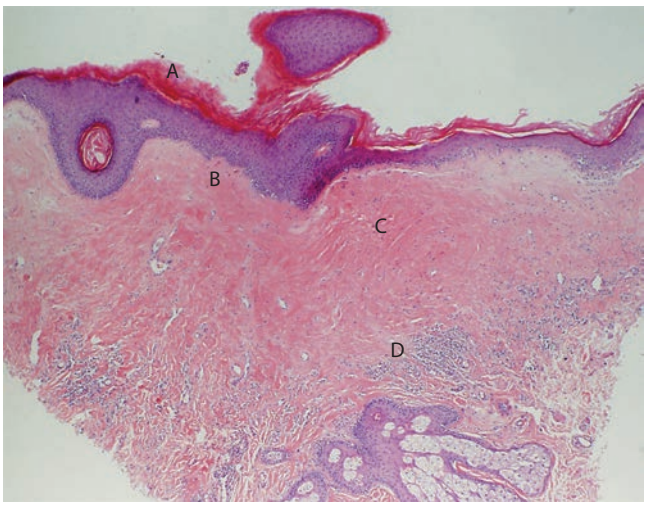

Figure 21.8 Classic histology of vulvar lichen sclerosus includes hyperkeratosis of the epidermis (A), epidermal atrophy with loss of rete ridges (B), homogenization of the collagen below the dermal–epidural junction (C), and lichenoid T-lymphocyte infiltrate near the basement membrane (D).

Medical Therapies

Topical Corticosteroids

Ultrapotent TCSs have shown the most promise in treating symptoms of vulvar LS. Chi et al. (41) performed a Cochrane review and meta-analysis of seven randomized controlled trials with 249 participants evaluating five topical treatments, including clobetasol propionate 0.05%, mometasone furoate 0.05%, testosterone propionate 2% cream, dihydrotestosterone 2% cream, topical progesterone, and pimecrolimus. The results of their analysis led to the recommendation that first-line treatment for vulvar LS should be the clobetasol propionate 0.05% ointment (41,42).

In a randomized controlled trial of 79 women with long-standing biopsy-proven vulvar LS, Bracco et al. (43) found that clobetasol proprionate 0.05% applied twice daily for 1 month, then once daily for 2 months was significantly better than placebo at improving symptoms, gross appearance, and histologic features. In a prospective cohort study of 233 women with LS, treatment with ultrapotent TCSs (89% received clobetasol propionate 0.05% ointment and 11% received another TCS) improved symptoms in 96% of patients, with 66% becoming symptom free and an additional 30% showing partial improvement. Total resolution of clinical signs occurred in 23% of the women treated, with an additional 68% of women showing partial resolution of hyperkeratosis, purpura, fissures, and erosions (5). This confirmed results from a previous retrospective study showing patients treated with clobetasol for 3 months displayed a 77% rate of complete remission and a 47% chance of improvement in clinical appearance of vulvar LS (44).

Long-term data have also been explored. A prospective study conducted between 1981 and 2001 of women with vulvar LS treated with clobetasol propionate ointment showed complete remission in 45 patients (54%), with a greater incidence of remission at 3 years for women under 50 years of age and no remission for women over 70 years of age. Patients tolerated long-term application of the TCS well, with no atrophic events observed. Relapse of symptoms was high, estimated at 50% at 16 months and 84% at 4 years from initial treatment (45).

Mometasone furoate 0.1% has also been shown to be equally efficacious to clobetasol and well tolerated for the treatment of vulvar LS, both with a tapering regimen and a continuous regimen for active disease, as well as maintenance therapy for up to 1 year (46–49). Triamcinolone ointment 0.1%, a medium-potency TCS, has also been shown to be effective at reducing patient symptom scores when applied once to twice daily for 3 months. Complete resolution of symptoms was noted in 72% (19 out of 22) of women with vulvar pruritus, 87% (19 out of 22) women with vulvar burning, 92% (12 out of 13) women with vulvar pain, and 47% (8 out of 17) women with dyspareunia (50).

Although there is no general consensus regarding the optimal dosing regimen, most experts recommend application once to twice daily at bedtime for 2–4 weeks, followed by tapering over weeks to months to a once- or twice-weekly maintenance application (35,42). In a survey of 96 women with chronic vulvar LS treated with clobetasol, 69% of patients achieved

freedom from itching, with a global Patient Benefit Index (PBI) of 3.06 and 93% of patients reporting a PBI >1, indicating improvement in quality of life with treatment (51).

Topical Calcineurin Inhibitors

Topical calcineurin inhibitors (TCIs), namely tacrolimus and pimecrolimus, have also been studied in the treatment of vulvar LS. TCIs act as immunomodulators to block the release of inflammatory cytokines from T lymphocytes in the skin (52). Because they do not inhibit collagen synthesis, they are not associated with atrophy of the skin, unlike TCSs (18).

In a prospective study of 26 women with severe vulvar LS who were unsatisfactorily treated with TCSs, treatment with pimecrolimus cream 1% applied twice daily for up to 6 months resulted in a 42% rate of complete remission. Adverse side effects included mild burning and itching in 50% of participants within the first 2 weeks of treatment (53). In a longer-term prospective study of 16 postmenopausal women with biopsy-proven vulvar LS, twice-daily application of pimecrolimus cream for 3 months led to complete remission in 11 patients (69%), which continued for over a year in seven of those patients. A third of women experienced mild to moderate burning at the site of application during the first week of treatment (54). Goldstein et al. (55) conducted a double-blinded randomized trial of 38 women with biopsy-proven vulvar LS. The participants were treated with either clobetasol 0.05% or pimecrolimus 1% ointment for 12 weeks, with outcome measures including symptoms of pruritus, burning, and pain, as well as inflammation on biopsy specimen. Both clobetasol and pimecrolimus were found to be safe and efficacious in the treatment of vulvar LS, with clobetasol the superior treatment at improving inflammation. Clobetasol was also found to be more effective than pimecrolimus at decreasing signs of inflammation on histological examination (55).

The TCI tacrolimus ointment 0.1% has also shown efficacy in the treatment of vulvar LS. In a pilot study of 16 women with refractory LS treated with tacrolimus ointment twice daily for 3 months, 12.5% experienced a complete response, which was maintained at 1 year, and an additional 50% showed partial improvement. A third of patients experienced mild burning as an adverse side effect (56). A second pilot study involving treatment for 6 weeks followed by tapering over 6 weeks yielded similar results (57). In a multicenter, phase II, open-label trial of 84 patients (men and women) with anogenital LS, application of tacrolimus for 16–24 weeks led to complete resolution of lesions in 43% and partial resolution in an additional 34% of participants, with recurrence rates of less than 10% and similar adverse effects (58). A long-term study monitoring patients for 54 months showed recurrence in 67% of patients, suggesting a need for long-term treatment (59). In 2014, Funaro et al. (60) conducted a double-blind, randomized study of 55 women with vulvar LS. Twenty-eight patients received tacrolimus and 27 patients received clobetasol for a 3-month treatment period. Both groups showed a significant decrease in signs and symptoms of LS, but a significantly higher number of patients in the clobetasol group had complete resolution of signs and symptoms.

There has been concern about the use of immunomodulating therapies, such as TCIs, given the increased risk of malignancy in patients with vulvar LS. Although studies have not shown an increased risk of malignancy in LS patients treated intermittently with TCIs for up to 4 years, there have been reported cases of vulvar SCC after TCI exposure (18,61). Given that the long-term safety profile is still unknown (62), TCIs are not current considered first-line treatments. They may be used for short-term or intermittent treatment in patients who are unresponsive or intolerant of TCSs (18).

Retinoids

Topical and systemic retinoids have also demonstrated efficacy in the treatment of vulvar LS. However, these medications are generally avoided in reproductive-aged women due to their well-known potential to cause teratogenicity (18). Topical 0.025% tretinoin applied once daily for 5 days a week led to improvements in symptoms, clinical appearance, and histopathologic features after 1 year of treatment (63). In a multicenter, randomized, placebo-controlled, double-blind trial of 46 women with vulvar LS, 64% displayed treatment response with the oral retinoid acitretin given daily for 16 weeks. All patients experienced retinoid-related adverse effects, including dry mucous membranes and sun sensitivity (64).

Topical Androgens and Progesterone

Historically, vulvar LS was treated with topical hormone preparations based upon the observation that the highest prevalence of LS occurs in physiological estrogen-deprived states (18). However, there is little evidence to support the efficacy of topical androgens or progesterone in treating vulvar LS (41). In two randomized controlled trials of a combined 137 women with biopsy-proven vulvar LS comparing testosterone versus placebo application at 3 months and 1 year, no significant difference in efficacy was found (41,43,65). Two very small randomized crossover trials of five participants each receiving either dihydrotestosterone versus placebo or dihydrotestosterone versus testosterone for 3 months also showed no improvement in symptoms or gross appearance with any of the preparations (66,67). A randomized controlled trial of 79 women comparing testosterone versus clobetasol propionate treatment for 3 months found that testosterone was significantly less effective compared to clobetasol in both participant- and investigator-rated improvement (43). Testosterone has also been shown to be a poor maintenance therapy after initial treatment with clobetasol propionate, with worsened symptoms compared to a placebo maintenance preparation (68). Like androgen preparations, progesterone 2% cream has also been shown to be ineffective for the treatment of vulvar LS (43). Given these results, topical hormone preparations do not have a role in the treatment of LS (18). However, it should be noted that topical hormones may play a role in treating concurrent vulvovaginal atrophy that may coexist in menopausal women with LS.

Human Fibroblast Lysate Cream

Human fibroblast lysate cream (HFLC), also known as cutaneous lysate, is a topical compound composed of growth factors, anti-inflammatory interleukins, and interferons derived from cultured human fetal fibroblasts. HFLC has not been shown to promote the proliferation of SCC (69). In a placebo-controlled crossover study, cutaneous lysate has shown promise in improving the symptoms of provoked vestibulodynia, another inflammatory vulvar condition (70). In a double-blind, randomized, placebo-controlled pilot study of 30 women with biopsy-proven vulvar LS, treatment with HFLC twice daily for 12 weeks showed significant improvement in vulvar pruritus and clinical disease severity; however, this was not significantly greater than treatment with the placebo topical preparation (69).

The study was limited by a small sample size and inadequate power. Additional studies of these newer treatment alternatives are needed.

Surgical Interventions and Physical Treatment Modalities

Vulvar Surgery

Historically, vulvectomy was considered to be an acceptable surgical option for vulvar LS (18). With high rates of recurrence and often disfiguring results, this approach is now rarely indicated and should be reserved for malignancy and complications of scarring (2). Surgical approaches alone may exacerbate scarring through the Köebner phenomenon, in which normal skin becomes sclerotic due to trauma, leading to additional scarring. Application of ultrapotent TCSs following surgical intervention can lessen this effect. There may be a role for surgery combined with medical therapy in cases of urinary complications or sexual dysfunction due to LS-related adhesions and scarring. Even in these cases, surgical intervention is only recommended when conservative treatments fail (18).

In a case series of 35 patients with either LS (28 patients) or lichen planus (8 patients) complicated by labial fusion who underwent lysis of vulvar adhesions (perinectomy) with suppression of inflammatory response, 89% of the patients had no re-fusion at 3 months and 83% had no late re-fusion at 2 years (71). In a small study of eight patients with clitoral phimosis due to LS, surgical repair with lysis of adhesions and midline incision of the clitoral prepuce combined with TCS suppression pre- and post-operatively led to improvements in clitoral sensation and ability to achieve orgasm (72). Patients who underwent correction of clitoral phimosis or lysis of vulvar adhesions due to vulvar LS reported an 84% satisfaction rate. Seventy-five percent of women with decreased clitoral sensation prior to surgery reported increased sensation postoperatively. Of the women with dyspareunia prior to surgery, 33% reported pain-free intercourse and 58% reported improved comfort with intercourse following recovery (73).

Surgical Tissue-Regenerative Approaches

Casabona et al. (74) explored a surgical tissue-regenerative technique involving grafting of adipose-derived mesenchymal cells and injection of platelet-rich plasma in areas damaged by vulvar LS. In a case series of 15 women with a histologic diagnosis of LS, patients experienced improvements in itching and burning within 1 month, with total resolution of symptoms and restoration of sexual activity within 4 months after the procedure (74). However, there were several limitations to this study. It was not blinded nor placebo controlled, there were two interventions applied at the same time making it impossible to determine if one or both of the treatments was effective, and no objective measurements of efficacy were measured.

In a more recent study, 36 patients with histologic diagnosis of LS underwent vulvar fat grafting after failure of first-line treatments. Ninety-four percent of patients showed improved clinical appearance, with 75% experiencing improvements in elasticity of the vaginal introitus. Patients also reported resolution of scratching lesions (94%), increased volume of the labia (83%), remission of white lesions (78%), and decreased degree of clitoral burying (50%). Quality of life and sexual function was significantly improved following the procedure (75). More research is needed in order to determine the safety and efficacy of tissue-regenerative techniques.

Phototherapy

Several case series have shown photodynamic therapy to be reasonably effective in treating genital LS that is resistant to conventional treatment (3). Ten of 12 women with vulvar LS treated with 5-aminolevulinic acid photodynamic therapy (argon dye laser) experienced decreased pruritus and pain for 6 months after treatment (76). In a study of 100 women with vulvar LS, treatment with photodynamic therapy resulted in remission of symptoms and clinical signs, as well as immunohistochemical improvement (77).

In a clinical trial of 26 patients with vulvar LS randomized to treatment with UV-A1 phototherapy or application of clobetasol ointment, there was no significant difference between the treatment groups for clinical grading, with both treatments reducing burning and pain. However, the phototherapy group did not show a significant improvement in pruritus or quality of life, whereas the clobetasol-treated group did show improvement (78). UV-A1 phototherapy may be considered in cases of vulvar LS that do not respond to conventional therapy, but may be more effective in the treatment of extragenital LS lesions than vulvar disease (3).

CO_2 Laser Ablation Therapy

Like phototherapy, CO_2 laser ablation has been investigated as a potential treatment for vulvar LS in small case series with initial improvements in symptoms. In seven patients with histologic evidence of vulvar LS, six of the participants were reported to be free of symptoms, with no recurrence for 12–37 months (79). Subsequent case reports have described symptom improvement with treatment, but high rates of relapse (80,81).

High-Intensity Focused Ultrasound

High-intensity focused ultrasound (HIFU), which stimulates cell proliferation and revascularization, has also been investigated as a potential treatment for LS. In a review of 41 cases of LS, 38 cases of squamous cell hyperplasia, and 17 mixed cases treated with HIFU, 90% of patients showed symptom improvement or resolution 6 months after treatment, with decreased signs of inflammation on biopsy. However, almost 10% of participants incurred adverse side effects, including skin burns with blistering (82).

More rigorous studies have been conducted in China. In a study of 382 patients with non-neoplastic epithelial disorders of the vulva, including 68 patients with vulvar LS, 51% of LS patients had complete resolution of symptoms and an additional 47% had improvements in symptoms. Twenty-five patients out of the total treated incurred blistering, which resolved with anti-inflammatory medication with no residual scarring (83). In a more recent retrospective study of 950 patients with vulvar squamous hyperplasia and LS treated with HIFU, complete resolution of signs and symptoms was found in 42% of patients, with improvements noted in an additional 56% of those treated. A 9.5% disease recurrence rate was noted, which was significantly higher in patients with LS. No severe complications were noted during or after treatment (84).

In all of these studies, HIFU treatment was more effective for younger patients with less severe squamous cell hyperplasia compared to older women with more severe vulvar LS. However, high reported rates of effective treatment with

relatively low recurrence rates and curative potential justifies further investigation of this treatment option (82–84).

FOLLOW-UP

Because there is no cure for LS and the potential for malignant transformation, patients should be followed throughout their lifetime. It is recommended that patients follow up 2–3 months after initiating treatment, followed by 6 months, and then annually if the disease is well controlled (2,35). Patients should be instructed to regularly inspect their vulva with a mirror for lesion modifications (2). Poorly controlled patients or those exhibiting ongoing hyperkeratosis or ulceration should undergo vulvoscopy-directed biopsy to evaluate for VIN and SCC (35).

MALIGNANCY

Vulvar LS is associated with the development of SCC of the vulva. There are two generally accepted pathways for the development of vulvar SCC: (i) HPV infection leading to usual-type VIN, resulting in basaloid or warty-type SCC; and (ii) a LS-mediated pathway leading to differentiated VIN resulting in keratizing SCC (85). Differentiated VIN accounts for less than 5% of VINs and often occurs in older women with LS or lichen planus with a long-lasting history of pruritic symptoms. The risk of developing vulvar SCC in women with LS has been estimated to be about 3%–5% (4,5). In biopsies of vulvar SCC, concomitant LS has been found in up to 60% of specimens (86). Women with vulvar LS have up to a 300-times greater risk of developing vulvar SCC compared to unaffected women of similar age (45).

Although it was previously unclear whether medical treatments of LS prevent malignant transformation, a recent study indicated that adequate long-term treatment with TCSs did indeed significantly lower the risk of developing VIN and SCC in the setting of LS (5,40). Former studies were not sufficiently powered to determine whether treatment prevents the progression of vulvar LS to SCC; however, previous findings did indicate that a lack of treatment or a history of inconsistent treatment of vulvar LS was more common in women presenting with vulvar SCC, and that rates of SCC were lower in women who complied with treatment (5,18,45,87–89). Prospective studies are needed in order to provide a definitive recommendation for long-term TCS treatment so as to prevent malignant transformation in the setting of vulvar LS.

SUMMARY

Vulvar LS is a potentially debilitating disease that may be encountered by clinicians in a variety of specialties. This condition is likely under-reported due to patient hesitation to disclose symptoms, clinician difficulty in identifying the disease, and a fragmented approach to diagnosis and treatment. Although the exact etiology is unclear, increasing evidence favors an autoimmune mechanism. Vulvar itching, especially at night, is the most common presenting symptom. Lesions are located predominately in the anogenital region, appearing as ivory-white atrophic patches. Fissures, ulceration, and scarring often occur with disease progression, leading to pain and loss of sexual function. Diagnosis is usually clinical, but histologic evaluation remains the only definitive confirmation of disease, despite potential difficulties in pathologic interpretation. There is no cure for LS and treatment should focus on symptom management and complication prevention. First-line treatment is high-potency TCSs, most notably clobetasol propionate 0.05% ointment. TCIs may be used in patients who fail first-line therapy. Newer treatments such as HIFU or tissue-regenerative techniques are promising, but must undergo additional methodically rigorous clinical trials before they should be offered to patients. Surgical treatment is reserved for complications of the disease in order to restore function or in cases of associated VIN or vulvar carcinoma. Follow-up with a knowledgeable provider is important in order to limit complications and to monitor for malignant transformation.

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Seborrheic keratosis

Pathogenesis, histopathology, and clinical aspects

Devinder Mohan Thappa and Munisamy Malathi

INTRODUCTION

Seborrheic keratosis (SK) is one of the most common benign epidermal tumors of the skin commonly encountered by dermatologists in their routine clinical practice. The prevalence increases with age, with a high occurrence of 80%–100% in those aged above 50 years. Despite SK being a very common condition, its pathogenesis is still obscure. Dermatologists need to be familiar with the differential diagnosis of SKs, as sometimes they may pose diagnostic confusion with other benign and malignant skin tumors, in which case dermoscopy and histopathology will guide the diagnosis. Given their benign and asymptomatic nature, they do not require treatment except when symptomatic or for cosmetic reasons.

DEFINITION

SKs (also known as seborrheic warts, senile warts, verruca seborrhoica, basal cell papilloma, basal cell acanthoma, and benign acanthokeratoma) are benign epidermal tumors composed of epidermal keratinocytes manifesting with varied morphological and histological presentations commonly in the elderly (1). However, controversies exist as to the usage of the term "senile keratoses," as SK has been reported to occur in a substantial proportion of individuals at less than 30 years of age (2).

EPIDEMIOLOGY

SKs are the most common benign epidermal tumors of the skin with unperceived onset occurring on almost any site of the body, especially in populations with fair complexions. Despite their frequency of occurrence, little is known about their epidemiology.

SKs usually appear in the fifth decade of life in people living in temperate climates, but may develop earlier in tropical regions (1). They are reported to be more common in Caucasian populations and are rare among blacks and Native Americans, although dermatosis papulosa nigra (DPN), a variant of SK, is common among dark-skinned people (3).

Though considered a disorder of the elderly, it can arise as early as adolescence with varying prevalence in various studies. An Australian study reported a prevalence of 30% in subjects under the age of 30 years, which increased to 100% in subjects older than 50 years, with more frequent occurrence and an earlier age of onset in comparison to a UK study wherein SK was reported in 75% of subjects over the age of 70 years (1,4). With a slight tendency to spontaneous disappearance, new lesions may continue to appear for many years (5). There are no significant differences in prevalence rates between males and females in the elderly; however, in British and Australian studies, a female preponderance was reported for those under the age of 40 years (1,5).

PATHOGENESIS

The etiology of SK is unknown and many factors, including genetic predisposition, sunlight exposure, human papilloma virus (HPV), and hyperplasia of melanocytes, have been implicated, although none of these factors is considered to be the sole cause of SK. In recent years, new insights have been gained regarding the molecular pathogenesis of SK.

Genetics: A genetic predisposition has been suggested involving a familial trait with an autosomal dominant inheritance, especially in patients with unusually large numbers of lesions (1,3).

Sun exposure: Cumulative sun exposure has been reported to have a possible causative role based on the high prevalence of SKs on sun-exposed skin (1,3). Lifetime cumulative sunlight exposure of more than 6 hours per day led to a 2.28-fold increased risk of SKs than a sun exposure of fewer than 3 hours per day (6). Aging and cumulative sunlight exposure have been implicated as independent contributory factors in the development of SKs (3).

HPV infection: HPV infection has been suggested in the pathogenesis of genital and non-genital SK based on the detection of HPV-like particles by electron microscopy (7) or HPV DNA by polymerase chain reaction (8). However, whether there is a causal relationship or whether this is a coincidence has not been established based on the fact that HPV DNA may also be detected in normal skin and HPV DNA in SK was detected only at the surface, but not deeper within the lesions, suggesting only surface contamination (1,3).

Molecular pathogenesis: SKs have been reported as monoclonal tumors rather than simple epidermal hyperplasias based on a clonality analysis (9). Somatic *FGFR3* and *PIK3CA* mutations have been implicated in the molecular pathogenesis of SKs (1,3). *FGFR3* mutations that are present in flat SK indicate that the mutations may be early genetic events. In addition, age has been identified as a major risk factor for the occurrence of somatic *FGFR3* mutations in the skin, corresponding with the appearance of SKs in middle to old age (1). Activating *FGFR3* mutations may provide proliferative signals for the keratinocytes in SKs. Increased Ki-67 and antiapoptotic bcl-2 expression has also been observed in SKs. Expression of DNp63a, the most abundantly expressed p63 isoform, has been found

to be significantly increased in SK as a result of activating *PIK3CA* mutations (1). However, no relationship has been found between the various *FGFR3* and *PIK3CA* mutations and the various histological subtypes, and varying proportions of SKs have neither a *FGFR3* nor a *PIK3CA* hotspot mutation, suggesting a role of other genes (1,3). The development of SK has also been associated with circulating epidermal growth factor and melanocyte-derived growth factor, in addition to increased expression of tumor necrosis factor-α and endothelin-converting enzyme (10).

Clinical Features

SKs are usually asymptomatic but may be pruritic and typically occur on hair-bearing skin, invariably sparing the mucosal surfaces and the palms and soles, predominantly on the head, neck, and trunk, and especially in exposed areas when compared to non-exposed areas (1,11). The lesions usually begin as oval, slightly raised, tan/light brown to black, sharply demarcated papules or plaques of sizes varying from 1 mm to several centimeters (Figure 22.1). As they grow, they become more papular, taking on a waxy, verrucous, or "stuck on" appearance. Many lesions display plugged follicular orifices representing "pseudohorn cysts" (10). Lesions may be solitary, but more often they are disseminated in large numbers, especially in older patients (3). Although usually asymptomatic, traumatized or inflamed lesions may become tender, pruritic, erythematous, crusted, and, rarely, pustular (11). Multiple SKs may be distributed along skin folds in a "Christmas tree pattern" or along Blaschko's lines (10). A distinctive pattern of SK occurs on the back of elderly patients, which appear as a linear, splayed, vertical distribution termed a "rain drop pattern" (12).

Clinical Variants of SK

- *Common SK*: Uniformly tan to dark brown, asymptomatic, stuck on verrucous papules with pseudohorn cysts, occurring predominantly over the face and trunk (Figure 22.2) (11,13).
- *Stucco keratosis*: Gray–white papules or small plaques measuring from 1 to 4 mm, with a dry surface that can be scraped off the skin surface with a fingernail, typically present on the extensor surfaces of extremities in large numbers of older adults, frequently seen in cold winter months, with men being four-fold more commonly affected than women (Figure 22.3) (1,3,11).
- *DPN*: Black or dark brown, flattened, or cupuliform papules, 1–5 mm in diameter, on malar regions, forehead, neck, chest, and upper back, common in black races, with women twice as likely to be affected as males, with a strong familial predisposition, and is considered a nevoid developmental defect of pilosebaceous follicles (Figure 22.4) (1,3).
- *Inverted follicular keratosis*: White–tan to pink asymptomatic solitary lesion, less than 1 cm, on the faces of middle aged and elderly individuals, usually on the cheek and upper lip, considered as inwardly growing irritated SK derived from the infundibulum of a hair follicle (1,11,13).
- *Flat SK*: Tan–brown patches or macules on sun-exposed areas of the skin, especially on the face, backs of the hands and wrists, extensor surfaces of the forearms, and chest, increasing with age and clinically resembling solar lentigenes (Figure 22.5) (13).

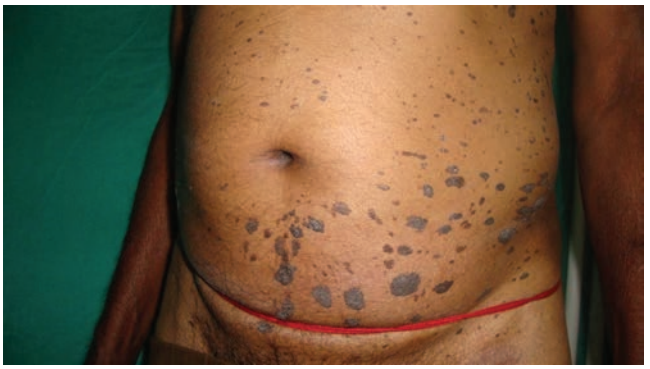

Figure 22.1 Widespread seborrheic keratosis over trunk.

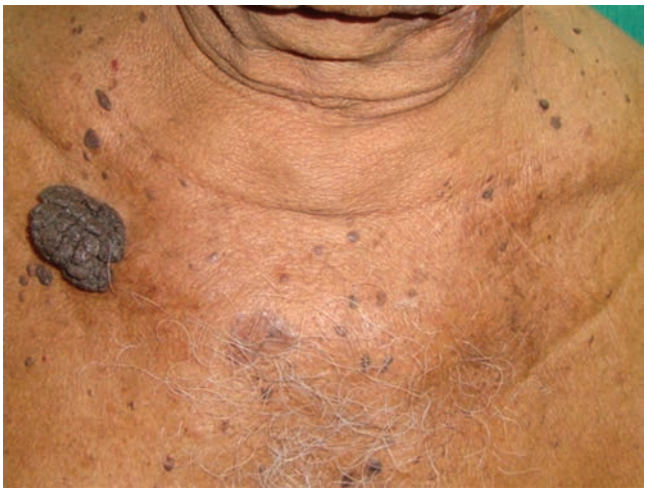

Figure 22.2 Common seborrheic keratosis on chest.

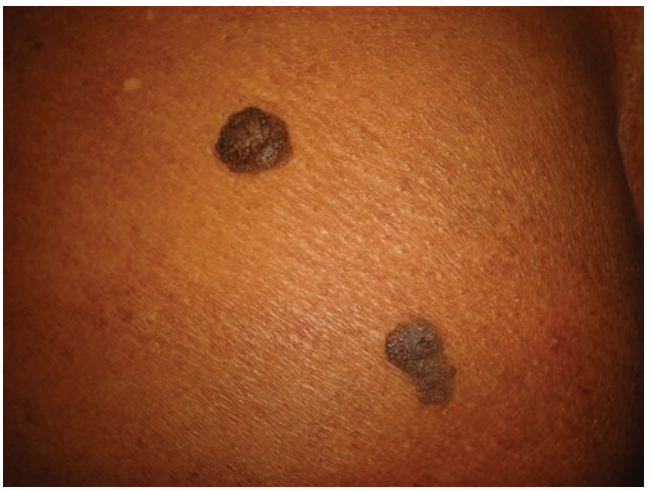

Figure 22.3 Stucco keratosis on gluteal region.

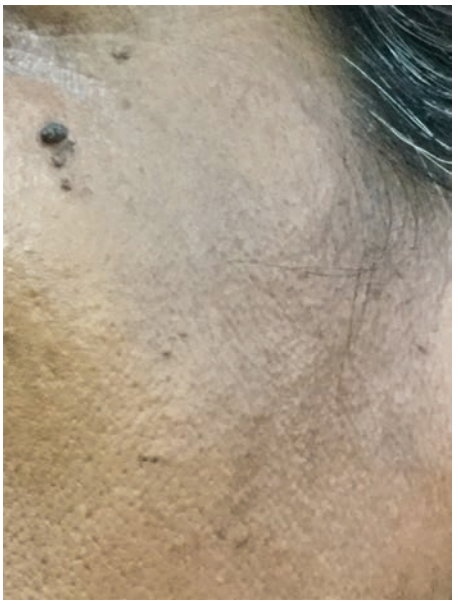

Figure 22.4 Dermatosis papulosa nigra on the face.

- *Skin tags*: Rough, 1–2–mm pedunculated papules commonly located in areas of friction, including axillae, inframammary areas, and the neck, more common in women, and may be manifestations of SKs (Figure 22.6) (10).
- *Large cell acanthoma*: Solitary, scaly, tan macules commonly occurring on sun-damaged skin of the face and neck, including the eyelids, and can also occur on the extremities and trunk, mimicking solar lentigo (13).
- *Lichenoid keratosis*: Solitary, slightly raised, red–brown plaques occurring on the upper chest, face, or forearms, more commonly in white-skinned women, and representing an immunological or regressive response to a pre-existing epidermal lesion of SK or solar lentigo (13,14).

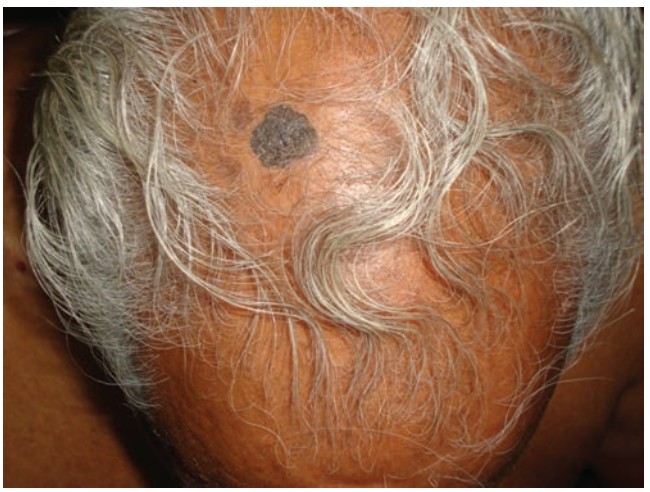

Figure 22.5 Flat seborrheic keratosis on scalp.

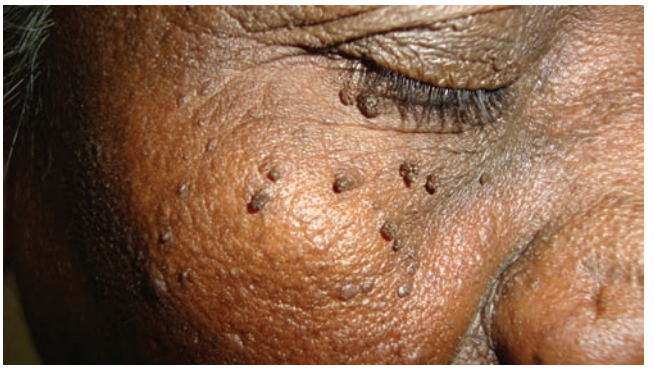

Figure 22.6 Skin tag-like seborrheic keratosis on face.

HISTOPATHOLOGY

SK is predominantly a clinical diagnosis. SK that has undergone recent change, is symptomatic, or looks suspicious clinically should be considered for dermoscopic and histopathological evaluation. All SKs have in common hyperkeratosis, acanthosis due to upward extension of the tumor, and papillomatosis. The lower border of the tumor is even and generally lies in a straight line that may be drawn from normal epidermis at one end of the tumor to the other end. Two types of cells are seen in acanthotic epidermis: squamous cells (resembling squamous cells normally found in the epidermis) and basaloid cells (resembling basal cells normally found in the basal layer of the epidermis) (15). Six histologic variants of SK are recognized, which include acanthotic, hyperkeratotic, adenoid, clonal, irritated, and melanoacanthoma variants (3,11).

Evaluation of epithelial keratin and filaggrin expression on SKs in order to study the origins of various histopathological variants demonstrated that hyperkeratotic SKs differentiated toward squamoid terminal keratinization, whereas acanthotic, irritated, clonal, reticulated, and adenoid SKs mainly differentiated toward basaloid undifferentiated cells. In addition, acanthotic SKs differentiated toward the hair bulge, and irritated SKs differentiated toward the follicular infra-infundibulum (16).

Histopathological Variants

- *Acanthotic SK*: Most common type characterized by slight hyperkeratosis and papillomatosis with greatly thickened epidermis, basaloid cells outnumbering squamous cells, numerous pseudohorn cysts and true-horn cysts, large amounts of melanin in keratinocytes limited to dermoepidermal junction and at interfaces between tumor tracts, and islands of dermal stroma and mononuclear infiltrate in dermis (Figures 22.7 and 22.8) (3,15).
- *Hyperkeratotic SK*: Also known as the digitate or serrated type and is characterized by pronounced hyperkeratosis and papillomatosis with inconspicuous acanthosis, predominant squamous cells with small aggregates of basaloid cells, and digitate upward extensions of epidermis-lined papillae resembling church spires without excess melanin (3,15).
- *Adenoid or reticulated SK*: Characterized by numerous thin tracts of epidermal cells extending from the epidermis and branching and interweaving in the dermis composed of

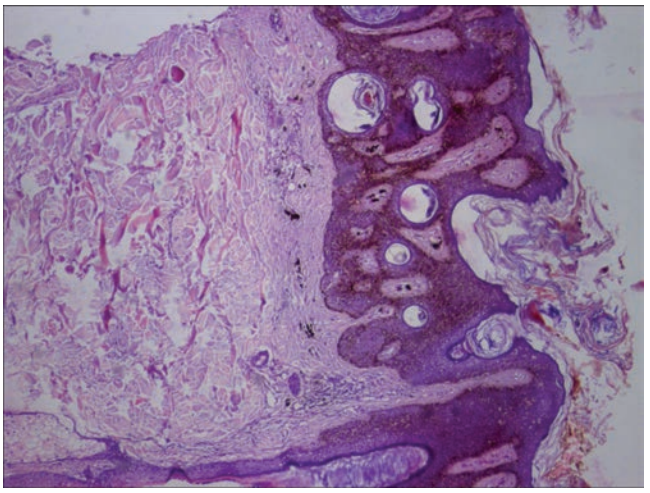

Figure 22.7 Photomicrograph showing hyperkeratosis, acanthosis, and papillomatosis with true horn cysts and pseudohorn cysts along with proliferation of basaloid squamous cells (hematoxylin and eosin, ×100).

double rows of basaloid cells with marked hyperpigmentation and absence of horn cysts and pseudohorn cysts in purely reticulated lesions, but can be present within areas of acanthosis. They can arise from solar lentigo (3,15).

- *Clonal SK*: Characterized by well-defined nests of fairly large cells showing distinct intercellular bridges, with the nests separated from one another by strands of cells exhibiting small, dark nuclei within the epidermis, resembling the Borst–Jadassohn phenomenon (foci of basal cell epithelioma) (3,15).
- *Irritated SK*: Characterized by numerous whorls or eddies composed of eosinophilic, flattened squamous cells arranged in an onion peel fashion due to "activation" of resting basaloid cells into squamous cells. In addition, may show areas of downward proliferation originating from the walls of keratin-filled invaginations, breaking through horizontal demarcations that are generally present in non-irritated SK. These features of activation and downward proliferation are the results of irritation. Inflammation beneath irritated SK is usually mild or absent, but can be associated with acantholysis (3,15).
- *Melanoacanthoma*: Characterized by a marked increase in concentration of large and richly dendritic melanocytes with variable amounts of melanin scattered throughout the tumor lobules associated with the distribution of well-defined islands of basaloid cells intermingled with many melanocytes throughout the tumor. The block in the transfer of melanin from melanocytes to keratinocytes is often only partial, although in some instances nearly all of the melanin is retained in the melanocytes (3,15).
- *Acantholytic SK*: A rare variant characterized by prominent acantholysis in the upper portion of epidermal growth, showing dyskeratotic cells and a disorderly arrangement of the squamous cells in addition to common features of hyperkeratosis, acanthosis, and papillomatosis (17).
- *Adamantoid SK*: Characterized by abundant intercellular mucin resembling adamantinoma (18).
- *SK with pseudorosettes*: Characterized by striking pseudorosette formation (18).Uncommon histopathologic features that have been described in SK include trichostasis spinulosa, tricholemmal, and sebaceous differentiation, SK with amyloid in the underlying dermis, and juxtaposition or "collision" of SK with malignant neoplasms, including basal cell carcinoma (BCC), squamous cell carcinoma (SCC), keratoacanthoma, and malignant melanoma (18).

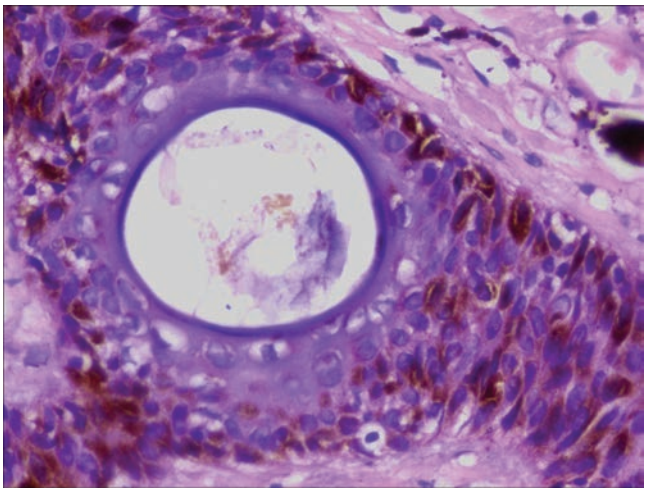

Figure 22.8 Photomicrograph showing true horn cysts (hematoxylin and eosin, ×400).

Histopathology of Clinical Variants of SK

- *Stucco keratosis*: Appearance of the hyperkeratotic type of SK with a church spire pattern of upward extending papillae and the absence of horn cyst and basaloid cells (15).
- *DPN*: Appearance of the acanthotic type of SK with thick, interwoven tracts of epithelial cells that are largely squamous in appearance, with only a few basaloid cells associated with pronounced melanin pigmentation.
- *Inverted follicular keratosis*: Appearance of the irritated type of SK with keratin-filled invaginations that are regarded as follicular infundibula, with the proliferations arising from them composed of cells of the follicular infundibulum and associated with squamous eddies.

DERMOSCOPY

SK is predominantly a clinical diagnosis; however, dermoscopy serves as a very useful tool in establishing the diagnosis in doubtful cases, especially in differentiating from malignant lesions in case of pigmented and irritated SK. The common characteristic dermoscopic findings of SKs are milia-like cysts and comedo-like openings (Figure 22.9). The various dermoscopic features that can be seen in SKs are summarized in Table 22.1 (19–22).

Irritated SK often poses a diagnostic challenge and the dermoscopic findings of irritated SK tend to show a low frequency of typical dermoscopic features such as comedo-like openings and milia-like cysts, but a specific feature characterized by "small pinkish round structures on a whitish background" corresponding histopathologically to dilated vessels and surrounding acanthosis of tumor cells is diagnostic of irritated SK (23).

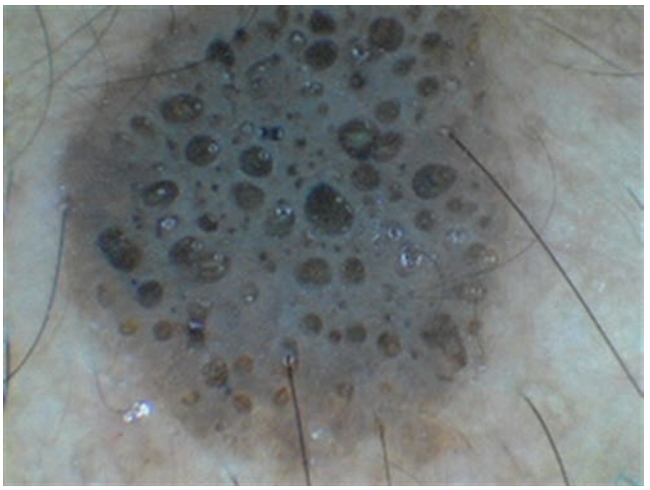

Figure 22.9 Dermoscopy of common seborrheic keratosis showing comedo-like openings and milia-like cysts and sharp demarcation.

Dermoscopy of pigmented SK can demonstrate globule-like structures histopathologically corresponding to intraepidermal horn cysts filled with cornified cells containing melanin that resemble brown globules seen in melanocytic neoplasms, thereby misleading the diagnosis (24).

Clonal SK is difficult to diagnose under dermoscopy as it can simulate either a melanocytic lesion or a BCC owing to the presence of variably sized, bluish, globular-like structures that are aggregated or irregularly distributed within the lesion. However, the presence of blue globules and milia-like cysts in the context of a sharply demarcated lesion is diagnostic of clonal SK (25).

Thus, SKs can be differentiated from melanocytic neoplasms based on the absence of pigment networks, branched streaks, and pigment globules, and their presence should raise the suspicion of a congenital melanocytic nevus or a collision lesion. By using the ink test for the visualization of the 3D features of SK, the possible misdiagnosis of SK as a melanocytic lesion can be limited (26).

DIGITAL MICROSCOPE

The digital microscope is a cheaper alternative to the dermatoscope for distinguishing non-melanocytic skin lesions from melanocytic tumors. Digital microscopy of SK can visualize four of the six morphological features of SK, which include multiple milia-like cysts, pseudofollicular (comedo-like) openings, hyperkeratosis/fissures/ridges, and a cerebriform appearance (sulci and gyri) (27).

REFLECTANCE CONFOCAL MICROSCOPY

Reflectance confocal miscroscopy (RCM) serves as an additional diagnostic tool in cases of irritated, regressive, clonal, or highly pigmented SKs, which may show clinical and dermoscopic features associated with malignant skin tumors. RCM of SK shows a cerebriform appearance with bulbous projections and round to linear keratin-filled invaginations with cords and dermal papillae of different sizes and shapes at the dermoepidermal junction. Other features include highly reflective round structures corresponding to milia-like cysts, corneal pseudocysts, a regular honeycomb pattern at the epidermal layers, melanophages, and looped vessels at the papillary dermis. The blood flow within dermal papillae can be observed by *in vivo* RCM. The predominant blood vessels in SKs are looped vessels that are oriented obliquely, reflecting changes in the orientation of the dermal papillae, in contrast to RCM imaging of SCC *in situ*, wherein the increased density of blood vessels in the dermal papillae loop perpendicular to the plane of imaging (28,29). In addition, RCM can be used as a valuable tool in order to diagnose clonal SKs, which demonstrate a peculiar clod pattern characterized by compact nests of polygonal keratinocytes and the presence of small, bright, and spaced papillae, in contrast to the clod pattern in melanocytic lesions, which is characterized by larger roundish or dendritic-shaped melanocytes (26).

DIFFERENTIAL DIAGNOSIS

SK needs to be differentiated from various benign and malignant skin tumors and infective and inflammatory cutaneous lesions both clinically and histologically (1,3,10,11,30).

Clinical Differential Diagnosis

- Flat SKs: Verruca plana, solar lentigo
- Raised SKs: BCC, Bowen disease, fibroma, verruca vulgaris, condyloma acuminatum, adnexal tumors, actinic keratosis
- Pigmented SKs: Melanoma, melanocytic nevus, pigmented BCC, angiokeratoma
- Irritated SKs: *In situ* or invasive SCC
- Stucco keratosis: Acrokeratosis verruciformis of Hopf, epidermodysplasia verruciformis, verruca plana
- DPN: Acrochordon, melanocytic nevus, lentigines, verruca, trichoepithelioma, follicular hamartoma, syringoma, angiofibroma
- Irritated follicular keratosis: Verruca, trichilemmoma, BCC, SCC
- Lichenoid keratosis: BCC, SCC, actinic keratoses, melanoma (14)

Histopathological Differential Diagnosis

- Epidermal nevus, acanthosis nigricans, papillomatosis confluens et reticularis of Gougerot–Carteaud, acrokeratosis verruciformis of Hopf, solar lentigo (flat SK), SCC (irritated SK)

GENITAL SK

SK rarely occurs in the genital region, with no more than 10 published cases in the English literature. Genital SK usually occurs at a relatively younger age than classic SK and it causes diagnostic confusion with condylomata acuminata caused by HPV infection, Buschke–Lowenstein tumor, and melanoma, which has therapeutic implications and psychosocial consequences (31).

A pathogenic relationship between HPV and genital SK has been reported based on the high rate of virus detection in these lesions, with a strong predilection for HPV6, and the scarcity of genital HPV types in non-SK cutaneous genital lesions

Table 22.1 Summary of Dermoscopic Findings in Seborrheic Keratosis

Dermoscopic finding	Description	Histopathologically corresponds to	Other conditions where it can be present
Milia-like cysts ("stars in the sky")	Round, whitish, or yellowish structures	Small intraepidermal, keratin-filled cysts	Congenital nevi and papillomatous melanocytic nevi
Comedo-like openings (pseudofollicular openings and crypts) with "blackhead-like plugs"	Round structures of brown to black color	Keratin-filled invaginations of the epidermis	Papillomatous melanocytic nevi
Fissures ("gyri and sulci" or "mountain and valley" pattern)	Irregular, linear pattern with multiple fissures giving a "brain-like" or "cerebriform" appearance (Figure 22.10)	Keratin-filled depressions	Nevi with congenital patterns and common melanocytic nevi
Fat fingers (22)	Thick digitate linear, curvilinear, branched, or oval/circular structures representing the hypo- or hyper-pigmented gyri (ridges) of their cerebriform surfaces	–	–
Hairpin blood vessels	Long capillary loops mainly found at the periphery of the lesions in pigmented seborrheic keratosis. Clusters of blood vessels are grouped together with a whitish halo around each of them giving a "grape-like" appearance in irritated seborrheic keratosis	–	–
Network-like structures	Pigmented seborrheic keratosis can have structures resembling a pigment network (reticulation) that is different from the classic pigment network characterized by a thin, grid-like network consisting of pigmented "lines" and hypopigmented "holes." In seborrheic keratosis, lines of the network-like structures are hyperpigmented, ending abruptly at the periphery, and the grids are larger	Mild, compact hyperkeratosis and epidermal hyperplasia and an increase of melanin in the keratinocytes lining the basal layer, whereas a classic pigment network corresponds to melanin pigment in keratinocytes or in melanocytes along dermoepidermal junction The holes do not always correspond to the tips of the dermal papillae, but to keratin-filled structures	–
Moth-eaten borders	Concave border with pigment ending with a curved indentation resembling a moth-eaten garment in early seborrheic keratosis	–	Solar lentigines
Fingerprinting	Thin, brown, parallel lines resembling fingerprints in flat seborrheic keratosis or early seborrheic keratosis	–	Solar lentigo
Sharp demarcation	Abrupt cutoff of pigmentation at the border	–	–
Wobble pattern (pattern 3)	The lesion follows the movement of the dermoscopic device, leaving the surrounding skin, but the static image of the pigmented skin lesion does not change because the stiff, papular component cannot be dissociated from the surface of the lesion itself, reflecting the stiff, rigid consistency of the lesion	–	–

and in extragenital SK. Since HPV could not be detected in a minority of genital SKs using highly sensitive techniques, other unknown factors may also play a role in the pathogenesis of these lesions (32).

Genital SK can manifest as macules, papules, or plaques, and, more commonly, as pediculated forms in the intertriginous areas, often as polypoidal masses (Figure 22.11). Rare variants like melanoacanthoma and inverted follicular keratoses have also been reported in the genitalia (33).

Diagnosis becomes more difficult in the genital region as the classical clinical features of SK, such as distinct keratotic and follicular plugging, stuck on appearance, etc., are absent owing to friction and maceration in the genital region (33,34). Classical dermoscopic features such as comedo-like openings, which are keratin-filled invaginations of the epidermis, are usually not seen in the vulva, due to the friction that prevents their formation in this anatomical site. However, milia-like cysts, which are histologically included in the epidermis, are not eliminated by friction, and maceration and can help in the diagnosis of SK in the genital region (33,34).

Making a histological distinction between condyloma and SK in the genitofemoral area can be difficult and a combination of histological and immunohistochemical findings may be useful for distinguishing the two. In a study conducted to find reliable histological and immunohistological criteria for diagnosing these two entities, it was reported that the diagnosis of

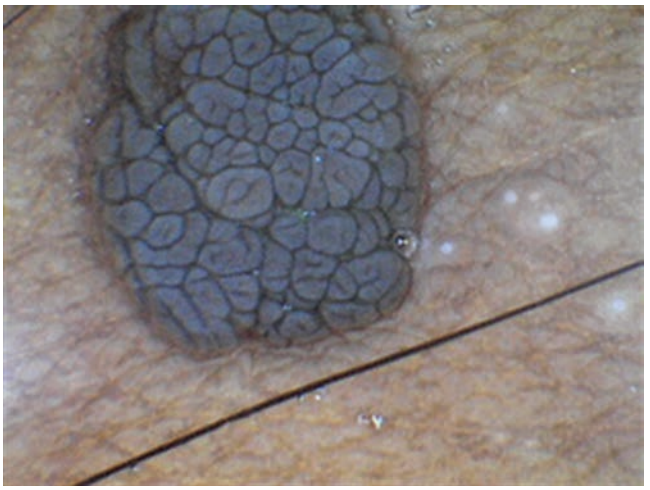

Figure 22.10 Dermoscopy of seborrheic keratosis showing a cerebriform appearance.

condyloma rather than SK was likely in the presence of broad, evenly distributed reticulated acanthosis, koilocytosis, a fascicular arrangement of keratinocytes, the absence of horn cysts, and positive immunohistochemical staining for HPV, Ki-67, and p21 (35). The features differentiating condyloma and SK are summarized in Table 22.2 (35,36).

Associations of SK

Malignancy

Several benign (solar lentigo and melanocytic lesions), premalignant (solar keratoses and SCC *in situ*), and malignant (BCC, SCC, melanoma, and keratoacanthoma) lesions have been described as occurring in association with SK (37,38). The associated malignancies can be either coincidental neoplasms developing in adjacent skin or contiguous with SK, arising from several cell types within the lesion. In theory, the basaloid cells could give rise to BCC, the squamous cells to SCC, and melanocytes to melanoma (37). BCC is thought to be the most frequent neoplasm seen in association with SK (37–39). Except for cases of malignant melanoma, the most common locations for skin malignancies associated with SK are the head and neck region or the thorax, as reported in various series (38).

Although the association of SK and skin malignancy appears to be relatively uncommon, the possibility of such an association cannot be completely ruled out. Hence, SKs that have undergone recent clinical change (rapidly growing, symptomatic, signs of inflammation, bleeding, ulceration, uneven pigmentation, or atypical lesions) should be considered for biopsy and histological examination (37,38).

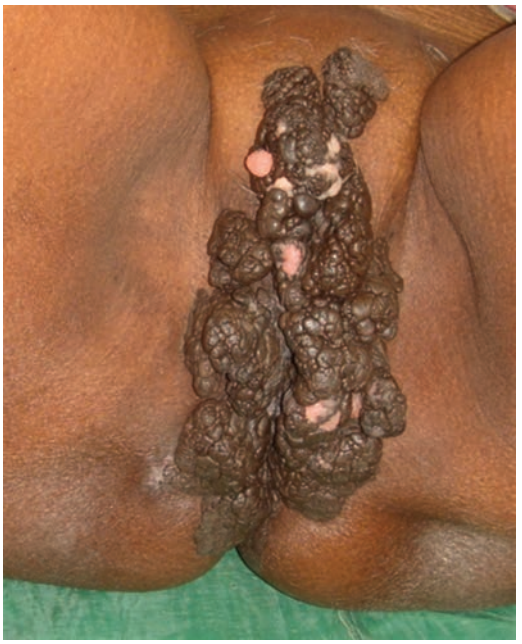

Figure 22.11 Genital seborrheic keratosis—large polypoidal mass on genitalia.

Table 22.2 Comparison of Condylomata Acuminata and Genital Seborrheic Keratosis

Condylomata acuminata	Seborrheic keratosis
Located on skin near or on mucocutaneous surfaces or on mucous membranes	Mucocutaneous surfaces or mucous membranes spared
Epithelial proliferation composed predominantly of spinous cells with pale cytoplasm	Epithelial proliferation composed predominantly of basaloid cells
Basaloid cells present in the lower portion of epidermis only	Spinous cells are confined beneath the cornified layer and around infundibular tunnels
Koilocytes present in the upper part of the epidermis within the foci of hypergranulosis	Absence of koilocytes
Compact orthokeratosis with subtle mounds of parakeratoses at summits of papillations	Delicate basket-woven or laminated orthokeratoses or subtle mounds of parakeratosis
Hypergranulosis present	Hypergranulosis absent
Dilated, tortuous capillaries spiral to reach the epidermis	Dilated, but not tortuous, capillaries in thickened papillary dermis
Base of lesion usually not flat	Base of lesion tends to be flat
Melanin, if present, is seen in the basal layer mainly	Melanin commonly present in basaloid cells throughout the lesion
Spindle-shaped spinous cells with pink cytoplasm	Spindle-shaped spinous cells absent
Solar elastosis absent	Features of solar elastosis present sometimes
Horn cysts absent	Horn cysts present

Leser–Trélat Sign

The Leser–Trélat sign is a paraneoplastic cutaneous manifestation characterized by an abrupt and striking increase in the number and/or size of SKs occurring before, during, or after an internal malignancy (11). Pruritus is present in nearly half of patients. It is associated with malignant acanthosis nigricans in about 35% of patients (40). Acquired ichthyosis, Cowden's disease, acrokeratosis paraneoplastica, hypertricosis lanuginosa, fluorid cutaneous papillomatosis, and tylosis can also be observed with the Leser–Trélat sign (41). Adenocarcinomas of the stomach and colon account for

the majority of malignancies, with the second most common being lymphoproliferative disorders, including leukemias, lymphomas, Sezary syndrome, and mycosis fungoides; others such as breast, pancreas, kidney, and lung cancers and melanoma have been reported (40,42).

The most common sites for eruption are the back and chest, followed by the extremities, face, abdomen, neck, axillae, and groin, with a "Christmas tree" or "splash pattern" of eruption (40). The sign is considered to be a marker of unfavorable prognosis, with the average survival rate of patients with the Leser–Trélat sign being 11 months after diagnosis (3).

The pathogenesis of the sign of Leser–Trélat is uncertain, but it is thought to be related to the secretion of a growth factor by the neoplasm, which leads to epithelial hyperplasia. Increased epidermal growth factor receptor expression has been observed as dense staining in all layers of the epidermis, except for the stratum corneum (10,41) and increased urinary levels of epidermal growth factor and transforming growth factor-α have been detected in patients with eruptive SKs and underlying malignancy (10). Subsequently, growth factor levels decreased following primary tumor resection (10).

The existence of this paraneoplastic condition is still controversial due to the extremely common nature of benign SKs and, furthermore, they occur in the age group that is most susceptible to malignancy (41). The SKs generally paralleled the course of the malignancy in many cases; however, there were instances in which these lesions did regress following removal of the cancer and the patient did not have recurrences of SKs but the patient died from metastatic disease, or there have been instances in which SKs persisted for years following treatment of the original cancer without evidence of the development of other neoplasms or metastatic disease (42).

Pseudo-Sign of Leser–Trélat

The term "pseudo-sign of Leser–Trélat" has been used to designate non-malignancy-associated eruptive SKs and has been reported in non-neoplastic tumors, HIV infection, erythroderma, and in association with the chemotherapeutic drug cytarabine. The initial reports of erythroderma-associated transient eruptive SKs (TESKs) included patients with underlying generalized eczema, benign renal tumor, pityriasis rubra pilaris, psoriasis, and erythrodermic drug eruption. TESK is a self-limiting condition, with the SKs involuting and disappearing as the erythroderma resolves and with the regression mediated through mononuclear cell infiltration (43).

Haber Syndrome

Haber syndrome is characterized by rosacea-like skin changes on the face and verrucous or bowenoid papules on the body, predominantly involving the axillae, which resemble SK on histology.

TREATMENT

Owing to the benign nature of the condition, treatment is not always warranted. However, when the SK becomes irritated or inflamed, either spontaneously or due to mechanical friction, or is cosmetically unappealing, then treatment is indicated.

The treatment of choice is complete removal of the lesions by any surgical procedure, including curettage, shave excision, cryotherapy, electrodessication, and electrical snaring for pedunculated lesions. Non-ablative 532 diode lasers for DPN and ablative lasers such as erbium Yttrium aluminium garnet (YAG) or CO_2 lasers can also be used. Ablative procedures such as electrosurgery, cryosurgery, and lasers are preferred for classical SK lesions that do not require histopathological confirmation, while in those cases wherein the diagnosis is in doubt, it is preferable to go for curettage or shave excision so that tissue is obtained for histopathological diagnosis. Complete excision, rather than a shave or curettage, will be more beneficial if malignancy is suspected. In patients with multiple lesions, multiple procedures can be performed based on the size and location of the lesions. For irritated and itchy SK, topical corticosteroids can be used prior to definitive treatment for the control of symptoms (3,30).

Curettage or shave excision or cautery can be used to remove raised SKs. Curettage or shave excision leave behind a raw surface that re-epithelializes in 1 week with good cosmetic results. However, cautery is rarely used owing to the risk of scarring (3,30).

Flat SKs can be managed with cryotherapy with liquid nitrogen, chemical peels with focal trichloroacetic acid, dermabrasion with fine sandpaper or wire brushes, and topical retinoic acid (tretinoin) with good results. In cryotherapy, the lesion is frozen for 2–3 seconds and is then allowed to thaw before the cycle is repeated once more in the same session. Cryotherapy may be repeated after a few weeks if necessary and photoprotection post-treatment is necessary to avoid hyperpigmentation. Cryotherapy, however, is not effective in the treatment of thick lesions, and such lesions may require a longer duration or a repeat spurt. Cryotherapy is also not advisable for DPN, as this variant, which is common in dark-skinned individuals, is associated with an increased risk of scar or keloid formation, as well as hyper- or hypo-pigmentation. Lasers are associated with more patient discomfort and prolonged recovery time (3,30).

Abnormal pigmentation, scars, and keloids can occur after any of these treatment modalities, but hyperpigmentation is common after cautery, hypopigmentation is more common after cryotherapy, and scars and keloids are more common after cautery than curettage (3,30).

Drug therapy is not well established for SKs and no topical or systemic therapy has been proven to be completely effective in its management, as such drugs need to be administered consistently for long durations and yet are inferior to surgical procedures. However, the discoveries made in the molecular genetics of SKs may pave the way for developing novel topical therapies.

Topical vitamin D analogues used once or twice daily for 3–12 months resulted in complete resolution or a more than 80% decrease in the volume of the tumor in 30.2% of cases, a 40%–80% volume reduction in 46.6% of cases, and a less than 40% reduction or no remarkable changes in 23.3% of cases. An experimental organ model exposing the SK material to varying doses of tacalcitol revealed apoptosis as the mechanism resulting in the clearance of SKs (44). Tazarotene 0.1% cream applied twice daily resulted in clinical improvement in lesions in 7 of 15 patients; however, it was associated with considerable irritation. Imiquimod was found to be ineffective (45). Recently, all-*trans* retinoic acid-loaded microneedle patches have been reported as a novel therapeutic option for SKs with proven safety and efficacy in animal and human studies. The mechanism of action was the induction of basal keratinocyte proliferation resulting

in accelerated stratum corneum turnover, causing the lesion to fall off the surface of the skin (46). By interfering with fibroblast growth factor receptor coupling, topical dobesilate has been reported to be effective in SK in a case report wherein a single daily application over 6 months resulted in complete clearance of lesions with good cosmetic results (47).

Systemic vitamin D therapy, owing to its potent antiproliferative action on keratinocytes, has been tried in patients with extensive SKs at two different doses, and it was observed that the response to treatment was dependent on the dose and the size of SKs, with a high dose of 0.5 µg/day producing an inflammatory response in 2 weeks, with the lesions resolving and the formation of atrophic scars or brown macules (48).

Prognosis

SK is a benign epithelial skin tumor and does not have a tendency for malignant transformation. However, reports of SKs coexisting with malignant skin tumors such as superficial BCCs, *in situ* or invasive SCCs, keratoacanthomas, and malignant melanomas have been reported, but it is still unclear if these tumors arise within the SK or are associated with it as collision tumors. As SKs increase with age, the appearance of *de novo* SKs is to be expected, even after the removal of multiple lesions, and after the removal of lesions, local recurrence can also occur; however, recurrence rate data are unavailable. No routine follow-up is required for confirmed SKs, but patients with newly appearing suspicious lesions should be examined in order to rule out premalignant or malignant conditions (3,30).

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Vulvodynia

Nancy A. Phillips, Lauren D. Arnold, and Gloria A. Bachmann

INTRODUCTION

Vulvodynia is a chronic vulvar pain disorder of unclear, likely multifactorial etiology, most often characterized by symptoms of vulvar burning in the absence of an identifiable cause. The prevalence of chronic vulvar pain (pain present for at least 3 months) ranges from 3% to 28% in population-based surveys, with 4%–7% reporting current pain (1–4). Vulvodynia is an idiopathic condition that is not well understood. Historically, much of what was known about vulvodynia originated from case reports and studies conducted in clinical populations, resulting in controversy regarding its classification, diagnosis, and management. In the late 1990s, increased research funding, especially that awarded by the National Institutes of Health, provided support for structured scientific and clinical protocols designed to study the pathophysiology, treatment, and epidemiology of this condition. As more data emerge, it is beginning to appear that vulvodynia is not a highly localized pain disorder confined to the vulva; rather, vulvodynia may be indicative of a more generalized sensory abnormality in affected women.

TERMINOLOGY AND HISTORY

One of the earliest references to chronic vulvar pain in the medical literature is credited to T. Galliard Thomas, who described hyperesthesia of the vulva in *A Practical Treatise on the Diseases of Women* in 1891 (5). He noted an extreme sensitivity of the nerves supplying the vulva that was distinct from other gynecologic conditions, such as vaginismus. With the exception of redness, there were no physical abnormalities, and symptoms were triggered by friction, air, bathing, and/or pressure. Dyspareunia, or pain with intercourse, was cited as the most devastating symptom and often the reason a woman consulted a physician. Thomas attributed the origins of this vulvar pain to menopause or a "morbid mental state." Because surgical removal of the labia minora and other vulvar tissues did not cure the patient, opium, chloroform, tannin, nitric acid, and local sedatives were recommended as potential treatments. Although this disorder was highlighted again by Skene in 1888 in *Treatise on the Diseases of Women* (6), there was little published literature until the late 1970s.

In 1975, the International Society for the Study for Vulvovaginal Disease (ISSVD) formally recognized a series of symptoms related to unexplained vulvar discomfort and termed the disorder "burning vulvar syndrome" (BVS) (7). An ISSVD task force was established in 1982 to further investigate the condition. The findings were presented at the 1983 BVS Congress, where the term "vulvodynia" was coined and defined as "chronic vulvar discomfort, especially that characterized by the woman's complaint of burning (and sometimes stinging, irritation, or rawness). Vulvodynia can have multiple etiologies, and use of this term for a patient's problem should prompt a thorough diagnostic evaluation" (8).

Recent decades have seen much controversy regarding the classification and description of vulvodynia. In 1989, McKay proposed five categories of vulvodynia: vulvar vestibulitis, essential vulvodynia, vulvar dermatoses, cyclic vulvitis, and vulvar papillomatosis (9). Ten years later, the 1999 ISSVD World Congress encouraged clinicians to replace the term "vulvodynia" with "vulvar dysesthesia" and argued that the disorder be classified as "generalized" or "localized," based upon the location of symptoms. Within the localized forms of disease, there were three proposed subclassifications: vestibulodynia (formerly vulvar vestibulitis), clitorodynia, and "other" (10). A 2001 review by Graziottin et al. (11) described seven subtypes of vulvodynia; the terminology and classification presented were not in agreement with the ISSVD's report.

When vulvodynia was revisited by the 2001 ISSVD World Congress, the terminology was again revised. "Vulvar dysesthesia" remained the preferred term, and two major categories, "provoked" and "spontaneous," were recognized based upon the nature of the pain stimulus; each of these was subdivided based upon the location of the pain (generalized vs. localized) (12). Yet this classification system was not accepted universally by clinicians and researchers. In April 2003, attendees of the National Institutes of Health Conference on Vulvodynia continued to debate the issue and resolved that two major subtypes of vulvodynia be recognized: dysesthetic vulvodynia and vulvar vestibulitis.

In early 2004, the National Vulvodynia Association supported the terminology and promoted it as follows (13):

Dysesthetic vulvodynia (generalized): Diffuse pain that is constant or intermittent; vestibular pressure does not always cause symptoms but may exacerbate symptoms.

Vulvar vestibulitis syndrome (dysesthesia localized in the vestibule): Localized pain that occurs when pressure is applied to the vestibule; a burning sensation is the most common symptom.

In October 2003, the ISSVD World Congress reinstated the word "vulvodynia" to describe unexplained vulvar pain and recommended eliminating the term "vestibulitis." They again divided vulvodynia into two subtypes—generalized versus localized—as defined by symptom location; each of these is further classified into three categories—provoked, unprovoked, or mixed—based upon inciting factors. The 2003 ISSVD World Congress recommended universal acceptance and promotion of these terms, bringing uniformity and clarity to the way the disease is recognized, diagnosed, and discussed by health care professionals (14).

In 2015, the ISSVD, in association International Society for the Study of Women's Sexual Health (ISSWSH) and the International Pelvic Pain Society (IPPS), adopted a new vulvar pain and vulvodynia terminology. This terminology was designed to better categorize vulvar pain, incorporate evidence-based information, and provide guidance for clinical practice. The Guidelines, similar to the 2003 Guidelines, are divided into vulvar pain (caused by a specific disorder) and vulvodynia (vulvar pain of at least 3 months' duration, without clear identifiable cause, which may have associated factors). Vulvodynia is further subdivided by descriptors:

- Localized, generalized, or mixed
- Provoked, spontaneous, or mixed
- Onset—primary or secondary
- Temporal pattern (intermittent, persistent, etc.)

The potential factors associated with vulvodynia—the newest addition to the terminology—add a dimension to the definition that allows clinicians to understand the multidimensional aspect of vulvodynia and should help guide individualized treatment (15). These factors include comorbidities and other pain syndromes, genetic influences, hormonal factors, inflammation, musculoskeletal contributions, neurologic mechanisms, central (spine, brain) or peripheral (neuroproliferation) nerve etiologies, psychosocial factors and structural defects (see "Etiology" section below) (15).

SYMPTOMS

Vulvodynia presents most often as chronic vulvar burning, but may also be characterized by soreness, rawness, stinging, itching, irritation, and/or stabbing pain (16,17). Women with generalized vulvodynia may have these symptoms involving most or the entire area between the mons and anus, whereas women with localized vulvodynia have symptoms restricted to a small area, such as the vestibule or clitoris. Symptoms may be unprovoked (present all the time) or provoked (present only with contact). Localized provoked vestibulodynia (PVD), the most common form of vulvodynia, is pain only with contact to the vestibule, the area immediately anterior to the hymenal ring. Women with PVD may describe pain present only with intercourse or tampon insertion. The definition of "chronic" previously varied between 3 or 6 months depending on the researcher or clinical reference, but should be considered 3 months as outlined by the recent consensus terminology (14,15).

ETIOLOGY

Several hypotheses have been proposed for identifying the etiological factors of vulvodynia. These are included in the 2015 "Appendix of Associated Factors," although the term "associated" implies that a causal effect has not been determined. In some instances, like musculoskeletal or psychosocial associations, cause or effect are difficult to ascertain.

Most agree that a *neurologic mechanism*, whether via a peripheral increased density of intraepithelial nerve fibers or a central sensitization, leads to hyperesthesia, such that even light touch is perceived as significant pain (allodynia) (18–21).

An association between *infection*, especially *Candida albicans* or bacterial vaginosis, and vulvodynia has been long suspected. Up to 70% of women with vulvodynia self-report repeated or severe yeast infections prior to onset of vulvodynia symptoms, but whether this represents true infection, an occasional co-current condition unrelated to the vulvodynia, or misdiagnosis is unclear (22,23). Altered *immune* reactions, which may be *genetically* mediated, have been demonstrated in women with vulvodynia, and as ongoing knowledge of the vaginal microbiome emerges, more information regarding the link to either infection or the response to infection may be uncovered (24–26).

Hormonal influences on vulvodynia are unclear. Onset of vulvodynia may be pre- or post-menopausal. Studies are inconsistent regarding the impact of oral contraceptives on the development of vulvodynia, although the lower androgens associated with their use are the suspected precipitating factors (27–30).

Musculoskeletal factors, including myofascial disorders, hypertonus, *structural defects*, or referred pain from the hip, back, or lower extremities, may present as vulvodynia (31). Conversely, vulvodynia may result in pelvic floor spasm and muscle dysfunction.

Women with vulvodynia have increased anxiety and depression in general when compared to unaffected women. However, as in musculoskeletal conditions, *psychosocial factors* may represent either a cause or effect of vulvodynia, but more likely both (32).

PREVALENCE

It is estimated that as many as 200,000 women in the USA have symptoms consistent with vulvodynia (15) and that up to 14 million U.S. women will experience chronic vulvar pain symptoms in their lifetime, 30% of whom will choose not to consult a clinician (3). Yet these numbers are only estimates, limited by a lack of population-based studies. The true extent of this pain condition is unknown.

In 1991, Goetsch reported that 15% of women screened in a gynecologic practice met the diagnostic criteria for vulvar vestibulitis (33). However, these findings cannot be extrapolated to the general population, which includes women who do not seek care for their symptoms. In 2001, Harlow and colleagues performed the first population-based study to assess the prevalence of chronic vulvar pain and found that 18.5% of 303 women surveyed randomly in a Boston, Massachusetts community indicated a minimum 3-month history of genital tract discomfort at some point in their life; 8.6% of the total population had symptoms at the time of the survey (34). A second Boston study found that of the 3358 eligible women surveyed, 16% reported a lifetime history of burning, knife-like chronic vulvar pain of at least 3 months in duration, and 7% of participants experienced symptoms at the time of the study (4).

Expanding on the work of Harlow et al., Reed et al. (2) conducted a web-based survey with a national sample of 1032 women and found a 27.9% lifetime prevalence of vestibular pain, with a 3% prevalence of symptoms lasting 3 months or longer. Reed et al. followed this study with a 2004 survey of 1046 women from the University of Michigan's Women's Health Registry, and found 7.6% of women to be currently experiencing vulvar pain of at least 3 months in duration (35). Reed et al. then examined a fraction of these women and found that the survey accurately identified women with vulvodynia. The same study group was resurveyed 2 years later. Of the 372 asymptomatic women controls at initial enrollment, 3.5% had developed vulvodynia during the 2-year follow-up period, and of the 45

women with vulvodynia at initial enrollment, 22% indicated that their symptoms had resolved. Reed et al. calculated that each year, 1 in 50 women developed vulvodynia and 1 in 10 women had resolution of vulvodynia symptoms (36).

DEMOGRAPHICS

A woman can develop vulvodynia at any time in her life, but studies report that the majority of afflicted women are of reproductive age. Although the incidence of vulvodynia decreases with increasing age, it is possible that the symptoms are more often attributed to vulvovaginal atrophy and therefore do not represent an accurate prevalence (37,38). Racial demographics have shown that Caucasian and African–American women have similar rates of vulvodynia, whereas Hispanic women are 80% more likely to experience chronic vulvar pain (4).

COMORBID CONDITIONS

Vulvodynia patients often have other medical complaints in addition to their vulvar symptoms. In a study of 301 vulvodynia patients at the University of British Columbia's Vulvar Disease Clinic, 55% indicated they had a suspected second chronic pain condition, including low-back pain, irritable bowel syndrome, migraine headaches, chronic fatigue syndrome, and fibromyalgia (39). This finding was confirmed by a later study using validated questionnaires that showed that the presence of vulvodynia was associated with the presence of interstitial cystitis, irritable bowel syndrome, or fibromyalgia (odds ratio: 2.3–3.3) (40).

GYNECOLOGIC HISTORY

Gynecologic history should aim to eliminate other causes of vulvar pain and identify potential contributing factors. Harlow et al. (34) suggested that women who began menstruating at the age of 11 years or younger were four times as likely to report chronic vulvar pain; however later work suggested there is no risk associated with age of menarche. Pain and/or difficulty with first tampon insertion, which does not resolve with continued use, is associated with seven-fold greater odds of chronic vulvar pain (4).

PSYCHOSOCIAL AND SEXUAL EFFECTS OF VULVODYNIA

It was once proposed (and accepted) that psychological factors contributed to the development of vulvodynia (5). This concept has been debated widely and today vulvodynia is not considered to have psychogenic origins. However, it is accepted that the condition has a (non-causal) psychosomatic component, and women with vulvodynia exhibit more somatic symptoms and harm-avoidance behavior than women without vulvodynia (41).

Similarly, the relationship between intercourse and vulvodynia is complex. Dyspareunia is one of the most common manifestations of pain, and nearly 75% of affected women experience painful intercourse (1,42). It has been demonstrated that women with vulvodynia are more likely to have had intercourse for the first time at the age of 18 years or younger, to have had only one sexual partner, and to have a history of sexual problems (43). Women with vulvodynia are also more likely to have lost interest in sexual activity and to rate intercourse as less important in their lives. To date, no relationship has been found between sexual victimization and vulvodynia (39,44,45).

DIAGNOSIS

In 1978, Dodson and Friedrich (46) proposed guidelines for characterizing vulvodynia as follows:

1. Chronic symptoms
2. A lack of abnormal physical findings
3. Refraining from sexual intercourse because of symptoms
4. Emotional lability
5. Reluctance of the patient to acknowledge a psychological component to the condition

Specific diagnostic criteria proposed by Friedrich in 1987 (47) and still in use today include:

1. Vulvar erythema as the sole physical finding
2. Pain upon vestibular touch or entry
3. Tenderness upon localized vestibular pressure

Vulvodynia remains a diagnosis of exclusion with pathologic findings limited to erythema, and other pathologies corrected or not believed to be the primary cause of the symptoms (15). Common presenting symptoms include vulvar burning, itching, aching, stinging, or stabbing pain (Figure 23.1) (45). A comprehensive diagnostic work-up includes a symptom history, medical history, pelvic examination, vaginal cultures, and pain mapping. The pelvic examination should yield no physical abnormalities. Medical conditions that could cause symptoms, such as cysts, ulcers, tumors, spinal cord lesions, and

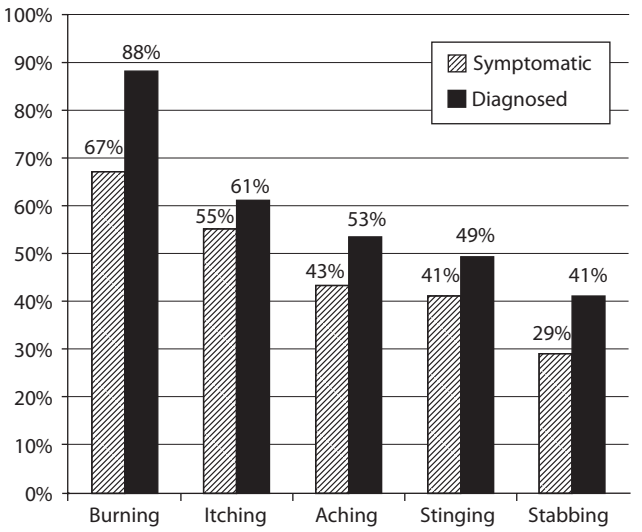

Figure 23.1 Self-reported vulvar pain descriptors obtained through University of Medicine and Dentistry of New Jersey survey data from a population of women with a clinically confirmed diagnosis of vulvodynia ("Diagnosed") and a population of women who reported symptoms of vulvodynia via a telephone interview ("Symptomatic"). (From Bachmann GA, Rosen R, Kelly SW, Rhoads GG. Vulvodynia: Characteristics and associations with comorbidities and quality of life. *Obstet Gynecol* 2006; 10: 617–24, with permission.)

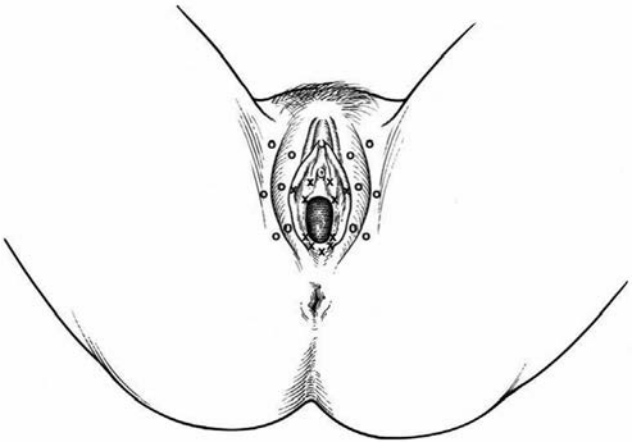

Figure 23.2 The cotton-swab test enables the clinician to map vulvar pain and allows the patient to rate pain sensation on a subjective scale.

dermatoses, must be ruled out, and vaginal cultures are needed in order to exclude urogenital infections (e.g., yeast infections, urinary tract infections, herpes simplex, etc.) as the etiology of pain.

Pain mapping is an integral part of the diagnostic process. The traditional procedure for this is the cotton-swab test (11,48), in which the clinician applies pressure to designated areas of the vestibule using the swab (Figure 23.2). The patient rates sensation on a scale of 1 (no pain) to 5 (maximum pain) (49). However, this test has limited reproducibility, because the outcome depends upon the clinician's subjective assessment of pain and the individual degree of pressure each practitioner exerts; the degree of pressure applied to the vulva varies from one clinician to another, and so this method lacks reliability.

The vulvar algesiometer is an instrument that is designed to provide a more reliable measure of pressure at each point on the vestibule. A hand-held device is programmed to deliver incremental pressures up to a maximum force of 8 milli-Newtons and is used to document the pressure needed to elicit pain. This examination is used mostly in research settings (50).

The pelvic floor muscles should also be examined by palpation laterally inside the vagina, assessing for tenderness over the levators (either with or without voluntary contraction), painful trigger points, or stinging.

Although the diagnostic process can be complex and there is no common protocol used by clinicians, the critical point in making the diagnosis is to exclude all other pathologic entities that can be causing the vulvar pain (Figure 23.3) (51).

TREATMENT

Just as there is no universal means of defining or diagnosing vulvodynia, there is no standard of care for treating this condition. No agent is Food and Drug Administration approved for the treatment of vulvodynia, and although various algorithms have been suggested, therapy is largely based on clinical judgment and often relies upon trial and error. Few randomized trials have been conducted for the treatment of vulvodynia, and even fewer have a placebo control. Treatment can be subdivided into three types: medical, surgical, and alternative therapies.

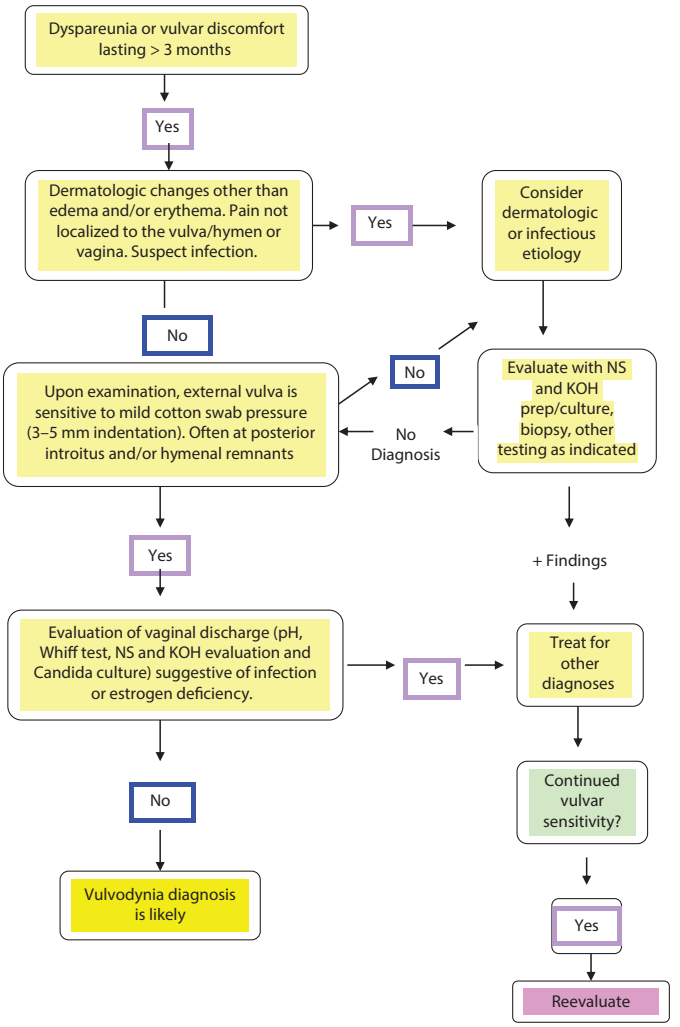

Figure 23.3 Diagnostic algorithm for vulvodynia. NS = normal saline; KOH = potassium hydroxide. (Adapted from Curnow JS, Barron I, Morrison G. *Med Biol Eng Comput* 1996; 34: 266–9.)

Medical therapies consist of general vulvar care; local pain relief; pharmacologic agents (tricyclic antidepressants such as amitriptyline or nortriptyline, gabapentin, and pregabalin, serotonin norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine or duloxetine, or hormonal agents such as locally applied estrogen or estrogen plus testosterone); pelvic floor physical therapy; or cognitive behavioral therapy.

Surgical/invasive therapies consist of botulinum toxin type A; nerve blocks; or surgical excision.

Alternatively, there are therapies consisting of acupuncture, mindfulness, yoga, and/or relaxation.

Commonly used treatment regimens are outlined in Table 23.1 (50). Practitioners should be familiar with the potential side effects and risks of all prescribed medications. All treatments should be started at a low dose and titrated upwards slowly. Clinicians should be well versed with the side effects and potential interactions of the medications. Women should be aware that maximum effect may not be seen for up to 6 weeks from initiation of therapy. Clinicians should consider the individual in initiating a treatment and a multidisciplinary team approach should be utilized, including female

Table 23.1 Treatments of Vulvodynia

Medical[a]	
General vulvar care	Avoid soap, perfumed products Cotton clothing, sanitary products Avoid tight clothing, biking, horseback riding
Local pain control	Ice packs, topical lidocaine, sitz baths
Pharmacological agents	
Tricyclic antidepressants	10 mg initial dose qhs,[b] increase by 10 mg weekly to maximum 150 mg Side effects generally limit dose (drowsiness, weight gain, anticholinergic) Nortriptyline/desipramine have fewer side effects than amitriptyline Topical compounded amitriptyline 2% with baclofen 2% twice a day
Gabapentin	100 mg initial dose qhs, increase by 100 mg weekly to maximum 3600 mg Topical compounded 2%, 4%, or 6% applied twice a day Black box warning regarding rhabdomyolysis
Pregabalin	50 mg initial dose qhs, increase by 50 mg every 3 days to maximum 600 mg More gradual increase may decrease side effects Cannot be stopped abruptly
Venlafaxine	37.5 mg BID[c] initial dose, increase by 37.5 mg weekly to maximum 375 mg Many side effects, may inhibit orgasm
Duloxetine	20 mg initial dose, increase by 20 mg weekly to maximum 120 mg Use higher dose with caution due to side effects and drug interactions
Hormonal agents	Topical estrogen applied daily for 4–6 weeks then twice a week Topical compounded estradiol 0.2%/testosterone 0.1% BID for 12 weeks
Pelvic floor physical therapy	Best for women with pelvic floor hypertonicity Includes biofeedback, massage, soft tissue mobilization Vaginal dilators and progressive relaxation are useful adjuncts Valium suppositories (compounded) 2–10 mg qhs for severe spasm/pain
Cognitive behavioral therapy	Positive effects with regard to control, pain management Relaxation and meditation may be useful adjuncts
Surgical/invasive	
Botulinum toxin	Injected into pelvic floor muscles May need anesthesia for placement, expensive May need repeated treatments
Nerve blocks	Pudendal blocks either vaginally or trans-gluteal Caudal–epidural blocks Trigger point injections May need referral to pain services, may need repeated treatments
Surgical excision	Limited to treatment of localized, provoked vestibulodynia Multiple surgical techniques, no studies randomized for comparison Success rate varies from 30% to 90% in the literature
Alternative therapies	Acupuncture, mindfulness, yoga, relaxation

Source: Adapted from Reed BD. *Female Patient* 2005; 30: 48–54.

[a] All medications listed are off-label use; dosages represent commonly prescribed regimens and should be individualized.

[b] qhs = take at bedtime.

[c] BID = twice a day.

health care specialists, physical therapists, psychologists, and pain specialists.

For example, a menopausal woman with vulvar pain, hypertension, and a new relationship after years of no sexual contact should be assessed and prescribed vaginal estrogen, unless contraindicated. Oral therapies should be added with close attention to interactions with her other medications, and attention should be paid to the possible need for pelvic floor

Table 23.2 Vulvodynia Treatment Guidelines

All medications should be started at the lowest dose and titrated upwards slowly, balancing effectiveness and side effects
Only one treatment should be introduced at a time
Pain and symptom diaries should be kept to help guide and monitor treatment
In the absence of direct contraindications, multiple therapies may be used simultaneously, although little to no data are available to support this strategy
Counseling should be offered as appropriate, including individual, couple, cognitive behavioral, or sexual
Surgery should be reserved for localized vestibulodynia, only after failure of medical therapy

Source: Adapted from Phillips NA, Bachmann G. *Menopausal Med* 2010; 18(2): S1–4.

physical therapy or the addition of dilators prior to attempted intercourse.

For a premenopausal woman trying to conceive, topical therapies or pelvic floor physical therapy may be preferred to oral therapies, which may be added if necessary after discussion of the potential effects of medications during pregnancy and possible consultation with a high-risk pregnancy specialist.

Treatment guidelines are outlined in Table 23.2 (37).

CONCLUSION

Vulvodynia is a multifactorial, chronic, painful condition that may affect nearly 15% of women at some time during their lives. Although it was identified as early as the 1800s, little published research exists prior to the late 1970s.

Vulvodynia remains a diagnosis of exclusion, as no objective tests are currently available. Although there is no cure for vulvodynia, making the appropriate diagnosis and systematically treating the woman with interventions that have shown efficacy are priorities in delivering optimal patient care for this condition. It will only be through continued, multicenter, randomized, prospective, placebo-controlled trials that the etiology (or etiologies) and optimal treatment(s) that are evidenced based and safe with minimal side effects will emerge.

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Impact of urinary incontinence and urogenital atrophy on the vulva

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INTRODUCTION

The vulva, which is the external genitalia of the female, collectively consists of the mons pubis, labia majora and minora, clitoris, vestibule, greater (Bartholin) and lesser vestibular glands, and vaginal opening (introitus). Vulvar medicine spans dermatology, gynecology, and sexual health. Many conditions affecting the vulva are dermatological, modified by anatomical, hormonal, and microbiological influences. Vulvar conditions may present to genitourinary medicine physicians, dermatologists, and gynecologists and treatment modalities also span across this spectrum.

The aim of this chapter is to specifically consider the urogynecological conditions that affect the vulva, principally urinary incontinence and genitourinary syndrome of menopause (GSM).

BACKGROUND ANATOMY AND PATHOPHYSIOLOGY

As the largest organ in the body, healthy skin provides a large natural barrier to moisture, harmful substances, and environmental irritants. The skin consists of the epidermis and the dermis layers and prevents harmful fluid gain or loss (1). The epidermis layer is the main and outermost barrier to harm. It consists of five different layers: stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale.

The stratum corneum is the uppermost barrier, constructed with protein-rich corneocytes (disc-shaped horny cells primarily made up of keratin) (2). These are bound together with a lipid-rich substance, creating a "bricks and mortar"-style defensive structure (1,3). The epidermis also contains enzymes that work with the phospholipids to produce a mixture of cholesterol and fatty acids known as ceramides, which cement the corneocytes together to form a rigid protein mass that is capable of attracting and retaining water within the stratum corneum. This has been described as a natural moisturizing factor (NMF) that increases intracellular water content, enabling the corneocytes to retain their shape and turgidity. This process creates and maintains an effective and well-hydrated skin barrier that is flexible (4). The NMF results from a breakdown of the protein filaggrin, creating a mix of salts, amino acids, and their derivatives. The NMF is capable of absorbing atmospheric water, enabling effective hydration of the outer skin layers in spite of environmental factors. Normal skin pH is 4.5–6.2, creating an acid environment that is an effective neutralizing barrier to viruses, bacteria, and other contaminants or irritants that are alkaline in nature.

Any disruption to this process may lead to an excess of skin moisture or dryness, which in turn may result in skin breakdown. This is well demonstrated in the extremities of the hands and feet after a prolonged soak in the bath (excess moisture with wrinkling of the fingers/toes) or with repeated handwashing episodes leading to dry skin. Excessive moisture also increases the risk of friction damage due to skin maceration (5).

URINARY INCONTINENCE AND INCONTINENCE-ASSOCIATED DERMATITIS

Urinary incontinence, the "complaint of any involuntary leakage of urine" (6), is a common and distressing condition known to adversely affect quality of life (7). Whilst the prevalence of urinary incontinence has been found to vary widely depending on the definition used, a large-scale epidemiological study found that approximately 25% of women complain of urinary leakage (8).

Incontinence-associated dermatitis (IAD) is a common skin disorder affecting patients with urinary and/or fecal incontinence. This is particularly difficult in the elderly and in individuals with medical or surgical comorbidities, in whom maintaining the skin's integrity is already a challenge. IAD is a complex issue with inconsistent recognition as its symptoms are often confused with those of pressure ulcers.

Urinary and fecal incontinence are thought to affect half of all of nursing home residents, and a third of community-dwelling adults may suffer from urinary incontinence (6,9). However, it is likely that the prevalence of IAD is underestimated (10) either due to failure to recognize or report it or misdiagnosis as pressure damage (11). The prevalence of IAD varies from 5.6% to 50% and is highest in those with fecal incontinence (12), while its incidence is 3.4%–25% (13). Consequently, the prevention and management of IAD presents a significant financial burden for health care systems. In England alone, 903,500 prescriptions for barrier products were issued in 2014, at a cost of £3.27 million (14).

IAD is a form of moisture-associated skin damage (9), the pathophysiology of which always starts with prolonged exposure of the skin to moisture, which in turn results in damage, particularly in the folds of the skin (9). Older people are at a higher risk of moisture-related skin damage due to a thinning of the overall epidermis that occurs with age. The intersection between the dermis and epidermis flattens with age. Elasticity is reduced, collagen synthesis decreases, loss of connective tissue might lead to a generalized atrophy of the skin, and enzyme balance is easily disrupted, reducing its resistance and increasing the risk of damage from friction. Once the skin is saturated it is more susceptible to friction and shearing force damage, which in turn allows the normally harmless skin flora to penetrate the barrier, resulting in secondary infection (6).

It is thought that the irritation and damage is a result of the disruption of the intracellular lipid mortar within the stratum corneum and the corneocytes, resulting in a dissolving effect on the physical barrier of the skin (15).

Experimental studies have shown that urine has an irritant property when in continuous contact with skin for 24–48 hours. With relatively short exposures of 4 hours, fecal material causes visible erythema and increases pH and transepidermal water loss (16).

Interestingly, some studies have shown a marked difference in the perception of skin sensitivity between those who are incontinent and continent controls. A significantly higher percentage of subjects with urinary incontinence describe their skin overall as "sensitive," although not specifically over the genital area. The researchers concluded that this may be a source of bias and incontinent subjects may be less likely to admit they have sensitive genital skin, perceiving this as an additional weakness they would prefer to deny, especially since this research was conducted in focus group sessions (17).

A typical presentation is an inflammation of the skin surface, redness, swelling, and possible blister formation. Urinary incontinence dermatitis typically affects the female labial area, the thighs, and the buttock area. Generally, most theories suggest that the combination of fecal incontinence and urinary incontinence leads to a significantly increased risk of IAD. Over-hydration of the epidermis and an increase in skin pH to a more alkaline level activates the richer digestive enzymes and bacteria contained in liquid feces, leading to damage of the epidermis (1), which may present as maceration (18).

The urea in urine can be broken down by the skin bacteria to form the highly alkaline ammonia, which shifts the pH of the skin, further disrupting the barrier. If feces are present, the change to a more alkaline pH activates enzymes present in the feces, which then further contribute to the damage caused to the epidermis. Liquid stool tends to be richer in digestive enzymes (lipases and proteases), which, when combined with its elevated water content, is particularly damaging to the skin (9,12). It is thought that penetration of skin bacteria through the damaged barrier also plays a role in the development of the inflammatory component of IAD. The combined effects of chemical irritants and physical elements of care causing friction or shearing result in weakened skin structure and breakdown (19).

More recently, Mugita et al. have explored the mechanisms of IAD in an animal model (20). They have shown that the histology of IAD is distinct from contact dermatitis and demonstrated the ability of gut flora to penetrate the skin along with proteolytic enzymes, producing inner tissue damage. The end result of these processes is the initiation of an inflammatory response and IAD, which, if not managed correctly, sets up a vicious cycle that further drives the inflammation and skin breakdown. This may be further complicated by secondary infection of the damaged skin by pathogens, with fungal infection being very common (21).

The increase in the incidence of incontinence is thus not only dependent on age, but also on the onset of concomitant aging issues such as infection, polypharmacy, and decreased cognitive function. If incontinence is left untreated, a host of dermatological complications can occur, including incontinence dermatitis, dermatological infections, intertrigo, vulvar folliculitis, and pruritus ani. Over time, a vicious cycle of skin damage and inflammation results because of the loss of cutaneous integrity (22).

The importance of optimal skin care after each episode of incontinence cannot be emphasized enough. When combined with a pressure ulcer prevention protocol, a structured care plan significantly lowers the incidence of IAD from around 25% to less than 5%. It is recommended that a skincare protocol should comprise gentle skin cleansing, application of moisturizers, and use of a skin barrier protection product. This will minimize the damaging effect of incontinence on the skin.

Patients at risk of developing IAD should have their skin assessed at least daily, or more frequently if they are considered to be at very high risk. This should form part of a general skin assessment and can easily be incorporated into routine skin inspection for pressure ulcer risk. In King's College Hospital, the Incontinence Associated Dermatitis Risk Assessment and Prevention tool is used by the continence nurse specialist for initial assessment and management (Figures 24.1 and 24.2).

Once the initial severity and grade of IAD has been assessed, an individualized care plan is put into place.

Nursing actions: examine the patient's skin for redness, inflammation, rash, or broken skin after every incontinence episode. Use this care plan when IAD total risk score is >1:

1. Do not use water on perineum/sacrum/buttock, groin areas.
   a. Intact skin: use a mild wipe after every incontinence episode.
   b. Mild IAD: use a mild wipe after each incontinence episode.
   c. Moderate IAD: use a mild wipe after each incontinence episode.
   d. Severe IAD: use Proshield® Foam and Spray Cleanser (ProshieldPlus: H&R Healthcare Ltd, Melton, Hull) in conjunction with Proshield Plus skin protectant and consider diverting urine/feces from skin by using urinary sheaths or catheters/fecal collectors/bowel management systems.
   e. Check perineal skin hourly if containment pads used to contain stool.
   f. Consider analgesia especially in severe cases of skin breakdown.
   g. Consider leaving a mild wipe over affected areas and remove every 2 hours if soiled or the wipe is no longer moist.
   h. If pressure damage is present, please complete wound assessment form and refer to tissue viability nurse.
2. Do not use a mixture of topical skin cleansers or barrier creams on the same incontinence episode cleansing unless specialist advice is given.
3. If there is no improvement in skin condition, then please refer to the continence team.

Management of IAD

The ideal solution in the management of IAD is obviously to treat the underlying condition (i.e., treat the urinary incontinence, or at least minimize it as much as possible). However, this may not always be possible, especially in the context of the elderly, frail patient who may have multiple comorbidities and be immobile due to these. As moisture is the main cause of IAD, it is obvious that reducing exposure to excessive moisture will be pivotal in the management and prevention of IAD. Robust continence management that is individualized will go a long way to reducing risk in individual patients. A structured

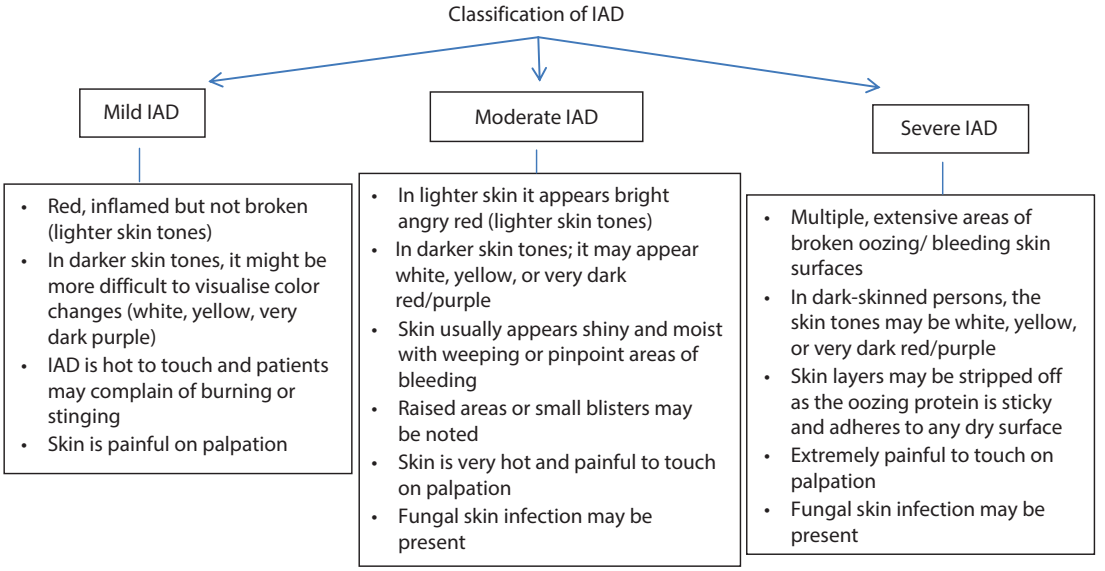

Figure 24.1 Classification of incontinence-associated dermatitis (IAD).

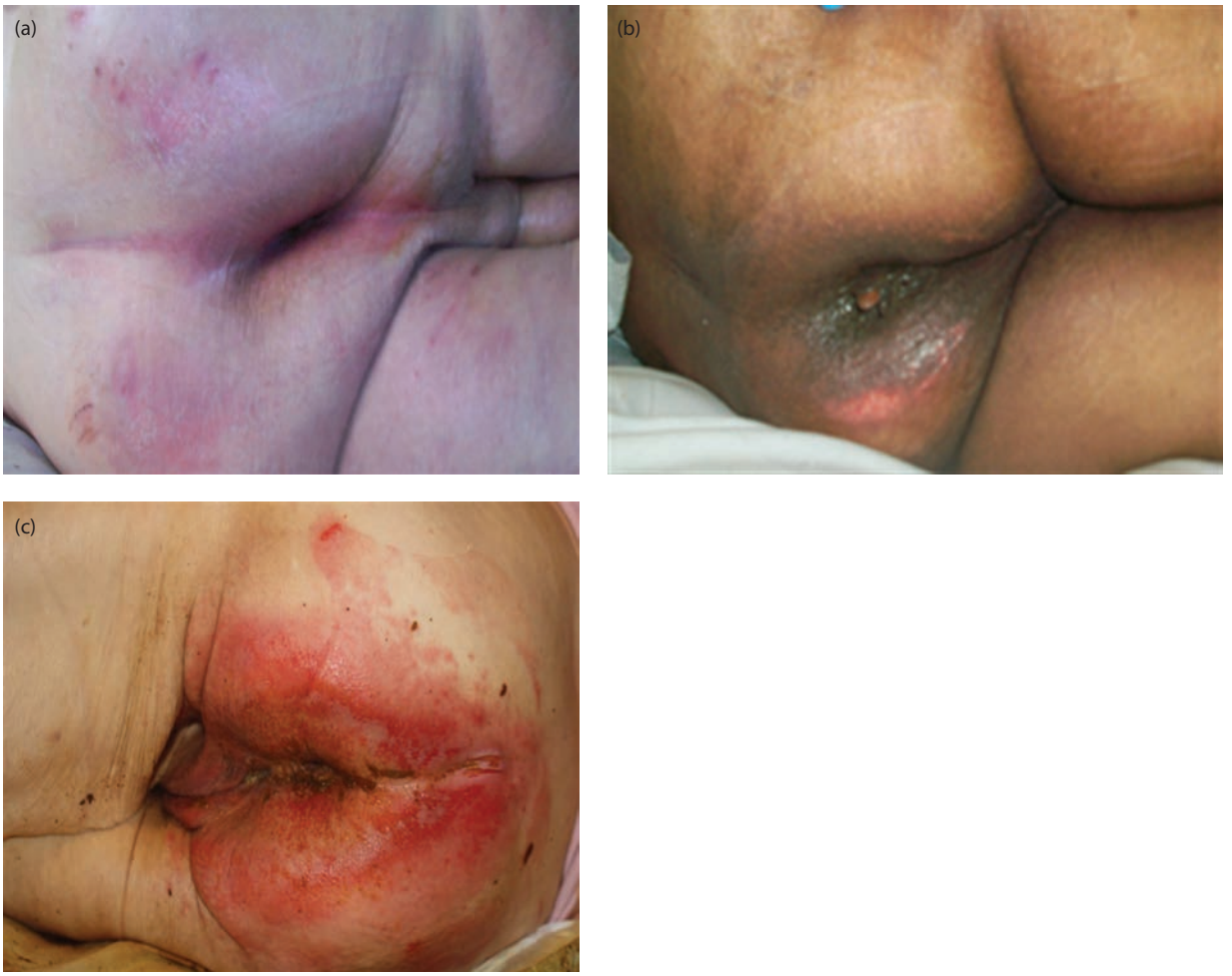

Figure 24.2 Pictorial representation of IAD. The descriptions of mild, moderate, and severe are provided in detail in Figure 24.1.

skin care regimen is useful in those at higher risk of IAD with appropriate use of containment products that encourage moisture away from the skin. It is essential to control or limit the amount of moisture that comes into contact with the skin from incontinence and to ensure prompt treatment of any secondary infections; this will help to minimize the risk and effect of IAD.

A review of the current evidence on the prevention and treatment of IAD concluded that IAD can be prevented and healed with timely and appropriate skin cleansing and skin protection, with a focus on the use of appropriate incontinence containment materials. However, further research is required in order to evaluate the efficacy and effectiveness of various interventions (19).

Identification of urinary or fecal incontinence during the nursing assessment should lead to the implementation of appropriate protocols aimed at preventing IAD or promoting healing if skin damage is already present, and should link with those for preventing pressure ulcers. Key factors in successful prevention and management are careful patient assessment, good continence care, and clear evidence-based skincare protocols, all of which can improve the patient's experience and improve clinical outcomes, thus demonstrating once again the importance of good "fundamental" care.

GENITOURINARY SYNDROME OF MENOPAUSE

Previously, the terms "vulvovaginal atrophy" and "atrophic vaginitis" were used to describe the range of menopausal symptoms associated with physical changes of the vulva, vagina, and lower urinary tract associated with estrogen deficiency. However, these have now been replaced by the term "genitourinary syndrome of menopause," or GSM (23).

GSM is defined as a collection of symptoms and signs associated with a decrease in estrogen and other sex steroids involving changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra, and bladder. The syndrome may include but is not limited to genital symptoms of dryness, burning, and irritation; sexual symptoms of lack of lubrication, discomfort or pain, and impaired function; and urinary symptoms of urgency, dysuria, and recurrent urinary tract infections.

The urogenital system is very sensitive to estrogen deprivation, and the low levels of circulating estrogen after menopause result in physiological, biological, and clinical changes in the urogenital tissues.

There is a reduction in squamous epithelial cells in the vulvovaginal area and uroepithelial lining, with a predominance of basal cells associated with a significant decline in epithelial collagen, glycogen, mucopolysaccharides, and hyaluronic acid. Consequently, the vaginal walls become thin, friable, pale, and hyposecretory, losing elasticity with progressive stenosis, while the urethra develops increased atrophy and laxity (24). The uterus, ovaries, vagina, and vulva also shrink in size. Anatomic changes include reduced collagen content and hyalinization, decreased elastin, thinning of the epithelium, altered appearance and function of smooth muscle cells, increased density of connective tissue, and fewer blood vessels.

Physiological changes result in reduced vaginal blood flow, diminished lubrication, decreased flexibility and elasticity of the vaginal vault, and increased vaginal pH (19,24,25). Furthermore, decreases in vaginal tissue strength and increased friability may predispose to epithelial damage with vaginal penetrative sexual activity, leading to vaginal pain, burning, fissuring, irritation, and bleeding after sex (22,26). Epithelial thinning with decreased glycogenated superficial cells leads to changes in vaginal flora and loss of lactobacilli, increased pH, and a change in the microbiome (13). Concomitant with these changes is a reduction in the vaginal *Lactobacillus* population, which in turn leads to greater vaginal alkalinity and further contributes to the greater risk of urinary tract infections (27).

Management of GSM

There is extensive literature on the management of urogenital symptoms in postmenopausal women. Symptomatic women should be counselled on adopting lifestyle changes to ameliorate vulvovaginal atrophy and the onset of urinary tract infections. Smoking cessation should be encouraged, as cigarette smoking is associated with accelerating vaginal atrophy (28). Regular sexual intercourse has been shown to improve vaginal atrophy, presumably as a result of stimulating increased blood flow to these organs (29). Vaginal lubricants (e.g., K-Y® [Reckitt Benckiser, USA], Yes® [The Yes Yes Company Ltd, Liss, Hampshire], and Sylk® [Sylk Limited, Geneva Marketing Limited, New Zealand]) may be useful in reducing discomfort during intercourse.

Non-hormonal polycarbophil gel vaginal moisturizers such as Replens® (WellSpring Pharmaceutical Corporation, Bradenton, FL) may be used for symptoms related to vaginal dryness, although the literature shows inconsistent results regarding their efficacy (30,31). In addition, Replens has not been shown to improve the maturation index of the vaginal lining (32) or reduce vaginal pH (33).

Ospemifene, a selective estrogen receptor modulator (SERM) derived from toremifene, has also been shown to be effective in treating vulvar and vaginal atrophy (34,35). It has been recently approved at the dose of 60 mg orally, and is indicated for the systemic treatment of moderate to severe dyspareunia associated with vulvovaginal atrophy in women who are unable to tolerate or unwilling to take local or systemic estrogens. Another SERM, lasofoxifene, is under investigation.

However, the most effective treatment for urogenital symptoms is the use of vaginal estrogen. This may be in the form of estrogen-containing creams, pessaries, silicone rings, or tablets. These agents work to restore vaginal epithelial maturation and vaginal lubrication, yielding an improvement in both symptoms and signs of vaginal atrophy. Use of vaginal estrogen has been shown to significantly improve the symptoms of atrophic vaginitis—vaginal dryness, itching, and discharge (36–38)—as well as reduce the frequency of urinary tract infections among postmenopausal women (39,40). The time to improved symptoms with topical vaginal estrogens is roughly 4 weeks (41) and, importantly, the agents have not been found to significantly increase endometrial thickness after 48 weeks of treatment (38). Local estrogen therapy minimizes the degree of systemic absorption and, although vaginal administration can increase plasma levels of estrogens during chronic administration, the observed levels are not above the normal range for postmenopausal women (42). The choice of modality for local estrogen administration should be guided by patient preference. The most recent meta-analysis of intravaginal estrogen treatment in the management of urogenital atrophy was reported by the Cochrane group in 2003. Sixteen trials with 2129 women were included and intravaginal estrogen was found to be superior to placebo in terms of efficacy, although there were no differences between types of formulation (31). There are few data on the use of vaginal estrogens in women with gynecological

Table 24.1 Vaginal Estrogen Therapy

1. Ovestin cream (estriol 0.1%): nightly × 3/52, twice weekly thereafter
2. Vagifem vaginal tablets (estradiol 10 μg); nightly for 2 weeks, twice weekly thereafter
3. Gynest cream (estriol 0.01%); nightly until improvement, twice weekly thereafter
4. Estring vaginal ring (estradiol 7.5 μg/24 hours); inserted into upper third of vagina, replace after 3/12 months; maximum continuous treatment 2 years

hormone-responsive cancers, so they should be used with discretion. Use of local estrogen in women on tamoxifen or aromatase inhibitors needs careful counselling and discussion with the patient and the oncology team (38).

The commonly used forms of vaginal estrogen used at King's College Hospital are detailed in Table 24.1.

CONCLUSION

IAD is a common condition that affects individuals in all areas of health care. It affects the physical, psychological, and social health of many individuals and is challenging for health care professionals to accurately identify and effectively treat. Appropriate risk assessment, early and effective identification, and the right treatment and management plan will improve the quality of life of many patients. A structured skin care regimen that focuses on effective cleansing, protection, and reduction in excess moisture must be routine in all patients who are at high risk of IAD. Education of staff and the use of appropriate risk assessment tools will improve the identification of this condition and ensure appropriate, effective, and timely management plans are adopted, thereby improving clinical outcomes and, more importantly, patients' quality of life.

Hormonal therapy remains the most effective therapy for urogenital atrophy. Consideration of hormonal therapy should be part of an overall strategy including lifestyle recommendations regarding diet, exercise, smoking cessation, and safe levels of alcohol consumption for maintaining the health of peri- and post-menopausal women. All local estrogen preparations (creams, pessaries, tablets, and vaginal rings) are effective at decreasing the signs and symptoms of vaginal atrophy. Vaginal moisturizers and lubricants as well as regular sexual activity may be helpful to such women wishing to avoid the use of hormonal therapy. The use of SERMs is another option in those women with atrophy-related symptoms who are unwilling or unable to take vaginal estrogen therapy, however a detailed discussion should be had with individual patients on the risks versus benefits before making final decisions on management.

Ultimately, all treatment options should be made after careful counselling of the potential risks and benefits with the patient, so as to individualize management strategies.

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Fecal incontinence

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INTRODUCTION

Fecal incontinence is a physical and social disability that can profoundly impact a person's quality of life. Unfortunately, the degree of its widespread impact is unknown. It is thought that the true incidence is vastly under-reported. Early reports cite rates of 2% of all comers in the USA, but more recent studies cite rates of ~11%–15.2% in patients over 65 years and up to ~20%–46% in institutionalized patients (1,2). Fecal incontinence is broadly defined as the involuntary loss of rectal contents (solid or liquid stool as well as flatus) through the anus. Though there are potential health consequences of fecal incontinence such as urinary tract infections and decubitus ulcers, the most costly consequence is the effect it has on quality of life. Many patients suffer significant shame and dramatically alter their lifestyles due to fear of inadvertent fecal soilage. A large study of over 5000 women demonstrated that, among women who suffer from fecal incontinence, 40% suffer severe symptoms impacting their quality of life, and less than a third of these women seek medical care for their bowel leakage (3,4). In this chapter, we will explore the etiology, anatomy, work-up, and treatment options of patients who suffer from fecal incontinence.

ETIOLOGY

Continence is a complex mechanism that involves over five distinct muscles that have complex innervation, each of which require conscious thought along with involuntary reflexes. Given this complexity, there are many ways in which malfunction can occur. These can be simplified into five categories: trauma, iatrogenic, neurogenic, congenital, and anorectal disease.

Obstetric trauma is thought to be the most common cause of fecal incontinence. Specific obstetric procedures that are more likely to cause incontinence include vaginal deliveries with episiotomies or perineal tears and vaginal deliveries with forceps. Tears of the external sphincter occur in up to 9% of vaginal deliveries, though most are clinically silent, and pudendal nerve damage is most common after prolonged labors (5). Common iatrogenic causes include anorectal surgery and radiation for gynecologic and rectal cancers. Neurogenic causes are made up primarily of spinal cord lesions, diabetes, and multiple sclerosis. Congenital causes include imperforate anus and spina bifida. Finally, anorectal diseases including hemorrhoids, rectal prolapse, malignancy, and inflammatory bowel disease, as well as the surgery to treat these diseases, are major contributors to the burden of fecal incontinence.

ANATOMY AND PHYSIOLOGY OF DEFECATION

The main anatomic structures involved in defecation include the internal and external anal sphincters, the levator ani muscle, the rectum, and the rectal folds. The internal anal sphincter is a smooth muscle continuation of the circular smooth muscle of the rectum and is innervated by the sympathetic and parasympathetic nervous system. The internal anal sphincter is tonically contracted and accounts for >80% of the resting pressure of the internal anal canal (6).

The external sphincter is a striated muscle that is innervated by the pudendal nerve and assists with voluntary control of continence. When contracted, the anal pressure doubles in intensity, but fatigues within a few minutes. There is a spinal reflex that allows the external sphincter to contract when a Valsalva occurs with coughing or sneezing in order to prevent incontinence (7).

The levator ani muscles are thought of as the pelvic diaphragm and consist of three individual muscles: the puborectalis, the iliococcygeal, and the pubococcygeal. Combined, the pelvic diaphragm encompasses a thin and broad muscle that attaches to the posterior pubic rami bilaterally and to the inner surface of the ischium posteriorly. The levator ani serves to support the pelvic viscera. The puborectalis is controlled by the somatic nervous system and serves as a major contributor to the anatomic angle that creates a barrier when at rest, and when contracted straightens out the rectum, allowing defecation. It attaches to the posterior pubic rami, then wraps posteriorly around the rectum and reinserts on the pubic rami, creating a sling (8).

The physiology of defecation involves a complex interaction of voluntary and involuntary mechanisms to control fecal continence (9). Stool entering the rectum causes rectal distention, which initiates a relaxation reflex of the internal anal sphincter. If defecation is desired, the anorectal angle is straightened by squatting, and then the external anal sphincter is inhibited, the rectum contracts, the pelvic floor relaxes, and stool is evacuated. Please refer to Table 25.1 for an overview of the essential physiologic functions for maintaining continence.

Evaluation

The cause of incontinence can often only be identified with a thorough history. The specifics of the onset, frequency, duration, consistency, and precipitating events are critical to identifying the cause and developing a treatment plan. Details including whether a patient feels the bowel movement coming and is unable to stop it or they are just completely surprised by soilage of undergarments can help differentiate whether it is a defect with rectal sensation or their ability to voluntarily control their continence.

In women, specific components of their childbirth history are also important, such as the number of vaginal births, history of episiotomies or perineal tears during birth, prolonged labors, the use of forceps, and the presence of post-delivery transient incontinence.

Table 25.1 Essential Mechanisms Needed to Maintain Continence

Rectal sensation	Intact rectal sensation of a stool burden allows the puborectalis and external sphincter to contract in order to prevent inadvertent soilage and allows rectal compliance to reduce pressures within the rectum
Resting tone	An intact anal sphincter with adequate perineal bulk is needed to provide resting tone in order to prevent seepage of stool
Voluntary tone	Maintains anorectal angle and anal closure during internal anal sphincter relaxation
Rectal accommodation	When rectal filling is occurring, it allows the rectum to become more compliant and decreases intrarectal pressures

In all patients, ascertain any previous history of anorectal disease to include hemorrhoids, anal fissures, rectal prolapse, and any related procedures for these issues. Patients with prior pelvic surgery or irradiation can be at risk, so it is important to obtain details of these prior procedures. Finally, neurologic trauma and neurologic disorders are frequent contributors to incontinence; it is critical to determine whether the onset coincided with back or leg pain.

The Cleveland Clinic Incontinence Score (i.e., Wexner score) is the most widely used and validated score that takes into account both objective and quality of life metrics. This questionnaire can be filled out in minutes and can give the practitioner an estimated severity of disease, which can then be used to determine which treatment options would be most appropriate. The scores range from 0 to 20, where 20 indicates complete incontinence with severe lifestyle restrictions. See Table 25.2 (10) for an example of the Cleveland Clinic Incontinence Score sheet.

Physical Examination

Although a complete history and physical examination is imperative for any patient, we will focus our discussion of the physical examination on the rectal examination for this chapter. While positioning the patient, it is important to note if the patient is wearing diapers or a pad. In addition, subtle clues may highlight the degree of leakage, such as looking for any external irritation or perianal fistulas. On rectal examination, assess for adequate sphincter tone at rest (internal sphincter) and when attempting to squeeze the sphincter (external sphincter). Additionally, it is imperative to evaluate for any masses. Asking a patient to bear down allows for gross evaluation of the function of the pelvic floor, largely controlled by the puborectalis. In women, it is important to feel the anterior external sphincter and perineal body, as this is the likely site of obstetric trauma.

The anal wink, also known as the anocutaneous reflex, is performed by gently stroking the skin surrounding the anus, which should cause the external sphincter to contract. This demonstrates an intact pudendal nerve reflex arc, which requires spinal roots S2–S4. An absence of this reflex suggests a neurologic etiology. Concomitant pathology such as rectal prolapse or large prolapsing hemorrhoids that may also need to be addressed should be documented. In some cases, patients who complain of fecal incontinence may simply have prolapsing tissue that leaves them with a permanently wet anus and drainage, yet they do not have true fecal incontinence.

Diagnostics

Although a thorough history and physical examination will often identify the source of incontinence, diagnostic tests are generally used as confirmation of an examination finding prior to performing a procedure on a patient. While endoscopy is not required for diagnostic reasons, it is the exception to the rule above and should be performed on all patients to rule out inflammatory or neoplastic conditions.

Evaluating the Sphincters

Endoanal ultrasound is considered the gold standard for identifying sphincter defects, as sensitivity for this test approaches 100% (Figure 25.1). When performing an endoanal ultrasound, you are evaluating sphincter continuity of both the internal and external sphincter, with particular attention to the anterior aspect of the sphincter. In particular, if the internal sphincter is less than 2 mm, it is considered abnormal or thinning. If there are any breaks in the concentric rings of the internal and external sphincters, it is an indication that they are disrupted. The perineal body can also be evaluated by placing a finger in the back wall of the vagina and measuring the distance across the muscle to the glove; if it is less 10 mm, it is likely abnormal. If the perineal body is greater than 12 mm in thickness, it is unlikely to be a source of the incontinence (11). A limitation of the endoanal ultrasound is that it relies on the expertise of the examiner to both perform and interpret the images, and often practitioners learn on the job without any formal training.

Magnetic resonance imaging (MRI) is also an excellent tool to evaluate the continuity of the sphincters and to evaluate the pelvic floor. It is more expensive and less widely available, and has more limitations then endoanal ultrasound. MRI has a higher sensitivity for diagnosing external sphincter defects, whereas endoanal ultrasound is superior at evaluating the internal sphincter (12). MRI can also be used to evaluate a dynamic defecography to gain an understanding of pelvic floor function and look for concomitant pelvic floor disorders that may need to be addressed (see below).

Table 25.2 The Cleveland Clinic Incontinence Score

	Never	Rarely (less than once a month)	Sometimes (less than once a week)	Usually (less than once a day)	Always (every day)
Solid stool leakage	0 points	1 point	2 points	3 points	4 points
Liquid stool leakage	0 points	1 point	2 points	3 points	4 points
Gas leakage	0 points	1 point	2 points	3 points	4 points
Pad use for stool	0 points	1 point	2 points	3 points	4 points
Lifestyle restriction	0 points	1 point	2 points	3 points	4 points

Source: Jorge JM, Wexner SD. *Dis Colon Rectum* 1993; 36(1): 77–97.

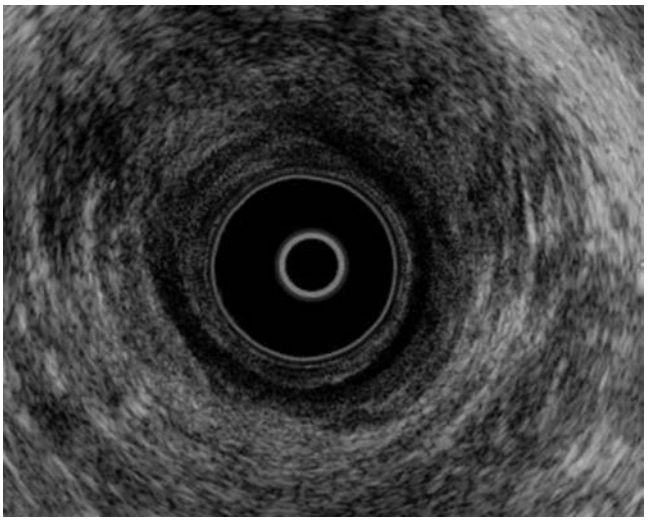

Figure 25.1 Endorectal ultrasound of a normal sphincter complex.

Functional Imaging

Defecography is generally reserved as a secondary diagnostic test if the initial studies are inconclusive. It is also user and interpreter dependent, and if not performed at a center that does such procedures routinely, can be misleading. Fluoroscopic defecography is most useful for identifying a rectocele, enterocele (if oral contrast is given), and intussusception/internal rectal prolapse. Contrast material is injected into the rectum, and the patient is then asked to sit and defecate under fluoroscopy. MRI defecography is now being used in some centers as it provides anatomic detail in addition to the functional images. MRI defecography can help identify whether the pelvic floor fails to relax during defecation—also known as anismus. It is important to note that if performed in a traditional MRI machine, the patient likely is defecating supine, which many criticize as not clinically relevant. Open MRI machines allow patients to be evaluated defecating in a sitting position, but costs and availability generally make these prohibitive (12).

Anal Manometry

Anal manometry provides numerical evidence of sphincter pressures and rectal sensation. Manometry measures resting and squeeze pressures and duration of squeeze. Despite the information that manometry can provide, it has not been shown to be clinically useful, as treatment largely depends on a patient's symptoms, and manometry is not predictive of which patients will benefit from procedures such as sphincteroplasty (13). Most manometry catheters have a balloon at the end that can be used to determine rectal sensation and compliance, but many patients with fecal incontinence will have reduced sensation, which results in impaired compliance and inability to hold a bowel movement. Manometry is not a test that should be routinely performed in patients with sphincter defects, but can be helpful in the subset of patients where the diagnosis is unclear (14).

Electromyography and Pudendal Motor Nerve Terminal Latency

The pudendal nerve provides sensation and motor signals to the anal canal and can be damaged in diseases such as diabetes and multiple sclerosis. For these reasons, this nerve has been a focus of electromyographic testing. The test evaluates the pudendal nerve terminal motor latency, which essentially elucidates how long it takes the pudendal nerve to transmit a signal that causes the external sphincter to contract (15). A glove with a fingertip provides a small electric stimulus to the pudendal nerve. This test is also user dependent and rarely influences clinical decision making; for these reasons, it is rarely used (16). However, when prolonged bilaterally, it is an additional metric that may provide some insight when counseling patients that outcomes may not be ideal with a sphincteroplasty.

Treatments

When considering various treatments for fecal incontinence, it is important to differentiate mild from severe incontinence and to determine whether or not there is an identified sphincter defect.

Patients with mild incontinence will likely improve with bulking agents, biofeedback, and possibly injectables. If a patient has severe fecal incontinence, then one has to ascertain whether it is an isolated sphincter-traumatic problem or a multifactorial or nervous system-related incontinence.

Stool Bulking/Dietary Modifications

Stool consistency is one of the most important and easy-to-modify factors influencing fecal continence. An empty rectum leads to continence; therefore, bulking stool to allow complete evacuation during defecation has been shown to be the most effective and least invasive way to prevent incontinence. Conversely, loose stools precipitate incontinence; therefore, avoiding fatty foods that are low in fiber can bulk stool and improve incontinence. A blinded randomized clinical trial has shown substantial improvement in fecal continence in 1 month with the addition of dietary fiber (17). A randomized controlled trial comparing psyllium and loperamide showed that they were both effective at reducing fecal incontinence, but loperamide had more complications, mainly constipation (18). For the majority of patients, stool bulking should be attempted before any invasive procedures, as it will likely provide some relief and can then allow for less invasive options to be attempted. In obese patients, along with a healthy diet, weight loss alone can improve continence (19).

Biofeedback

Biofeedback is a broad term that essentially refers to retraining an individual to gain awareness of physiologic functions such as defecation. Data are recorded using surface sensors or rectal balloons, and a patient can visualize the strength of contraction they are performing. It is primarily used in fecal incontinence to train an individual to improve their strength and endurance by giving them visual cues about how strongly they are contracting the pelvic floor and sphincters, which allows them to use this information to perform more efficacious exercises. Success rates for biofeedback therapy are in excess of 70% when evaluating for a substantial improvement in incontinence. This diminishes over time, but some advocates recommend refresher sessions scheduled periodically to maintain the initial benefit (20).

Biofeedback is also used to train an individual to recognize the sensation of rectal filling. A balloon is inserted into the rectum and it is gradually filled with fluid until they recognize the sensation; this is repeated with smaller amounts of

volume. With better rectal sensation, a patient can reach a restroom sooner before an accident. There are additional biofeedback therapies that attempt to improve coordination between the rectum and anal sphincters (21).

Overall, biofeedback is an effective treatment that should be tried in a majority of patients that suffer from mild to moderate incontinence, as a substantial cohort of patients will benefit from therapy and there are no risks involved with undergoing therapy. The main limitations involve obtaining access to centers with therapists that are skilled in this very specific rehabilitation modality and having insurance companies that will reimburse for biofeedback therapy (22).

Injectables

Though the mainstay of therapy for complex combined or external sphincter defects has been sphincteroplasty, it has been unsuccessful at significantly improving incontinence in patients with isolated internal sphincter defects. In this light, it is important to remember that the internal sphincter is what provides the constant resting tone. One potential option for these patients was adapted from urologists who have been using injections of biocompatible non-dissolving solutions to bulk dead space in order to improve urinary incontinence. These same injectables have been adapted for fecal incontinence. They are injected into the anal submucosa or the intersphincteric space to provide bulk and improve the resting tone, and thus improve overall continence. Currently, injectables are most appropriate for patients who have failed medical management and are not ready to undergo surgery. Other patients may include those with prior anorectal surgery (i.e., fistulotomy) and may have an anatomical "valley" in the canal where stool seepage occurs. The most commonly used substances currently are silicone, carbon-coated microbeads, and, most recently, dextranomer in hyaluronic acid gel (23).

The overall success of injectables is modest at best with improvement seen early on, though with diminished results over time. One of the few randomized controlled trials did show a significant improvement when using silicone as compared to carbon-coated microbeads (23). A 2013 Cochrane review found only one large, properly performed trial, from which the results supported dextranomer in hyaluronic acid gel that demonstrated 50% of patients had significant improvements in the short term, with no studies having significant long-term data (24).

Injectables are relatively new therapies that are minimally invasive and have shown some benefit in the short term for improving fecal incontinence with minimal side effects. Injectables should be considered in patients with mild to moderate incontinence, especially if their defect involves the internal sphincter. More studies will be needed in order to identify the best substance, injection strategy, and long-term benefits.

Sacral Nerve Modulation

Sacral nerve modulation is another method that was adopted from urologists when it was noticed that the patients they were treating for urinary incontinence were experiencing improvements in their fecal continence. A percutaneous wire electrode is placed through the sacral foramina, generally S3, so that it abuts the nerve root (Figure 25.2). The electrostimulation unit is similar to what is used in a heart defibrillator and is connected to the electrode, which causes contraction of the levator ani and external anal sphincter, and, when positioned appropriately, will cause the first two toes to curl. This is done in a staged

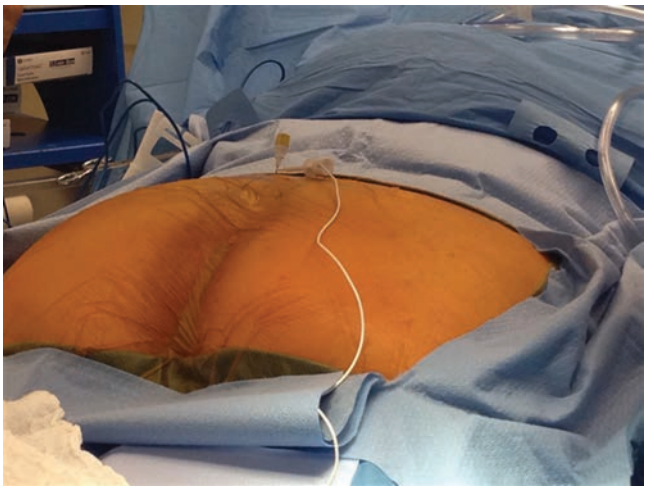

Figure 25.2 Sacral nerve modulation with the electrodes in place.

procedure: the first phase is placement of the electrodes in the foramina and connection to an external electrostimulation unit that is worn for 2 weeks. If after 2 weeks the patient has a 50% improvement in incontinence, then a permanent device is placed subcutaneously in a pocket made over the superior aspect of the buttocks.

The largest study to date included 120 patients and, after 12 and 24 months, 83% of patients had therapeutic success (defined as a 50% reduction in incontinence episodes), and 41% had 100% continence (25). Of patients who have had sacral nerve stimulators in for over 5 years, 89% have significant continued reductions in fecal incontinence compared to medical therapy, and 36% had complete responses that were still present after 5 years (26). Sacral nerve stimulators have been shown to be a great option in patients with fecal incontinence that can provide substantial relief with a minimally invasive procedure that precludes further interventions, should they be needed.

Radiofrequency Energy (Secca Procedure)

The Secca procedure is a procedure in which radiofrequency energy is applied to the internal anal sphincter in order to induce collagen deposition and fibrosis so as to cause tightening of the sphincter. This fits the same niche as injectable therapies for fecal incontinence, in that it is best for patients with mild to moderate incontinence who have failed medical management and are not yet ready to undergo a surgery (27). Small studies (19 patients) in patients with mild incontinence have shown benefits 5 years out in upwards of 80% of patients, with a 50% reduction in fecal incontinence episodes (27). This benefit appears to drop off considerably in patients with more severe incontinence, with long-term improvements seen in only 22% (28). In the properly selected patient with mild to moderate incontinence, radiofrequency ablation may be a reasonable next step after medical management, as it does not burn any bridges for future surgical options (29). However, data to strongly support its use are lacking.

Anterior Overlapping Sphincteroplasty

In a patient with fecal incontinence and a documented external sphincter defect, the primary surgical option is an anterior overlapping sphincteroplasty. The obstetric trauma population

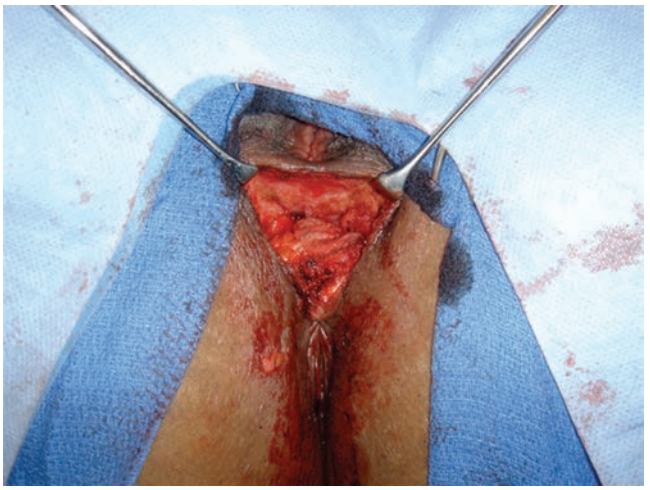

Figure 25.3 Overlapping sphincteroplasty with the two muscle/scar complexes dissected out.

does the best with this repair, as the anatomy of their injury is addressed by this procedure. The basics of the operation include a curvilinear incision over the anterior perineum and a lateral dissection of the external anal sphincter musculature, sparing the posterior–lateral aspect of the external sphincter, as this is where the nervous innervation enters the muscle. Once the external sphincter is dissected out, it is brought together in the anterior midline, where the two ends are overlapped and sutured together (Figure 25.3). This overlap helps recreate the perineal body, and a strong musculofibrous bridge is created in order to give resting tone to the anal canal (30).

Anterior sphincteroplasty in recent studies has shown a 50%–60% long-term >5-year success rate when defined as incontinent episodes having decreased by 50%, and when only considering patients that have complete resolution of fecal incontinence, the long-term success rate is approximately 40% (31). The patients that had the best results were younger females that had anterior defects from obstetric trauma.

Gracilis Muscle Transposition

If a patient is incontinent from a significant loss of tissue defect either from trauma, iatrogenesis, or a congenital anomaly, a muscle flap can be considered to wrap the anal sphincter with a native muscle in order to provide bulk and contractility. Initially, the gluteus maximus was the muscle of choice for recreating the external sphincter, but now the gracilis is mainly used as it is easy to mobilize, has an ideal neurovascular bundle location, and does not affect posture or leg strength. Graciloplasty can be performed with or without stimulation. When stimulated, an electrode is placed within the muscle, similar to a sacral nerve stimulator, and the electrostimulation unit is placed in a subcutaneous pocket on the abdomen. Patients also undergo biofeedback therapy in order to train them in how to contract their neosphincter maximally. Recent small studies (31 patients) showed a success rate as high as 70% with an improvement in the Cleveland Clinic fecal incontinence score from 19 to 5 when evaluated after 5 years (32).

Muscle transposition is a highly technical surgery that requires a high volume of patients in order to achieve adequate results and reduce complications. Given the high complication rate and the limited amount of providers who can perform this procedure, it is generally reserved for patients who have large sphincter defects in which no other therapy is suitable.

Artificial Anal Sphincter

Artificial anal sphincter is another potential option in the patient with severe fecal incontinence that has not responded to less invasive therapies and have evidence that a sphincter defect is the underlying reason for their incontinence. An incision is made in the perineum and a tunnel is created around the rectum, into which a fluid-filled cuff is placed around the anal canal. A pressure-regulated reservoir balloon is placed in the prevesical space and a manual pump is placed in either the labia or scrotum. If implanted properly, artificial anal sphincters have been shown to be successful at creating normal resting anal tone, and two-thirds of patients have normal fecal continence (33). Unfortunately, artificial anal sphincters have an exceedingly high complication rate from infection, erosion, and device failure, with revision and explantation rates of over 50% in multiple studies (34,35). Currently, artificial sphincters are an option, and the concept appears to be valid for improving continence, but the complication rate is prohibitive to most centers widely adopting this practice. In addition, at any given time, these devices have been withdrawn from the market and so become unavailable. It will likely require a new technology or adaptation of the current device that reduces the complication rate before these are routinely used for severe fecal incontinence.

Diversion

When other therapies have failed and patients have significant distress from their fecal incontinence, fecal diversion can be performed. It is sometimes helpful to describe to patients that they are essentially living with a perineal ostomy, and creating an abdominal ostomy would allow significant improvements in hygiene and maintenance. An end ileostomy or end sigmoidostomy can be performed. A colonic transit test should be performed prior to ostomy placement in order to ensure that there is adequate motility of the colon, and if there is decreased colonic transit, an ileostomy is likely the best option for the patient. Of patients living with fecal incontinence who had a colostomy performed, 84% would "probably" or "definitely" choose to undergo the colostomy again. The median score for satisfaction with the colostomy was 9 out of 10 (36). A colostomy should remain a last resort, but it can provide significant relief from fecal incontinence in patients that have exhausted other options.

CONCLUSION

Fecal incontinence is a vastly under-reported, yet common disease that can have dramatic effects on the quality of life of patients. There are numerous treatment options, many of which are dietary or minimally invasive, to help reduce this burden. As providers, it is our responsibility to initiate this conversation, as it has been shown that most patients will not do so, and to provide them with access to treatments that can allow them to live life to the fullest.

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The menstrual cycle and the skin

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INTRODUCTION

The menstruation of a sexually mature woman is a sign of a cyclic hormonal stimulation of the endometrium. It is well documented that the menstrual cycle influences many systemic disorders, such as asthma, porphyria, epilepsy, migraine, myasthenia gravis, and allergic rhinitis (1). Estrogen and progesterone, the two female sex hormones, can also lead to cycle-dependent variations in the activity of many skin disorders. Although detailed data on the cycle-associated, hormonally mediated changes in the target organs, such as the uterus, vagina, cervix, and mammary glands, are available, less is known about the effects of the menstrual cycle on the skin (2). It is the goal of this chapter to provide an overview of the most important skin disorders with cycle-dependent variations.

HORMONAL CHANGES IN THE COURSE OF THE MENSTRUAL CYCLE

The menstrual cycle is controlled by two ovarian hormones. Under the stimulating and determinant influence of the gonadotrophins follicle-stimulating hormone (FSH) and luteinizing hormone (LH), cyclic morphological changes take place in the ovaries of the sexually mature woman. At the beginning of the cycle, after completion of menstruation, the buildup of the endometrium and the synthesis of the endometrial progesterone and estrogen receptors are triggered as a result of an increasing secretion of estradiol. The ovarian estrogen synthesis takes place via the intermediate products androstenedione and testosterone, which are subsequently aromatized to estrone and estradiol (3).

The processes are stimulated by LH in synergy with FSH, which is presumably responsible for the development of a large number of primary follicles in the early follicular phase. Via negative feedback, estrogen production—which increases in the preovulatory phase and reaches the first peak at the time of ovulation—causes FSH to decrease, which leads to a regression of most of the stimulated follicles. Only a dominant follicle becomes independent of the stimulation by pituitary FSH and reaches ovulation maturity. The ovulation in the middle of the cycle is associated with a peak in LH production and a peak in FSH production, although the latter is less pronounced. The LH peak lasts approximately 36 hours and is controlled by the pulsatile release of gonadotrophin-releasing hormone (GnRH) from the hypothalamus. After ovulation, the corpus luteum develops, accompanied by an increased secretion of gestagen, which is responsible for the increase in the thickness of the endometrium and which, via negative feedback, inhibits the release of FSH from the pituitary gland and thus the further maturation of the follicles in the corpus luteum phase. As the luteal phase progresses, estradiol reaches the second peak. The new premenstrual increase in FSH, which is the result of a decrease in progesterone formation in the corpus luteum, causes the stimulation of a new generation of follicles in the ovaries. The secretory phase is controlled jointly by estradiol and progesterone. The endometrial breakdown that causes menstrual bleeding is caused by decreases in the levels of these two sex hormones. Cyclic hormonal changes, however, have an influence not only on the endometrium, but also on the vaginal epithelium and the skin (2,3). Figure 26.1 shows the patterns of the pituitary hormones LH/FSH and the two sex hormones estradiol/progesterone during a normal menstrual cycle.

INFLUENCE OF THE SEX HORMONES ON THE SKIN

The skin contains receptors for estrogen and progesterone and is as highly sensitive to the effects of these two steroid sex hormones as it is to androgens (4–6).

Estrogens

At a high concentration, estrogens suppress sebum production, but have only an insignificant or no influence on the apocrine glands (7). The sebum content of the skin is related to the menstrual cycle, with the lowest sebum level following the peak of the estrogen level (8). Estrogens improve the water-binding capacity of the stratum corneum and, through an increase in acid mucopolysaccharides and hyaluronic acid, of the dermis as well (9). There is a significant increase in the thickness of the skin, with the increase in the estradiol level in the middle and at the end of the menstrual cycle, which can be explained by an increased fluid retention under the influence of estradiol (3,10,11).

By increasing the transformation of soluble collagen into the cross-linked insoluble form, estrogens slow the breakdown of dermal collagen. Eighty percent of the collagen of the skin is made up of type I collagen and 15% of type III collagen, with type I collagen being principally responsible for the skin's thickness and type III collagen for its elasticity. A deficiency of estrogen leads to a decrease of type I and III collagens, which leads to a shift of the type I:type III ratio in the direction of type III collagen, and to a corresponding decrease in skin thickness (3,7,9,12).

Estrogens stimulate epidermal melanogenesis, which can lead to a transient hyperpigmentation that generally appears in the premenstrual phase, especially around the eyes and nipples (3,4,7,12–14). The anti-inflammatory effect of estrogens alone seems to be more pronounced than when combined with the effect of progesterone, which is the case in the premenstrual phase and is attributable to the antiestrogenic effect

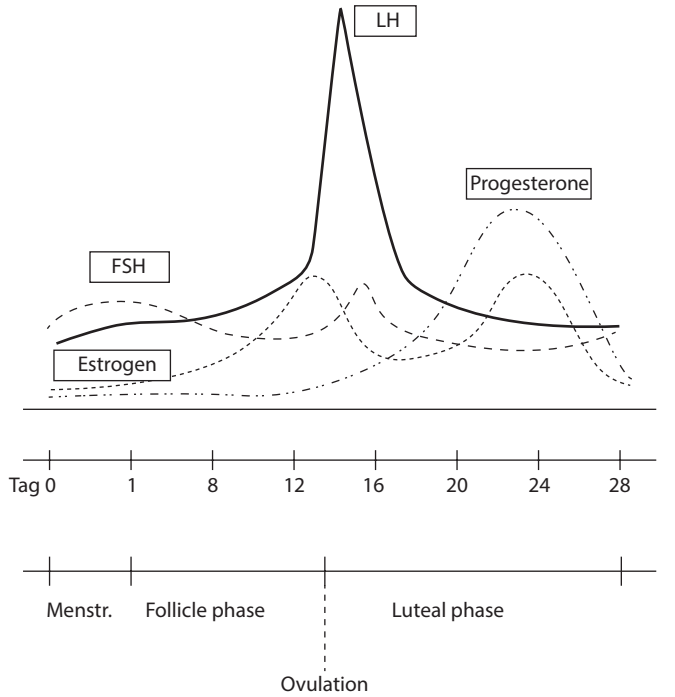

Figure 26.1 Serum levels of pituitary and sexual steroid hormones during a normal menstrual cycle. FSH: follicle-stimulating hormone; LH: luteinizing hormone. (Modified from Stephens CJ. *Clin Dermatol* 1997; 15: 31–4.)

of progesterone (2,7). Estrogens suppress the cellular immune response, which may be due to an influence on regulatory T cells. Furthermore, estrogens inhibit the activity of natural killer cells and neutrophilic granulocytes and have a regulatory influence on the interferon-γ promoter. Together with the previously mentioned effects on the skin barrier, this immunological effect of estrogen gives rise to cyclic changes in the activity of the skin (15,16). The general effects of estrogen on the skin are:

- Decreased sebum
- Increased water-binding capacity (stratum corneum and dermis)
- Increased skin thickness
- Increased fluid retention
- Decreased collagen breakdown
- Increased epidermal hyperpigmentation
- Decreased cellular immune response
- Increased vasodilation (in combination with gestagen)

Progesterone

The influence of progesterone on the skin is less understood. Research has demonstrated an immunosuppressive effect of progesterone that is potentially caused by the inhibition of monocytic functions (16). As progesterone is the dominating circulating hormone in the premenstrual phase, it is hypothesized that the premenstrual exacerbation of many skin disorders is caused by the influence of this hormone.

The blood supply to the skin increases in the second phase of the menstrual cycle. Harvell et al. (17), demonstrated that the basal blood flow at the time of maximum progesterone secretion was significantly higher than on the day of maximum estrogen secretion. In another study, researchers observed a gradual dilation of the venous lumen, which reached its maximum diameter approximately 1 week prior to the onset of menstrual bleeding. This phenomenon may also be responsible for the subjective symptoms of chronic venous insufficiency in patients with varicose veins, in whom symptoms often increase in the second half of the cycle (18). In the premenstrual phase, not only does progesterone reach its highest level, but a high estrogen concentration is present as well; the combined effect of both hormones may be causally responsible for dilation of the vessels (18).

More recent studies demonstrate that the combination of high estrogen and gestagen levels, such as is seen in the middle of the luteal phase, influences the vasodilatory system of the skin. Independently of the sympathetic innervation, local warming of the skin leads to vasodilation, which is presumably mediated by the formation of nitric oxide. This vasodilatory response to local thermal stimuli is intensified by high estrogen and gestagen levels. There seems to be no apparent effect of the active, adrenergically controlled vasoconstriction following cold application (19).

PREMENSTRUAL SYNDROME

Premenstrual syndrome (PMS) is accompanied by cutaneous manifestations that emerge in the premenstrual phase of the menstrual cycle. Accordingly, approximately 70% of women report that prior to the onset of menstrual bleeding, they suffer from mild acne eruptions, often in association with an increased greasiness of the skin and hair; a premenstrual exacerbation of perioral dermatitis is also reported frequently, especially by young women (7). Additional clinical symptoms of PMS include:

- Migraine and other forms of headache
- Tiredness and lethargy
- Depression
- Irritability and nervousness
- Feeling of tenseness in and swelling of the breasts
- Abdominal pain and feeling of fullness
- Increased thirst, appetite, and weight gain
- Constipation and flatulence
- Hot flush symptoms
- Acneiform cutaneous efflorescences and perioral dermatitis
- Oily skin and hair
- Hyperpigmentation of the skin

To date, the definite endocrinologic mechanism responsible for PMS has not been found. Given the temporal association of the symptoms with the luteal phase of the menstrual cycle, it is possible that progesterone plays an important role. Various hypotheses have been offered to explain the pathogenesis, such as an individual progesterone deficiency, an imbalance between the estrogen and progesterone levels, and even an allergy to progesterone (7,20). One confirmed fact is that the β-endorphin level in the premenstrual phase is decreased in patients with PMS (2). Research has confirmed the thesis of an immunological mechanism of PMS by the finding of a positive intracutaneous test reaction to female sex hormones in women with PMS and

associated cutaneous manifestations (21). A hypersensitization treatment led to a significant reduction of the PMS symptoms, as well as to an improvement of the cutaneous manifestations. A connection with autoimmune progesterone and autoimmune estrogen dermatitis seems possible (3,22).

MENSTRUAL CYCLE AND ASSOCIATED SKIN DISORDERS

Chloasma and Hyperpigmentation

The stimulation of epidermal melanogenesis by means of hormones has long been known. During pregnancy, for example, hormonal influences can cause an increased pigmentation in the face (chloasma), the areolae, the linea alba, and the perineal skin. After administration of estrogen-containing oral contraceptives, facial hyperpigmentation was observed in 8%–29% of women. The application of estrogen-containing ointments to children can also lead to hyperpigmentations in the genital area and in the areas of the nipples and the linea alba (4). One study found that of 62% of the women tested, hormonal influences in the premenstrual phase led to increased pigmentation, particularly in the periorbital region (12).

Acne Vulgaris and Rosacea

A high percentage of women with acne vulgaris experience a premenstrual exacerbation. The figures in the literature vary between 27% and 70% (23,24). A study of 400 acne patients found a premenstrual exacerbation in 44% of the cases. Women older than 33 years of age appear to be affected more frequently than younger women between 20 and 33 years of age (25). A comparison of acne lesions in the late follicular phase and the luteal phase found that in the premenstrual phase, 63% of the women studied had an increase of inflammatory acne efflorescences, on average by 25%. In 54% of the women studied, the comedo rate increased by an average of 21% (26).

The definite mechanism of premenstrual exacerbations of acne vulgaris is not known. It is possible that premenstrual skin edema causes a narrowing of the lumen of the ducts of the sebaceous glands, which leads to sebum accumulation and/or to variations in sebum secretion (8,23). Treatment with oral contraceptives with an antiandrogenic component has proved successful, although increased androgen levels in women with acne were found in only some of the relevant studies (25).

Patients with rosacea can also experience premenstrual exacerbation (7). It is possible that the previously mentioned changes in sebum secretion and/or an increased blood supply to the skin in the luteal phase play pathogenetic roles.

Psoriasis

It has long been known that psoriasis can be influenced by hormones. During pregnancy, the cutaneous manifestations frequently improve, but 15% of the cases can experience an exacerbation. After giving birth, more women report an exacerbation rather than an improvement of the cutaneous manifestations (27). In particular, generalized pustular psoriasis can be provoked by pregnancy or by the premenstrual phase (28). Researchers found that it is possible to trigger episodes of general pustular psoriasis through the experimental administration of progesterone and indirectly by the induction of ovulation by means of clomiphene (28,29). Thus, progesterone appears to play an important role pathogenetically, although the exact pathomechanism remains unknown.

Atopic Dermatitis

An exacerbation of the cutaneous symptoms of atopic dermatitis frequently takes place as a function of the menstrual cycle, although data on the cycle-associated exacerbation of atopic dermatitis vary widely (9%–100%) (30,31). Some authors report an exacerbation of the skin condition during menstruation, whereas others report that the skin condition deteriorated approximately 1 week prior to the onset of menstrual bleeding (30,31). A study involving 286 Japanese women with atopic dermatitis found that 47% reported a monthly exacerbation of the cutaneous symptoms that were observed in 96% of the patients in the premenstrual phase (31). Only 4% reported a deterioration of the skin during menstruation. Interestingly, in all of the patients affected, a premenstrual deterioration of atopic dermatitis occurred, along with other symptoms of PMS (20), such as headaches, sensation of tension in the breasts, abdominal pain, edema of the legs, or psychological symptoms, such as irritability or depression. Another study also reported a significant correlation between a premenstrual exacerbation of atopic dermatitis and PMS and, again, the mechanism was unclear (30). Skin reactivity to antigens and irritating substances increases during the premenstrual phase (32,33); it is possible that the immunological influence of estrogen and progesterone mentioned previously plays a role in the pathogenesis of this disorder.

Aphthous Ulcerations and Herpes Simplex Labialis

In some women, the occurrence of relapsing aphthae of the oral mucous membrane is associated closely with the drop of progesterone in the luteal phase of the menstrual cycle. In these cases, a hormonal treatment with progesterone in order to suppress ovulation can be successful. The exact hormonal or immunological mechanism, however, again remains unknown (34).

Many women report a monthly eruption of herpes simplex infections, although relapses are not always strictly cycle dependent. Frequently, herpes simplex labialis can erupt both prior to or during menstruation (35), but there are also reports of eruptions in the preovulatory phase (36). Possibly, decreased interleukin (IL)-2 levels, as well as increases in tumor necrosis factor-α and IL-6, play a pathogenetic role (37).

Keratosis Follicularis (Darier's Disease)

The intensity of keratosis follicularis can vary in association with hormonal status. One study involving eight women found that the disease presented most often at the beginning of puberty and continued for years without interruptions. Invariably, the cutaneous manifestations worsened during menstruation. In three patients, treatment with estrogen-containing oral contraceptives led to a marked improvement in skin condition. Thus, it appears that higher estrogen levels improve the symptoms of keratosis follicularis (38).

Cyclic Vulvovaginitis, *Candida* Vaginitis, and Pruritus Vulvae

Cyclic vulvovaginitis is marked by pain during certain cycle phases (luteal phase and perimenstrual phase), although the local findings are in most cases non-pathologic. In the final analysis, the genesis is again unclear, although the hypothesis of a hypersensitive reaction to *Candida albicans* is advanced frequently (39).

There have long been indications that the incidence of *Candida* vaginitis is hormone dependent (2,40). Thus, a *Candida* infection is observed more frequently in pregnant women than in non-pregnant women. The use of ovulation inhibitors, in particular those with a high estrogen content, also increases the risk of an infection. In postmenopausal women who do not use estrogen-replacement therapy, the incidence is low. Relapses of a *Candida* infection with pruritus vulvae occur frequently in the luteal phase prior to the onset of menstruation. Kalo-Klein and Witkin demonstrated an inhibition of the cellular immune response to *C. albicans* during this phase, which they attributed to variations in the progesterone and estradiol levels (40). However, even independent of the menstrual cycle, patients with relapsing *Candida* vaginitis were shown to have a reduced *Candida*-specific T-cell reaction. *In vitro*, both a reduced T-cell proliferation and a reduced interferon-γ secretion were demonstrated after stimulation with *Candida* antigen (16). The immunological effects of progesterone and estrogen discussed previously influence the cycle-dependent occurrence of *Candida* vaginitis. In addition, the presence of an estrogen-binding protein on *C. albicans* was demonstrated. It is via this estrogen binding protein that the transformation of *C. albicans* into the invasive hyphal form is directly stimulated (16).

Lupus Erythematosus

A premenstrual exacerbation of the cutaneous manifestations of lupus erythematosus (LE) was described in 25% of patients with systemic LE (41) and in 13%–16% of patients with discoid LE (41,42). There are several indications that estrogen is an important cofactor for the development or exacerbation of LE. This is corroborated by the facts that the disorder affects females predominantly and that it is well known that estrogen-containing oral contraceptives may cause an exacerbation, as well as by the described association of LE with Klinefelter syndrome. In an *in vitro* study, the administration of estrogen was shown to lead to an upregulation of the binding capacity of antiRo/SSA antibodies (antinuclear autoantibodies that are associated with autoimmune diseases like LE) to keratinocytes (41).

It is hypothesized that in patients with LE, a changed estrogen metabolism with increased estrogen and decreased androgen levels acts as an etiopathogenetic cofactor. In conjunction with these suggestions, the physiologically increased premenstrual estrogen levels would lead to a perimenstrual exacerbation of LE (41).

Porphyria Cutanea Tarda

Porphyria cutanea tarda (PCT) is a defect of uroporphyrinogen decarboxylase that can be acquired or inherited through autosomal dominant transmission. This disorder becomes active only after additional liver-specific precipitating factors, such as alcohol, drugs, or viral infections (hepatitis or HIV) are present. Among the precipitating factors of hepatic porphyria, estrogens also play an important role; estrogen-containing contraceptives have been implicated in the manifestation of PCT in young women. It is known that all of these factors either inhibit uroporphyrinogen decarboxylase or lead to liver damage as a result of direct or indirect deposition of iron in the liver. Perimenstrual improvement of PCT has been explained by menstrual bleeding, which, similar to therapeutic bloodletting, leads to a reduction of iron (43).

Herpes Gestationis

Herpes gestationis (HG) is a rare, pruriginous, blister-forming disorder that occurs, in most cases, in the second or third trimester of pregnancy (44). It can also occur in association with a cystic mole or a chorionic carcinoma (44). Both in pregnancy and in the presence of trophoblastic tumors, the immune system is confronted with foreign antigens of the sex partner, which may potentially play an important role in the pathogenesis of HG. In addition to a certain constellation of human leukocyte antigens in the mother and father, hormonal effects also have an important pathogenetic influence. For example, administering oral contraceptives with a high estrogen level in order to treat trophoblastic tumors can exacerbate HG. Furthermore, the ovulation phase of the cycle may cause an exacerbation of HG, possibly because of estrogen's immunostimulating effects at certain concentrations (44). In most patients, however, an exacerbation of HG occurs more frequently in the premenstrual phase, possibly because of the steep decline of the high progesterone level prior to the onset of menstrual bleeding. The clinical activity of HG during pregnancy is also dependent on hormonal changes. In the last weeks of pregnancy, for example, when the progesterone level is high, there is a relative remission of the cutaneous manifestations, which are exacerbated immediately after delivery, when the progesterone level decreases markedly (44).

Dermatitis Herpetiformis

Although a report describing a premenstrual exacerbation of dermatitis herpetiformis was published in 1906 (45), the medical literature contains few reports that refer to the influence of the menstrual cycle on the activity of this disease. Clinically, it is difficult to distinguish the perimenstrual exacerbation of dermatitis herpetiformis from an autoimmune progesterone dermatitis (APD). The diagnosis must be based on histopathology, direct immunofluorescence, and a lack of evidence for an autosensitization to progesterone (46).

Autoimmune Progesterone Dermatitis

APD is a rare skin disorder that is marked by relapsing cyclic eruptions during the luteal phase of the menstrual cycle when the serum progesterone level increases (13,47). Pathogenetically, an autoallergic reaction to endogenous progesterone is involved in APD, which can be demonstrated by a positive intracutaneous test reaction to progesterone. An allergic genesis of the skin disorder is also corroborated by a positive basophilic degranulation test following provocation with progesterone (48). Cutaneous manifestations can also be provoked by the intramuscular or oral administration of progesterone. Indirect immunofluorescence can detect progesterone antibodies in the serum of some women affected with APD. Ovulation-inhibiting drugs can suppress the clinical symptoms of APD (47).

There are several hypotheses concerning the mechanism of autosensitization. One is based on the assumption that the previous use of exogenous progesterone leads to the formation of antibodies, which, as a result of cross-reactivity with endogenous progesterone, subsequently leads to premenstrual cutaneous manifestations (7,49). However, not all women with APD have taken synthetic progesterone preparations previously. Alternatively, a cross-reactivity to steroids has been proposed as the mechanism of sensitization (7). The clinical morphological picture of APD is extremely variable (Figures 26.2 and 26.3).

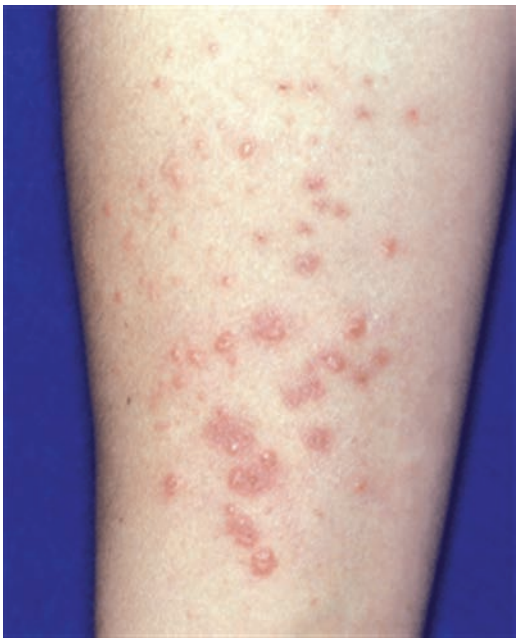

Figure 26.2 Autoimmune progesterone dermatitis, eczema type.

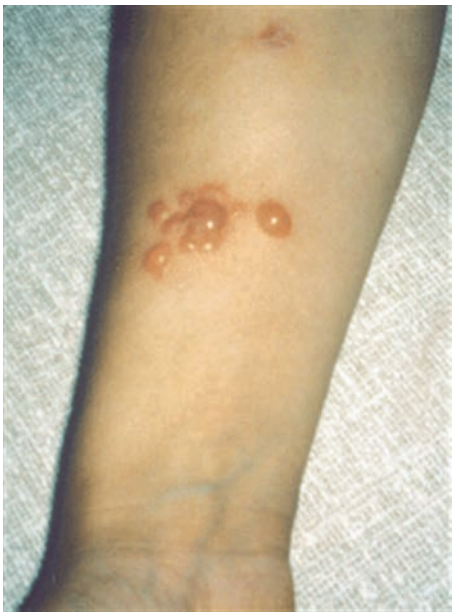

Figure 26.3 Autoimmune progesterone dermatitis, pompholyx type.

The cutaneous manifestations of APD include:

- Eczema (49)
- Erythema multiforme (49,50)
- Urticaria (49,51,52)
- Angioedema and anaphylaxis (1)
- Pompholyx (49)
- Stomatitis (53)
- Dermatitis herpetiformis (46)
- Erythema annulare centrifugum (54)
- Prurigo simplex subacuta (48)
- Nonspecific maculopapulous exanthemas (47)

However, the cutaneous manifestations differ neither morphologically nor histologically from the cycle-independent variants. One characteristic feature, however, is that they occur in the premenstrual phase. As a rule, the different manifestations of APD do not respond to conventional therapeutic regimens of the individual disorders. Treatment options include the use of conjugated estrogen-containing preparations, the ovulation-inhibiting antiestrogen tamoxifen, the androgen danazole (7,47), or—in severe cases—an elimination of the ovaries by bilateral oophorectomy or by administering buserelin, an analogue of GnRH (7,55).

Autoimmune Estrogen Dermatitis

Estrogen sensitivity also can imitate the clinical picture of APD. Clinical manifestations include papulovesicular exanthemas, eczemas, urticaria, and localized or generalized pruritus. The face, upper arms, and trunk are the regions affected principally, which may be attributable to an increased density of estrogen receptors in these regions. This disorder is considerably rarer than APD but, like APD, it is marked by a cyclic occurrence prior to menstruation (56). Murano and Koyano (57) described a patient in whom an exacerbation of the cutaneous manifestations occurred twice within the course of each menstrual cycle (i.e., premenstrually and at the time of ovulation). This can be explained by the two-peak course in the estrogen curve within the menstrual cycle. The diagnosis of autoimmune estrogen dermatitis can be corroborated by a positive intracutaneous test for estrogen; progesterone provocation will be negative. Treatment options include antihistamines, corticosteroids, tamoxifen, progesterone, and a surgical or drug-induced elimination of ovarian function (56).

Hereditary Angioedema and Urticaria

Hereditary angioedema results from an inherited autosomal dominant deficiency or a functional defect of the C1 esterase inhibitor. A study to examine the influence of the steroid sex hormones found a positive correlation between the frequency of angioneurotic edema episodes and the serum progesterone level, with an increase in the incidence during the luteal phase of the menstrual cycle.

The mechanism by which progesterone influences angioedema is largely unknown. It has been hypothesized that progesterone influences the equilibrium between the coagulation and the complement cascade and thus enables the cleavage of the C1 esterase inhibitor by proteases. An inhibition of the synthesis of the C1 esterase inhibitor in the liver has also been discussed (58).

Wilkinson et al. described a patient with relapsing urticaria in the premenstrual phase (59). In spite of the possibility of provoking such cutaneous manifestations by systemic progesterone or estrogen administration, it was not possible to demonstrate an immunological reaction to progesterone or estrogen either in the epicutaneous test or in the intracutaneous test. Therefore, it appears more likely that metabolic rather than direct autoimmunological mechanisms are responsible

for triggering urticaria in the premenstrual phase. In predisposed women, independent of an autoimmunological reaction, progesterone-induced urticaria can be provoked by hormonally triggered changes in the immune system. There are indications that, as a result of a metabolic effect, increased progesterone levels in the premenstrual phase of the menstrual cycle can lead to an intensification of type I and IV hypersensitivity reactions (59).

Contact Dermatitis and Skin Reactivity

Contact dermatitis can be exacerbated in the premenstrual phase. Alexander described a patient whose patch test of a fragrance mixture led to positive results only in the premenstrual phase, but was negative 1 week after menstrual bleeding (33). This can be explained by the suppression of the cellular immune response by estrogens mentioned previously (15). Considering the increased skin reactivity to contact allergens during the premenstrual phase, in special cases of premenstrual aggravated contact dermatitis, clinicians are advised to consider the phase of the menstrual cycle when interpreting the results of epicutaneous tests (5,32,33,59,60). In case of negative skin testing, the repetition of epicutaneous tests during the premenstrual phase might yield positive results.

CONCLUSION

Many skin disorders are associated with various phases of the menstrual cycle. Although there are many indications that female sex hormones influence the disease activity via both direct immunological and metabolic mechanisms, an examination of the relevant literature shows that in the final analysis, the pathogenesis of these cycle-associated changes can be explained only in very rare instances. With regard to potential therapeutic approaches, this topic should be the focus of further dermatological research.

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Women's perceptions of sensitive vulvar skin during different life stages

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Sensitive skin is a condition effecting large segments of the population and can have considerable psychological impact (1,2). Patients with sensitive skin have a significantly higher level of somatization, anxiety, interpersonal sensitivity, and hostility when compared with individuals with non-sensitive skin (3). Further, the reported impact of the psychological component of the quality of life increases as a function of the severity of skin sensitivity (4). We are just beginning to understand the wide variety of factors that may contribute to sensitive skin, including: physiologic factors such as skin type and hormonal influences; environmental factors such as extremes of weather; and cultural factors such as societal expectations and exposures to consumer products (5). This chapter discusses the perceptions women have about the sensitivity of their skin in the vulvar area, the changing perceptions at different life stages, and the impacts of aging, incontinence, and menopause.

INTRODUCTION TO "SENSITIVE SKIN"

Individuals with sensitive skin report a variety of unpleasant sensory reactions in response to common external factors and intrinsic stressors (6,7). Often, the sensory effects that are the hallmark of sensitive skin (such as prickling, burning, tingling, or pain) are not accompanied by erythema or other objective signs of irritation or immunological responses (6). In fact, little correlation exists between individuals' perceptions of the sensitivity of their skin and demonstrable signs of skin reactivity to irritants (8). The pathogenesis of sensitive skin is unknown, but believed to be the product of multiple etiologies, including deficiencies in barrier function, neurosensory dysfunction, compound-specific irritancy, and cultural influences (5,9).

A sizeable proportion of people in the general population in many geographies claim to have sensitive skin (5,10). For example, in Europe, some degree of skin sensitivity was claimed by 50%–90% of responders in several studies in France (11–13), 75% of responders in Germany (14), over 50% in Italy (15), and 64% in Greece (16). In the UK, 38% of the men and 51% of the women claimed to have sensitive skin (17). In the USA, the prevalence of self-declared sensitive skin has been reported at 44%–83% (18–22). In Japan, "very" or "rather" sensitive skin is claimed by 53% of men and 56% of women (23).

In other geographies, the proportion of the population who perceive they have sensitive skin is lower than in Europe and the USA. In a study conducted in Mexico using 246 subjects, self-diagnosed sensitive skin was found in 36% of subjects (24), with a higher prevalence of sensitive skin among subjects with lighter skin phototypes (type II and III) compared to darker ones (type IV and V). Two survey studies have been reported from China. In a study of 9154 individuals (25), the prevalence of self-proclaimed sensitive or very sensitive skin has been reported as 9% among men and 16% among women. In a study among 408 women in China (26), 2% claimed they had very sensitive skin, 5% claimed they had moderately sensitive skin, and 16% claimed they had slightly sensitive skin.

The explanation for differences in prevalence between countries regarding the perception of sensitive skin is unclear, but may be related to some of the underlying physiological causes and environmental triggers of sensitive skin, such as prevailing weather conditions and fairer versus darker skin types. Also, it is likely that cultural influences account for some of these differences. In the study conducted in urban areas in China, Xu and colleagues (25) hypothesized that some of the participants, especially older individuals, were not familiar with the concept of "sensitive skin" and, therefore, the condition may have been under-reported. This hypothesis was supported by the observations that some individuals who did not claim to have sensitive skin responded that they experienced adverse sensory effects after using cosmetic products. Further, the reported prevalence was inversely proportional to the age group of the responders.

The expectations of the general public may also play a role. Manufacturers of consumer products have increasingly marketed products targeted at sensitive skin. As a consequence, the public has likely become more aware of this condition. This may partially explain why the proportion of the population that claims sensitive skin appears to be increasing (26). Results of a study conducted in eight European countries are consistent with a cultural component (27,28). In Portugal, Italy, and Spain, 80%–90% of the subjects in the survey population reported at least some skin sensitivity, while in Germany, Belgium, and Switzerland, the proportion was just a little more than half. Since the European population is considered to be highly mobile and crossbred, the authors attributed this unexpected finding to substantially more fashion- and beauty-related advertising in specific European countries (28).

As skin ages, certain physiological changes occur, including reduced epidermal and dermal thickness, reduced hydration, increased permeability, and slower wound healing (29–31). Such changes would lead to the conclusion that skin becomes more susceptible to irritation with aging. However, clinical assessments of responses to irritants indicate that older people tend to be less susceptible to skin irritation compared to younger individuals (32–36).

In contrast to any changes in the physiological response to irritants with age, the perceptions of general skin sensitivity in western countries do not appear to change with aging.

In a phone survey conducted in the USA among a nationally representative sample of 994 subjects, 45% declared themselves as having "sensitive" or "very sensitive" skin (21). There were no significant differences in the prevalence when the data were considered based on age subgroups of 18–24 years, 25–34 years, 35–44 years, 45–54 years, 55–64 years, and ≥65 years. In a survey conducted in the Midwest in a major metropolitan area of the USA (Cincinnati, OH) (19), among the 1039 subjects, 68% claimed some degree of overall skin sensitivity. When subgroups of the responding population were considered, the proportion claiming to have sensitive skin was 67% for those aged 30 years and under, 69% for those aged 31–39 years, 61% for those aged 40–49 years, and 74% for those aged 50 years and older. There was no correlation between age and the perception of sensitive skin ($p = 0.65$).

As mentioned earlier, the survey conducted in China (25) indicated that there was a statistically significant inverse relationship ($p < 0.001$) between age and the prevalence of reported sensitive or very sensitive skin: 16% in the youngest group (<25 years), 14% in the middle group (25–49 years), and 10% in the oldest group (≥50 years). Younger age groups may be more aware of the concept of sensitive skin, partially due to beauty-related advertising.

Sensitive skin appears to be related to gender, fair skin phenotype, and dry skin. Misery and colleagues conducted a study on overall perceived skin sensitivity in four different regions of the USA (East, Central, West, and Mountain) (21). These investigators found no significant differences in relation to geographic region, age, or ethnicity. However, there was a higher prevalence among women, fair skin phenotypes, and individuals with dry skin. In a study conducted in the UK among 3300 women and 500 men, Willis and colleagues (17) found the incidence of perceived skin sensitivity to be 51% among women and 38% among men. Dry skin and a predilection for blushing/flushing were associated factors for sensitive skin. In a study conducted in Japan, Kamide and colleagues reported that sensitive skin was more likely to be reported by individuals with dry, oily, or combination skin (23).

PERCEPTIONS OF SENSITIVE SKIN OF THE VULVA

When evaluating sensitive skin, it is common to focus on the face. However, it is becoming increasingly clear that individuals can have different perceptions about the degree of skin sensitivity at distinct anatomic sites (6,10,19). Structural variations in the skin of different body sites can contribute to differences in barrier function, which may contribute to differences in skin sensitivity. Also, potential triggering factors for skin sensitivity would be expected to vary by body site. For example, the face is exposed to all ambient environmental conditions in the course of daily life, and to a number of products (e.g., cosmetics for women) and practices (e.g., shaving for men) that may lead to the adverse sensations associated with sensitive skin. In contrast, the skin of the genital area is more protected from ambient environmental conditions, but this anatomic site is almost constantly semi-occluded throughout the day.

Few studies have probed sensitivity at multiple anatomic sites among the same group of individuals. Saint-Martory and colleagues (6) reported on a survey questionnaire study conducted in 2004–2005 among 400 individuals in France. The face was most often reported as the site of sensitivity (85% of responders). However, other anatomic sites were also reported as sensitive: the hands (58%), scalp (36%), feet (34%), neck (27%), torso (23%), and back (21%), in order of frequency. The prevalence of some degree of perceived sensitive skin of the scalp has been reported as 24% in the UK (17), and 32%–70% in France (37,38). In a study conducted in 2006, 1039 men and women completed a questionnaire related to their perceptions of sensitive skin. Within this group, 77% reported some degree of perceived sensitivity of the face, compared with 61% for the body and 56% for genital skin (19).

We have conducted several studies in the USA (Cincinnati, Ohio, and rural Mississippi) and China in order to evaluate perceptions of sensitive skin at various anatomic sites, including the genital area (20,22,26,39). The following sections focus on the perception of genital skin sensitivity among women during different life stages and some of the environmental conditions and other triggering factors associated with sensitive genital skin. In addition, some recent observations of differences in biomarkers evaluated in women with sensitive genital skin provide intriguing directions for future research into understanding sensitive skin.

The vulvar epithelium exhibits marked regional differences in structure (40). The cutaneous epithelium of the mons pubis and labia majora exhibit a keratinized, stratified, squamous structure that is similar to skin at other sites. However, skin in this area is more hydrated than skin at other body sites and, therefore, more permeable to some materials and more susceptible to friction effects (41). Moving toward the labia minora, the degree of keratinization and thickness of the epidermis decrease. The inner third of the labia minora is nonkeratinized mucosal tissue (10). The nonkeratinized vulvar skin of the labia minora exhibits increased permeability related to the absence of keratin and a loosely packed, less structured lipid barrier (40,42). In addition, the thinner inner epithelium represents a shorter distance for penetration of substances (40). Differences in susceptibility to irritant materials seem to be dependent on the relative permeability of the skin of the vulva to the irritant. In addition, vulvar tissue is highly innervated (43).

The overall prevalence among women of perceived sensitive skin in general and sensitive genital skin was evaluated in three separate studies conducted among the general population using the same survey instrument. A first study was conducted in a metropolitan area of the central USA, and included 869 women with a mean age of 35.0 years (19,39,44,45). Subjects were asked to complete a written questionnaire probing perceptions of sensitive skin. Study participants were not selected based on any criteria related to sensitive skin or hyper-reactivity to consumer products, but were participating in unrelated consumer product studies. A second study was conducted in Mississippi using the same written questionnaire (22). In this study, participants were recruited from local organizations with no selection based on any dermatologic or other criteria, and were from a predominantly rural environment. The study population consisted of 89 women with a mean age of 45.5 years. In these two studies, the proportions of African–American and Caucasian subjects were similar. A study using a similar protocol and a translation of the same written questionnaire was conducted in China and included 408 women with a mean age of 39 years (26).

Results on perceptions of sensitive skin in the genital area and sensitive skin in general are presented in Figures 27.1a and 27.1b, respectively. When the results from the Cincinnati and Mississippi studies were compared, the proportions of subjects who claimed some degree of genital skin sensitivity were

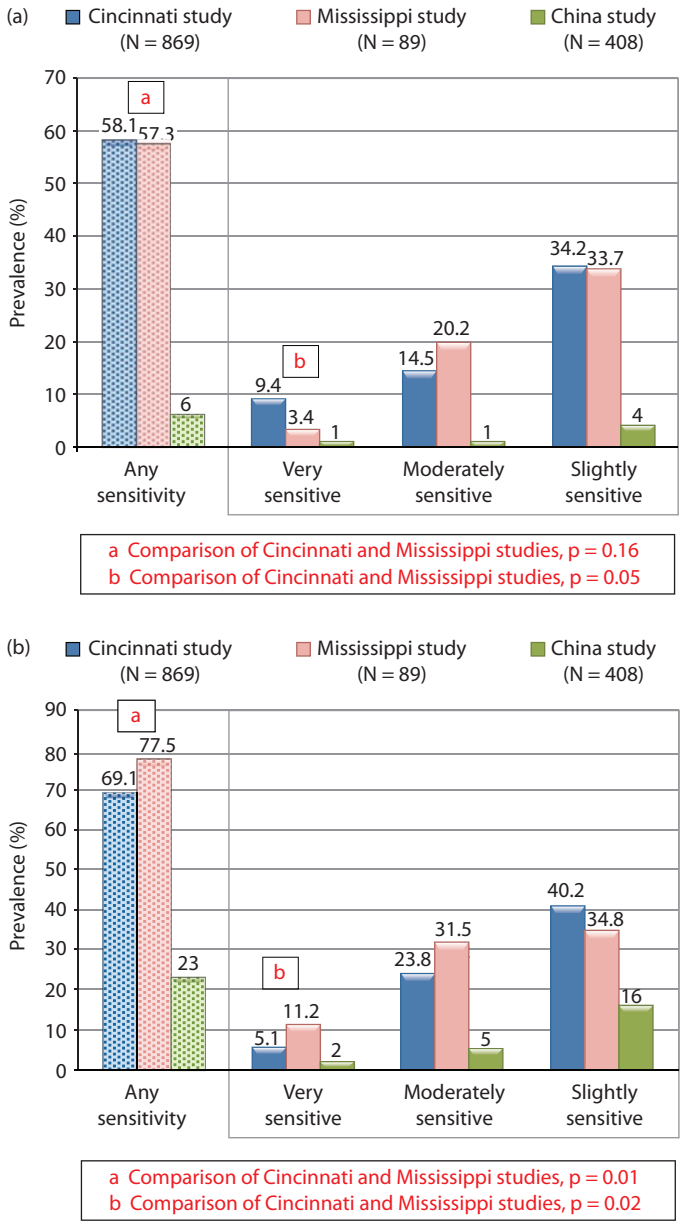

Figure 27.1 Prevalence of perceived sensitive skin among women. Subjects in three different geographies (urban Ohio, rural Mississippi, and China) were asked to complete a sensitive skin questionnaire. Participants were asked to describe their skin sensitivity as very, moderately, slightly, or not sensitive. Subsequently, participants were asked to describe the skin of specific anatomic sites, including the genital area, using the same four-point scale. The percentages of participants claiming any degree of skin sensitivity and the percentages giving each degree of response (i.e., very, moderately, or slightly) are plotted. Results from the Cincinnati and Mississippi studies were compared using a χ^2 analysis. (a) Sensitive genital skin. (b) Sensitive skin in general (19,22,26).

not significantly different between the two studies (58.1% and 57.3%, respectively; p = 0.16) (22). A higher proportion of subjects from the Cincinnati study claimed their genital skin was very sensitive (9.4% and 3.4%, respectively; p = 0.05). When asked about sensitive skin in general (Figure 27.1b), a slightly higher proportion of subjects in the Mississippi study claimed some degree of sensitivity (77.5% compared to 69.1% from the Cincinnati study; p = 0.01) or that there genital skin was very sensitive (11.2% compared to 5.1% from the Cincinnati study; p = 0.02). The prevalence rates of perceived sensitive skin at the specific anatomic sites of the face and body were also slightly higher for the Mississippi study (data not shown).

In the study conducted in China (26), the proportion of women who claimed to have sensitive genital skin was much lower than in both studies in the USA, at only 6% (Figure 27.1a). For sensitive skin in general, the prevalence was 23% (Figure 27.1b). These results are consistent with the observations of Xu and colleagues, who reported a lower prevalence of perceived sensitive skin in China compared to Europe and the USA (25).

We have reported previously that the proportion of subjects who perceive their genital skin as sensitive increases with age (46). The Mississippi population was older than that surveyed in Ohio (mean ages of 45.5 and 35 years, respectively), so the slight but significant difference in perception of sensitive genital skin cannot be explained by an age difference.

The Cincinnati and Mississippi studies provide an opportunity to compare different geographic locations within the same country and to compare a metropolitan versus a rural environment. Neither of these factors appeared to be related to the prevalence of the perception of sensitive genital skin. The two geographic regions have differing climates. Mississippi experiences mild winters, but long summers characterized by high temperatures and high levels of humidity. Cincinnati, Ohio, has mild summers but cold winters. However, when asked about perceived environmental conditions that trigger skin reactions, there were no differences between the two regions with regard to those conditions relevant to sensitive genital skin.

Misery and colleagues conducted a study on overall perceived skin sensitivity in four different regions of the USA (East, Central, West, and Mountain) (21). These investigators found no significant differences related to geographic region. There is no obvious biological explanation as to why our results differed, with a higher prevalence of sensitive skin in general in Mississippi compared to Cincinnati (Figure 27.1b). Significant regional differences may be difficult to explain on a solely biological basis; however, cultural factors that may influence southern women (i.e., the stereotypical "southern belle") may contribute.

Gender and ethnicity appear to play roles in the perception of sensitive genital skin. In the Cincinnati study (Table 27.1), a significantly higher proportion of women perceived themselves to have sensitive genital skin compared to men (58.1% compared to 44.2%; p = 0.0009). The gender difference seemed to be driven by the Caucasian subjects, who composed the highest proportion of the test population. Among Caucasian subjects, a significantly higher proportion of women perceived some degree of sensitive genital skin compared to men (57.0% and 37.3%, respectively; p < 0.0001) (45). In contrast, among African–Americans there was no difference between genders (66.7% of women and 65.0% of men; p = 0.84) (45). Overall, a significant relationship was found between ethnicity and a perception of sensitive skin in the genital area (data not shown; p = 0.012). Gender differences may be related to the structure of the female genitalia and the growing variety of products used by women. Specific changes that occur during aging may also play a role. There is no obvious explanation at this time for why

Table 27.1 Perceptions of Self-Declared Sensitive Genital Skin by Gender and Ethnicity

	Women		Men		Comparison of women vs. men
	Number	(%)	Number	(%)	p-value
All ethnicities (N = 1032)	869		163		
Sensitive (any degree)	505	58.1	72	44.2	0.0009
Not sensitive	364	41.9	91	55.8	
Slightly sensitive	297	34.2	53	32.5	
Moderately sensitive	126	14.5	13	8.0	
Very sensitive	82	9.4	6	3.7	
Caucasians (N = 802)	684		118		
Sensitive (any degree)	390	57.0	44	37.3	<0.0001
Not sensitive	294	43.0	74	62.7	
Slightly sensitive	238	34.8	32	27.1	
Moderately sensitive	101	14.8	9	7.6	
Very sensitive	51	7.5	3	2.5	
African–American (N = 128)	108		20		
Sensitive (any degree)	72	66.7	13	65.0	0.84
Not sensitive	36	33.3	7	35.0	
Slightly sensitive	26	24.1	8	40.0	
Moderately sensitive	20	18.5	4	20.0	
Very sensitive	26	24.1	1	5.0	

Note: Statistical comparisons were conducted for sensitive (any degree) vs. not sensitive using a Mantel–Haenszel χ^2 test. Other ethnicities were not compared statistically due to the low number of participants (44,45).

African–American men apparently perceive their genital skin as more sensitive compared to Caucasian men (45).

In contrast, in the same study, no significant relationships were found between ethnicity and sensitive skin in general, or sensitive skin of the face or body ($p = 0.15$, $p = 0.24$, and $p = 0.13$, respectively; data not shown) (19). This is consistent with the findings of Misery and colleagues in a study conducted in the USA (21). These investigators noted that the prevalence of sensitive skin in general was similar among ethnic groups, varying slightly from 43% for Caucasians to 52% for African–Americans, with no statistically significant difference ($p = 0.35$). Jourdain and colleagues conducted a study of perceived sensitive facial skin among a population in San Francisco specifically selected to include approximately equal numbers of four ethnicities (18). These authors found no differences between the proportions of women in the four ethnic groups who perceived that they had some degree of sensitive facial skin (African–Americans, 52%; Asians, 51%; European–Americans, 50%; and Hispanics, 54%).

In our survey studies, the questionnaire included lists of external factors (environmental and physiologic conditions) and certain consumer products, and asked the responders to indicate if these items ever triggered a skin reaction. In the Cincinnati study (Table 27.2), a large proportion of the entire study population perceived each of the triggering factors as causing skin reactions on some occasions. However, for the group of individuals claiming some degree of sensitive genital skin, the proportion was consistently higher compared with those individuals who claimed their skin was not sensitive. Among environmental and physiologic conditions (Table 27.2), rough fabrics, hot weather, stress, and the menstrual cycle were factors that were identified by over 50% of the sensitive group and less than half of the non-sensitive group (44). Dry and cold weather conditions were identified by the majority of both the sensitive and non-sensitive individuals. Similar patterns were observed with personal care items (Table 27.2) and certain feminine products (Table 27.2). For all of these products, a significantly higher proportion of women with sensitive genital skin claimed the products sometimes cause skin reactions. Comparison of the sensitive to non-sensitive groups indicated that the differences were consistently significant ($p < 0.00001$).

Similar results were obtained in the Mississippi study (data not shown) (22). Common external and physiologic conditions that were identified were rough fabrics (74.4%), hot weather (49.3%), stress (68.8%), and the menstrual cycle (56.5%). There were no significant differences between the two geographies for any of these conditions. In the study conducted in China, the number of individuals who claimed to have sensitive genital skin was small; however, the most commonly reported environmental conditions causing skin reactions were rough fabrics (42%) and weather (22%) (26).

A comparison of personal care items and feminine products for the entire test population is presented in Table 27.3. The Cincinnati and Mississippi studies were compared using a χ^2 analysis, and the results showed a significant difference between the proportions of individuals who identified three triggering factors. A significantly higher proportion of the Mississippi study population identified undergarments/clothing as a triggering factor compared to the Cincinnati study population (56% and 37%, respectively; $p = 0.007$). In contrast, the Cincinnati population identified perfumes/colognes ($p = 0.03$) and tampons ($p = 0.03$) more frequently than the Mississippi population. A statistical comparison was not conducted for the responses from the study conducted in China; however, visual inspection demonstrates a smaller portion of the responding population identifying each of these factors as triggers for adverse skin reactions.

In a study of sensitive facial skin, Jourdain and colleagues (18) found significant differences between ethnic groups with regard to some environmental factors, including wind, fast temperature changes, cold weather, and sun.

Table 27.2 Perceptions about Factors and Products Perceived to Trigger Skin Responses among Women Claiming to have Sensitive Genital Skin

Triggering factors	Sensitive genital skin		Not sensitive genital skin		Difference between groups (%)	Comparison of groups	
	Total responders	% sensitive to factor	Total responders	% sensitive to factor		p-value	Spearman coefficient
Environmental and physiologic conditions							
Rough fabrics	478	75	323	46	29	ND	ND
Hot weather	474	69	322	44	24	ND	ND
Stress	477	64	319	41	23	ND	ND
Menstrual cycle	441	61	305	40	21	ND	ND
Humid weather	460	48	319	29	19	ND	ND
Dry weather	476	78	326	66	12	ND	ND
Cold weather	478	87	334	80	7	ND	ND
Personal care items							
Soaps (bar or liquid)	485	70	343	22	48	<0.00001	0.49
Undergarments/clothing	481	57	336	9	48	<0.00001	0.48
Perfumes/colognes	307	52	343	38	14	<0.00001	0.38
Deodorants/ antiperspirants	335	50	280	16	34	<0.00001	0.35
Toilet paper	472	32	335	7	25	<0.00001	0.30
Feminine products							
Menstrual pads	451	59	315	12	46	<0.00001	0.45
Feminine wipes	282	43	225	7	36	<0.00001	0.41
Douching products	194	35	179	3	32	<0.00001	0.40
Panty liners	455	45	325	8	37	<0.00001	0.39
Tampons	388	38	296	4	34	<0.00001	0.39

Source: Data on feminine products adapted from Farage MA. Perceptions of sensitive skin of the genital area. In: Surber C, Elsner P, Farage MA, eds. *Topical Applications and the Mucosa*. Basel: Karger, 2011, 142–54.

Note: In the Cincinnati study, responders were given lists of environmental factors and products and asked to indicate if these items ever caused skin irritation (never, sometimes, frequently, or always). Statistics compared responses of the group claiming to have some degree of genital sensitivity to those whose genital skin was not sensitive. Statistical analysis was via a Mantel–Haenszel χ^2 test using all levels of perceived irritation frequency (never, sometimes, frequently, or always). These were grouped for presentation in the above table. ND: not done.

Table 27.3 Perceptions about Products Perceived to Trigger Skin Responses among Women in Three Geographies

Triggering factors	Cincinnati		Mississippi		China	
	Total responders	% sensitive to factor	Total responders	% sensitive to factor	Total responders	% sensitive to factor
Personal care items						
Soaps (bar or liquid)	828	50	81	49	323	9
Undergarments/clothing	817	37[a]	82	56	401	17
Perfumes/colognes	650	44[b]	58	28	257	9
Deodorants/antiperspirants	615	35	65	26	96	1
Toilet paper	807	21	80	18	384	16
Feminine products						
Menstrual pads	766	40	62	32	133	4
Feminine wipes	507	27	53	34	405	29
Douching products	373	20	41	15	139	2
Panty liners	780	30	62	24	127	1
Tampons	684	24[c]	63	10	163	5

Source: Data for responders from Mississippi and China adapted from Farage MA et al. *Family Med Medical Sci Res* 2013; 2: 1–8. Farage MA et al. *Journal of Cosmetics, Dermatological Sciences and Applications* 2012; 2: 184–95.

Note: In all three studies, responders were given lists of personal items and products and asked to indicate if these items ever caused skin irritation (never, sometimes, frequently, or always). A χ^2 analysis was conducted to compare the results of the Cincinnati and Mississippi studies, with the following comparisons indicating significance.

[a] $p = 0.007$.

[b] $p = 0.03$.

[c] $p = 0.03$.

Generally, a lower proportion of African–American responders reported skin reactivity to these factors. Importantly, the overall proportion of African–American responders who perceived that they had sensitive skin was not different from the other ethnicities (i.e., approximately 50%). In their study of regions within the USA, Misery and colleagues reported that the percentage of subjects experiencing cutaneous reactivity to emotion, climatic, and environmental factors was always significantly higher in the "sensitive skin" group than in the "non-sensitive skin" group (21).

Effects of Aging

In the Cincinnati study, the prevalence of sensitive skin of the genital area differed significantly based on age, increasing from 53.3% in the <30 years of age group to 66.3% in the >50 years of age group ($p = 0.012$) (Figure 27.2a) (19,44). Among women, sensitive skin of the genital area was more likely to be declared by women aged 50 years and older (i.e., 70.2% of the age group) than by women in the other age groups (55.2% among women ≤30 years of age, 57.2% among women 31–39 years of age, and 61.4% among women 40–49 years of age). The association between age and prevalence was significant among women ($p = 0.012$). Among men, there was no apparent association between age and perceived sensitive genital skin ($p = 0.17$) (45). In contrast to the perception of sensitive skin of the genital area, sensitive skin in general does not appear to change with age for either gender (Figure 27.2b) (19,44). The differing perceptions among age groups with regard to skin sensitivity of the genital area may be related to specific changes that may occur as a woman ages, such as the onset of menopause.

Table 27.4 presents the perceptions of the age groups regarding feminine products and the association with skin responses. For all feminine products, individuals with sensitive genital skin in the ≤30, 31–39, and 40–49 years of age groups are more likely to experience skin effects compared to those who do not have sensitive skin (all $p < 0.005$). For the women in the ≥50 years of age group, all feminine products except tampons are identified as triggering skin responses in a significantly higher proportion of the subjects claiming sensitive genital skin ($p \leq 0.02$). The small number of responses regarding tampons likely reflects a much smaller proportion of women who use such products in this age group, where a substantial portion of the women would be expected to be postmenopausal.

Findings regarding perceived sensitive skin and aging have been mixed. For example, in a study conducted in the USA, Misery and colleagues concluded that overall sensitivity does not vary with age (21). However, these investigators also reported that perceived sensitivity of the scalp increased with age (38). In a study in France, Guinot and colleagues reported that the prevalence of perceived sensitive skin of the face decreased with age for both women (67% in 35–39-year-olds to 55% in 55–60-year-olds) and men (35% in 45–49-year-olds to 29% in 55–60-year-olds) (46). In a study conducted in Mexico, Hernández-Blanco and colleagues did not see a trend with regard to the incidence of self-diagnosed sensitive skin and age (24). We have found that sensitive skin of the face and body does not appear to change with age (47).

Taken as a whole, these results serve as a reminder that sensitive skin continues to be a complex problem involving a complicated interplay of physiological, psychological, and cultural factors. As we unravel this phenomenon, the importance of understanding differences between ethnicity, gender, age group, and anatomic site is becoming increasingly clear.

Effects of Incontinence

Urinary incontinence is extremely common among women. Reports vary with regard to the precise percentage of the female population who suffer from incontinence. In a study conducted in Sweden among 3071 women, Hagglund and colleagues reported an overall prevalence of 26%, with a prevalence of 12% among women under 30 years of age (48). Jolleys (49) reported an overall prevalence of urinary incontinence of 41% in a survey among 833 women in the UK, whereas Thomas and colleagues (50) reported that 16.6% of women reported occasional incontinence and 8.5% reported regular incontinence in a survey of 9323 women in the London area.

The risk of incontinence increases with age (51,52). In a review of the relevant literature, Botlero and colleagues reported that the prevalence among younger women who had at least one episode of urinary incontinence within the previous year was about 13%, compared to 46% among women in their 50s and 60s (53). Brown and colleagues reported a prevalence of 28% among a cohort of 2763 participants in a survey of postmenopausal women (54). Roberts and colleagues reported on the results of a community-based study involving 762 women and 778 men (55). The mean age (±SD) of the subjects was 65.9 (±9.2) and 66.3 (±9.2), respectively. The prevalence of urinary incontinence was 48.4% among women and 25.6% among men. In a study conducted in the UK among 314 randomly selected female patients at a health promotion clinic (56), the prevalence of incontinence was 53.2% for the entire test population, with incidences rates of 34.7% among women 20–29 years of age and over 50% in women in age groups spanning 40–79 years. In contrast, 21,590 male heads of households in the USA participated in a survey to determine whether the respondents had symptoms of urinary incontinence (57). Overall, 12.7% reported symptoms during the previous 30 days. The association between urinary incontinence and age was significant, with prevalence among the youngest age group (men aged 18–34 years) at 7.2% and among the oldest age group (men aged ≥75 years) at 30.2%.

We conducted a study to evaluate perceptions of sensitive skin in women with urinary incontinence compared to a group of age-matched controls (20). The participants included women who suffered from light urinary incontinence aged 50 years and above who participated in focus groups as part of development efforts aimed toward incontinence products. Responses were compared to age-matched control subjects who did not have incontinence. Results are presented in Figure 27.3. We expected that the incontinent subjects might have an increased perception of sensitive skin in the genital area since these individuals may experience periodic wetness and may wear pads or incontinence products in order to control wetness. However, this was not the case. A directionally higher proportion of incontinent women reported some degree of sensitive genital skin (very, moderately, or slightly) compared to the controls (86.2% and 68.3%, respectively), but the difference between this group and the age-matched control group was not significant ($p = 0.08$) (Figure 27.3a). A directionally lower percentage of incontinent subjects described their genital skin as "very" sensitive compared to the control subjects (6.9% and 12.2%, respectively; $p = 0.08$). It is possible that incontinent individuals may attribute adverse sensory effects or irritation to their incontinent status, rather than to the notion that they have sensitive skin of the genital area (44). With regard to sensitive skin in general (Figure 27.3b), there was no difference between the test populations in the proportions claiming to have some degree of sensitivity (82.8% of incontinent subjects and 76.2% of

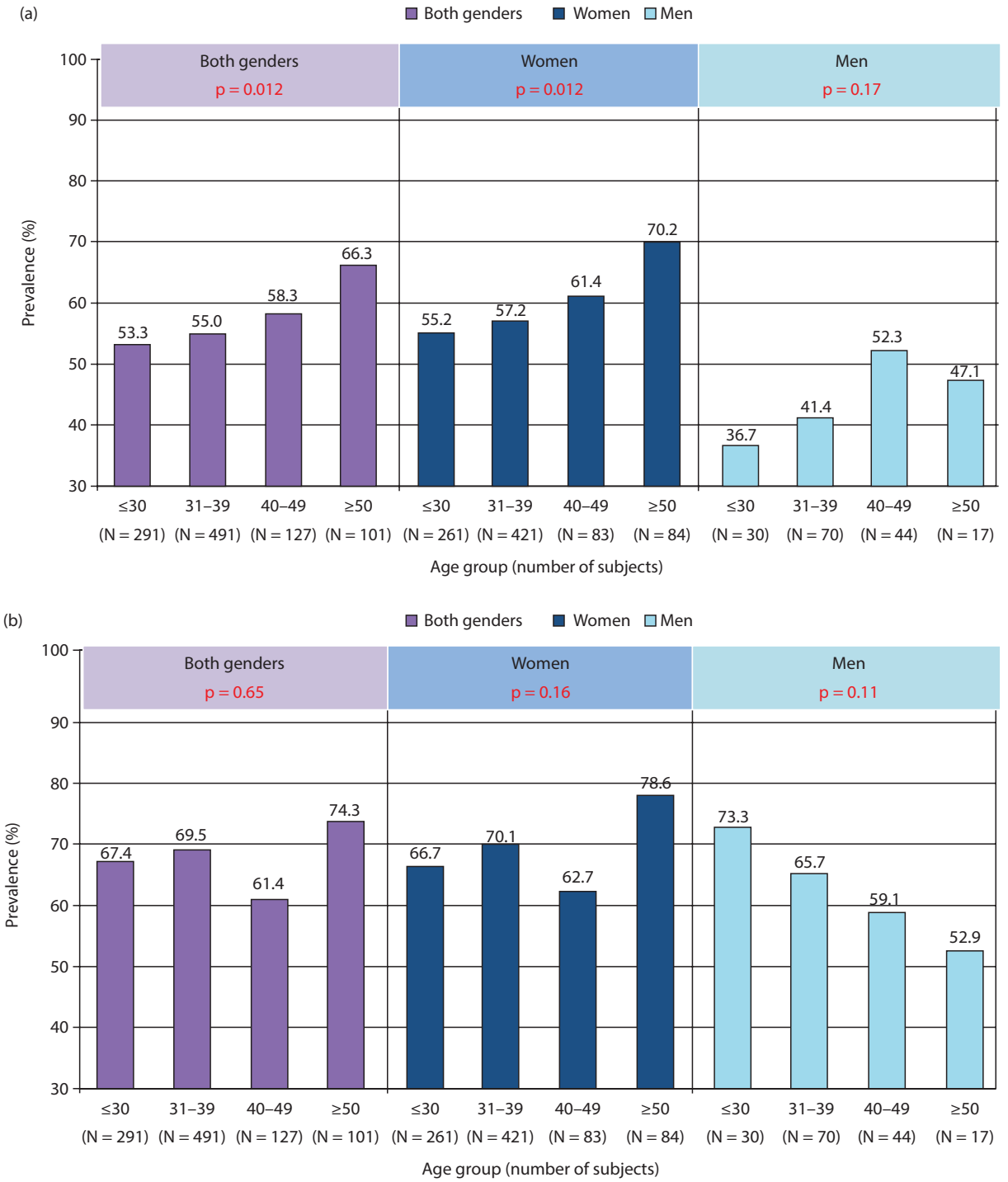

Figure 27.2 Perceptions of sensitive skin among women and men in different age groups. Responses in the Cincinnati, Ohio study were evaluated based on age group. A Mantel–Haenszel χ^2 analysis was conducted to determine if increasing age was associated with an increase in the prevalence of sensitive skin (any degree). (a) Sensitive genital skin. (b) Sensitive skin in general. (Data adapted from Farage MA. *Clin Exp Dermatol* 2009; 34: e521–30; Farage MA. *Cutan Ocul Toxicol* 2010; 29: 153–63.)

control subjects; p = 0.50). Interestingly, the incontinent women were directionally more inclined to describe their skin in general as "very" or "moderately" sensitive (p = 0.014). There are no apparent reasons for this tendency.

Large proportions of both study groups perceived each external factor as causing skin responses on some occasions (Table 27.5). With regard to environmental and physiologic factors, there were no significant differences between groups, with the exception of "cold weather" (Table 27.5). Note that "menstrual cycle" was not applicable to most of the individuals in this study, since the study population was aged 50 years and above; therefore, there were few responses reported for this

Table 27.4 Perceptions about Feminine Products Perceived to Trigger Skin Responses among Women of Different Age Groups

Triggering factors	All women in age subgroup		Sensitive genital skin		Not sensitive genital skin		Difference between sensitive and non-sensitive (%)	Comparison of sensitive and non-sensitive	
	Total responders	% sensitive to factor	Total responders	% sensitive to factor	Total responses	% sensitive to factor		p-value	Spearman coefficient
Age ≤30 years									
Menstrual pads	246	36	137	54	109	13	41.2	<0.00001	0.42
Panty liners	240	25	133	39	107	7	32.6	<0.00001	0.42
Tampons	229	24	127	42	102	3	38.8	<0.00001	0.42
Feminine wipes	172	22	90	39	82	4	35.2	<0.00001	0.42
Douching products	120	17	59	32	61	2	30.6	0.00003	0.41
Age 31–39 years									
Menstrual pads	394	39	228	58	166	13	45.6	<0.00001	0.45
Panty liners	390	31	223	47	167	9	37.6	<0.00001	0.40
Tampons	349	21	194	35	155	5	29.3	<0.00001	0.35
Feminine wipes	220	27	118	44	102	8	36.3	<0.00001	0.40
Douching products	158	20	74	37	84	5	31.7	<0.00001	0.41
Age 40–49 years									
Menstrual pads	72	42	43	65	29	7	58.2	0.00001	0.56
Panty liners	76	37	46	52	30	13	38.9	0.0005	0.41
Tampons	64	31	39	49	25	4	44.7	0.001	0.44
Feminine wipes	54	24	30	33	24	13	20.8	0.001	0.44
Douching products	43	14	26	23	17	0	23.1	0.005	0.29
Age ≥50 years									
Menstrual pads	46	54	34	68	12	17	50.9	0.001	0.45
Panty liners	59	37	44	48	15	7	41.0	0.001	0.45
Tampons	27	22	19	32	8	0	31.6	0.12	0.34
Feminine wipes	53	47	41	56	12	17	39.4	0.02	0.34
Douching products	43	30	31	42	12	0	41.9	0.02	0.40

Note: Responders were given lists of personal items and products and asked to indicate if these items ever caused skin irritation. A Mantel–Haenszel χ^2 test was used to compare responses of the group claiming to have some degree of genital sensitivity to those whose genital skin was not sensitive.

factor. For the personal care items and feminine products (Table 27.5), there were no differences between incontinent and control groups (20).

Effects of Menopause

Recently, we conducted a study to evaluate potential differences in biomolecular and physical measures of the urogenital skin among women in different stages of life (58,59). Subjects were categorized into three groups of 15 subjects each: the "Pre-M" group consisted of premenopausal women (mean age ± SD = 33.0 ± 6.4 years); the "Post-M Non-HRT" group consisted of postmenopausal women who were not receiving any hormone-replacement therapy and who exhibited a vaginal atrophy score ≥6 and vaginal pH ≥5 (mean age ± SD = 60.7 ± 3.6 years); and the "Post-M HRT" group consisted of postmenopausal women who had been taking some form of hormone-replacement therapy for a minimum of 1 year (mean age ± SD = 60.5 ± 3.6 years). Evaluations were conducted on three genital sites: introitus, labia minora, and labia majora. Physical measures at these sites included skin temperature and pH. In addition, sequential tape strips were used to collect material for the quantitative analysis of a variety of biomarkers and cytokines. We also collected information about perceived sensitive skin and urogenital symptoms.

Group sizes in this study were relatively small, resulting in a low likelihood of significant differences between groups or observations. However, some interesting trends emerged that provide directions for further investigation regarding an understanding of sensitive skin.

Figure 27.4 shows results of the perception of sensitive genital skin and the presence of subjective symptoms in the three test groups. The proportion of this population who perceived they had sensitive skin of the genital area was smaller in this study compared to previous studies in the same geographic area (Cincinnati, Ohio; i.e., about a third in this study compared to 58%) (shown in Table 27.1). There is no apparent reason for this difference; however, it may be related to the small sample size (15 individuals per group). As expected, symptoms associated with vulvovaginal atrophy (i.e., dryness, itch, and difficulties with intercourse) were reported by very few of the Pre-M subjects. Compared to the Pre-M group, a directionally higher proportion of both Post-M groups (HRT and Non-HRT) reported external and vaginal dryness and difficulties with intercourse. The differences between the Pre-M group and the Post-M HRT group were significant for vaginal dryness ($p = 0.035$) and intercourse difficulties ($p = 0.006$). External itch was reported by a significantly higher proportion of the Post-M Non-HRT group compared to both the Pre-M and Post-M HRT groups ($p = 0.035$ for each comparison).

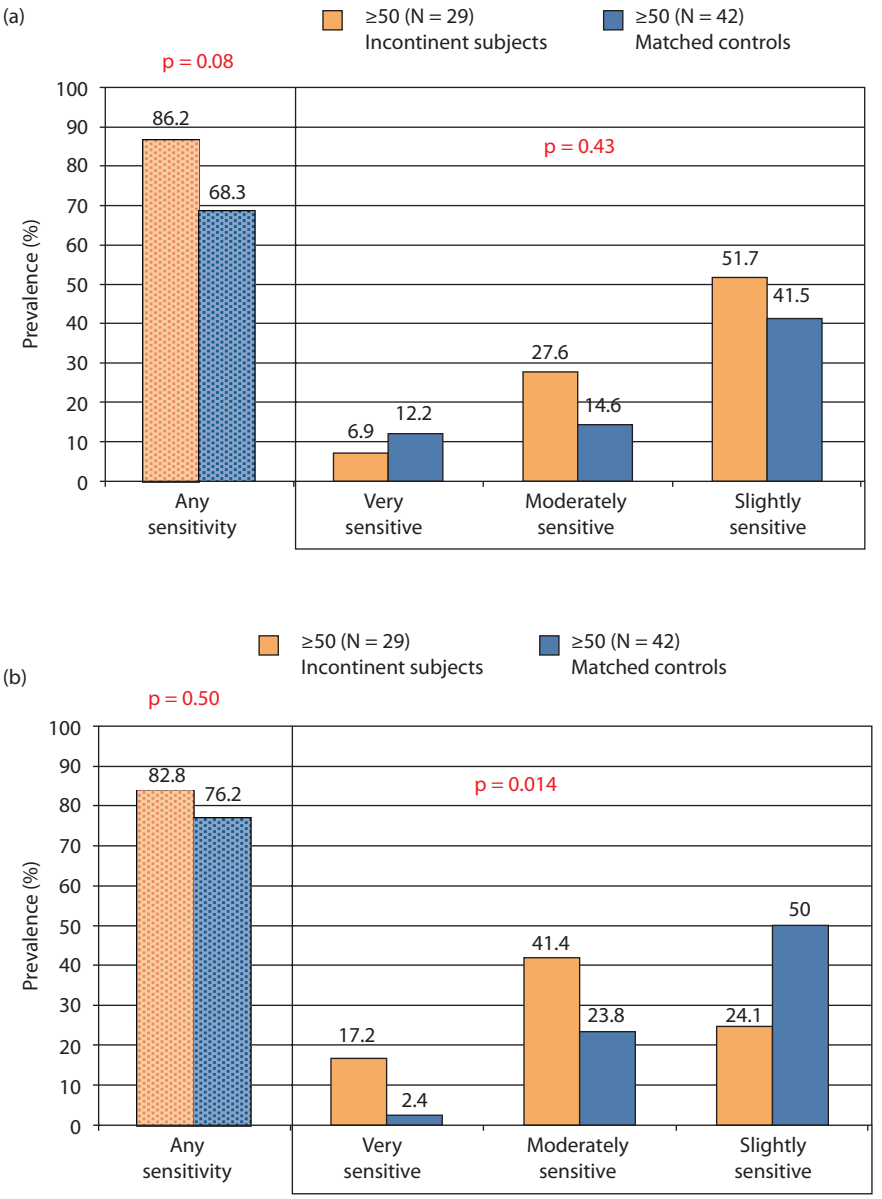

Figure 27.3 Perceptions of sensitive skin among women with incontinence. The sensitive skin questionnaire was administered to women who suffered from light urinary incontinence aged 50 years and above. Responses were compared to age-matched control subjects who did not have incontinence. The percentages of participants claiming any degree of skin sensitivity and the percentages giving each degree of response (i.e., very, moderately, or slightly) are plotted. Results were compared for any degree of sensitivity using a χ^2 analysis, and for all three degrees of sensitivity using a Mantel–Haenszel χ^2 analysis. (a) Sensitive genital skin. (b) Sensitive skin in general. (Data adapted from Farage MA. *Arch Gynecol Obstet* 2009; 280: 49–57.)

The pH was evaluated at four anatomic sites: vaginally and at the introitus, the labia minora, and the labia majora (58). Differences in pH were small (not reaching statistical significance); however, within each test group, women who claimed to have sensitive genital skin tended to demonstrate a higher pH vaginally and at the introitus compared to those who did not claim to have sensitive skin (Figure 27.5). As expected, HRT appeared to result in a vaginal pH that was close to that of the Pre-M group. As mentioned, differences between this small test population did not reach significance, but an interesting area for future research with a larger number of subjects would be an investigation into whether or not pH is related to sensitive genital skin and the impact of HRT on the pH of genital tissues other than the vagina.

The content of IL-1α and IL-1ra and the ratio of IL-1ra/IL-1α were evaluated in the study groups (Figure 27.6) (58). In both postmenopausal study groups, the IL-1α content recovered from tape stripping at the introitus was significantly higher in women claiming to have sensitive genital skin (Post-M Non-HRT, $p = 0.002$; Post-M HRT, $p = 0.004$) (Figure 27.6a). For those claiming to have sensitive skin in the Post-M Non-HRT group, the IL-1α content was also significantly higher at the labia

Table 27.5 Perceptions about Skin Responses Due to Relevant External Factors among Women with Incontinence

External factors	Incontinent (N = 29)		Control (N = 42)		p-value
	Total responses	% sensitive to factor	Total responses	% sensitive to factor	
Environmental and physiologic conditions					
Rough fabrics	27	84	38	81	0.45
Hot weather	24	87	34	83	0.25
Stress	26	58	36	47	0.57
Menstrual cycle	8	13	18	22	1
Humid weather	27	41	36	61	0.38
Dry weather	27	71	37	72	0.28
Cold weather	27	100	34	83	0.033
Personal care items					
Soaps (bar or liquid)	28	57	38	66	0.72
Undergarments/clothing	28	47	34	56	0.81
Perfumes/colognes	22	68	25	60	0.71
Deodorants/antiperspirants	21	53	27	59	1
Toilet paper	27	37	33	36	0.81
Feminine products					
Menstrual pads	18	61	17	53	0.60
Feminine wipes	23	39	20	60	0.19
Douching products	14	28	17	47	0.79
Panty liners	24	38	22	37	1
Tampons	8	26	10	20	0.72

Note: Responders were given lists of environmental factors and products and asked to indicate if these items ever caused skin irritation. A Mantel–Haenszel χ^2 test was used to compare responses of the group claiming to have some degree of genital sensitivity to those whose genital skin was not sensitive (20).

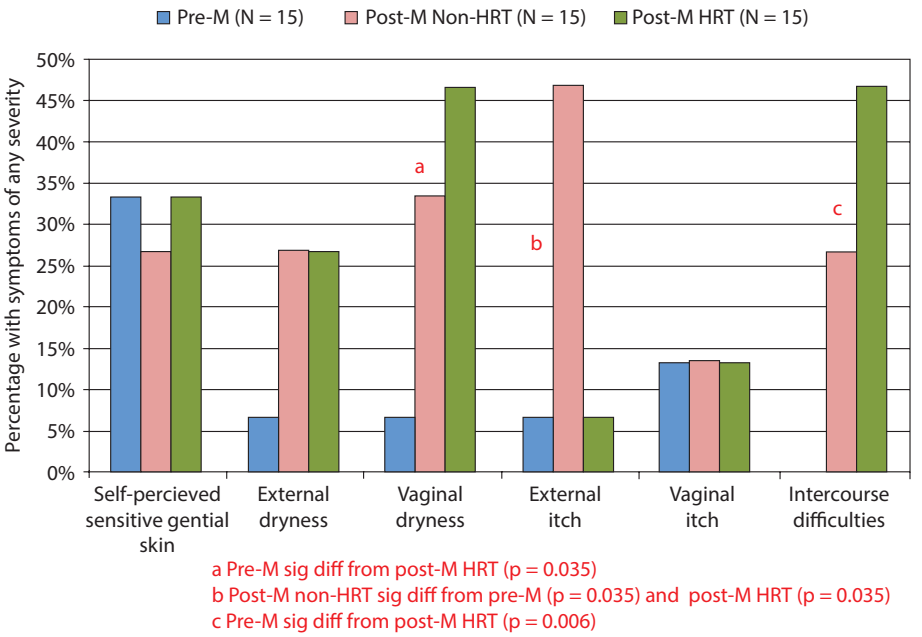

Figure 27.4 Changing perceptions after menopause. A study was conducted to evaluate potential differences in the biomolecular and physical measures of the urogenital skin among women at different stages of life. Participants were asked about perceptions of sensitive genital skin and about specific subjective symptoms (i.e., external and vaginal dryness, external and vaginal itch, or difficulties with intercourse). The groups (15 each) consisted of women who were premenopausal (Pre-M), postmenopausal on no hormone-replacement therapy (Post-M Non-HRT), and postmenopausal receiving hormone-replacement therapy (Post-M HRT). The proportions of individuals in each test group claiming any degree of sensitive genital skin or any of the subjective symptoms are plotted. Pairwise comparisons were conducted using Fisher's exact test.

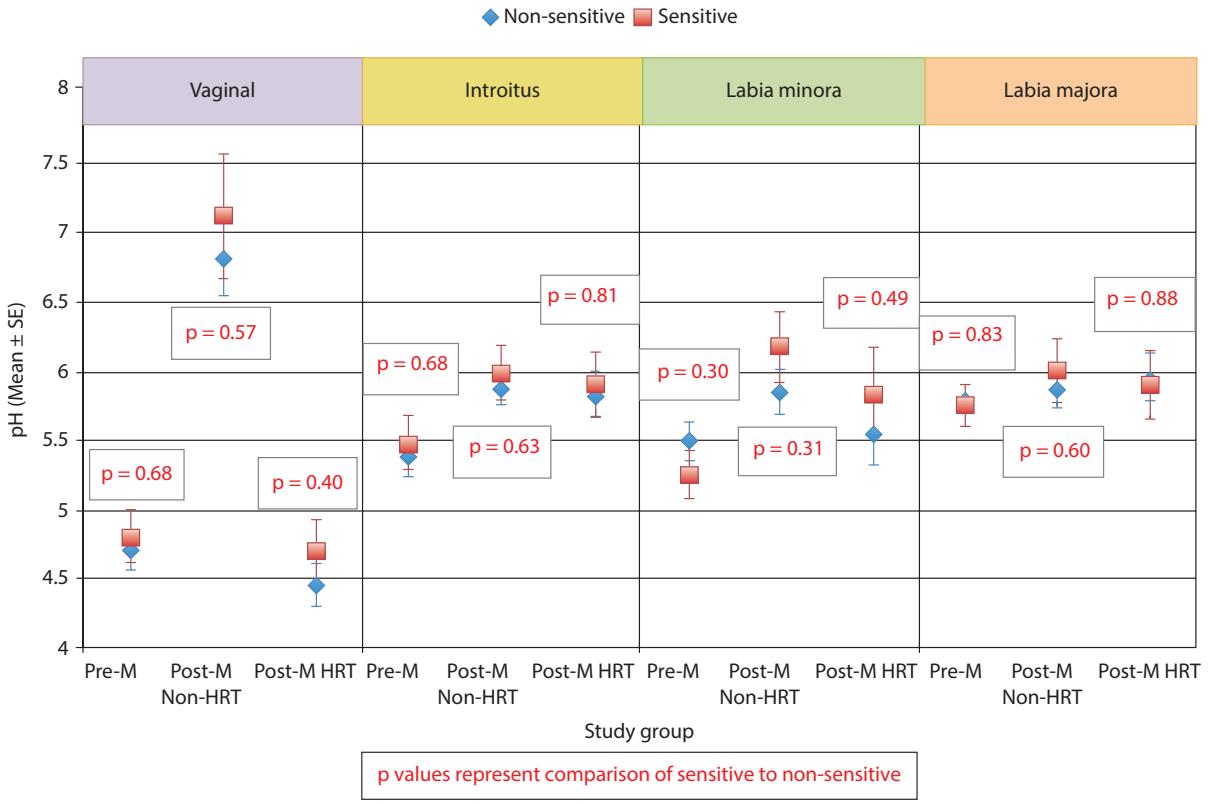

Figure 27.5 Comparison of skin pH at genital sites among women with sensitive genital skin. In the study to evaluate biomolecular and physical measures of the urogenital skin, evaluations of skin pH were conducted at the following anatomic sites: vaginally and at the introitus, the labia minora, and the labia majora. For each group, the mean pH for those who did not have sensitive genital skin was compared to those claiming to have sensitive skin. The numbers claiming to have sensitive genital within each group were: Pre-M, 5; Post-M Non-HRT, 4; Post-M HRT, 5. A mixed linear model was used to analyze the pH at different anatomic sites. None of the comparisons were significantly different (i.e., $p \leq 0.05$).

minora ($p = 0.01$). There were no significant differences in the IL-1ra content or the ratio of IL-1ra/IL-1α when individuals with sensitive genital skin were compared to those without (Figures 27.6b and 27.6c, respectively).

The cytokine IL-1α is produced by epithelial cells, and the normal human epidermis acts as a major reservoir of this material. Regulated cytokine expression is essential to the quality and function of the epidermal barrier, and deregulation of this complex signaling mechanism can result in multiple consequences in skin barrier function (60). The cytokine IL-1ra functions as a competitive inhibitor to block the response to IL-1α (61). There is evidence that levels of IL-1α and IL-1ra measured in the stratum corneum may be related to inflammation. Hirao and colleagues (62) reported that the stratum corneum of an area of skin unexposed to sunlight (i.e., the inner side of the upper arm) contained more IL-1α than a sun-exposed area (i.e., the face). In contrast, the IL-1ra content was reversed, with the sun-exposed area containing higher amounts than the unexposed area (62). The ratio of IL-1ra to IL-1α was over 100 in the sun-exposed area, and only 8 in the unexposed area (62), leading to the conclusion that IL-1ra activity was predominant in sun-exposed areas and IL-1α was predominant in unexposed areas. These same authors reported that the IL-1α content in the unexposed site increased with age, while the content of IL-1ra decreased, resulting in an age-dependent decrease in the IL-1ra/IL-1α ratio. In infants suffering from diaper rash, Perkins and colleagues (63) reported a positive correlation between IL-1ra levels recovered from the buttocks and diaper rash severity. The ratio of IL-1ra/IL-1α for sun-exposed skin (i.e., skin on the face and lower leg) was significantly higher (three- and six-times, respectively) than skin that was minimally sun-exposed (upper back, underarm, and upper leg) (63).

Histamine is derived from the decarboxylation of the amino acid histidine (64). An altered ratio of histamine to histidine may indicate a change in the induction of histidine decarboxylase or a shift in the equilibrium between these two materials. Overall histamine and histidine levels did differ significantly when individuals with perceived sensitive genital skin were compared to non-sensitive individuals (Figures 27.7a and 27.7b). Previously, we reported that the ratio of histidine to histamine was significantly higher at the introitus and labia majora in individuals with perceived sensitive genital skin compared to individuals who were non-sensitive (59). However, after this publication appeared, corrected statistical analyses indicated that, although individuals with sensitive skin tended to have higher ratios of histidine to histamine, the differences were not significant (Figure 27.7c).

Histamine is commonly associated with itch in a dose-dependent manner. Generally, we did not see an increase in histamine levels among the Post-M Non-HRT group of women

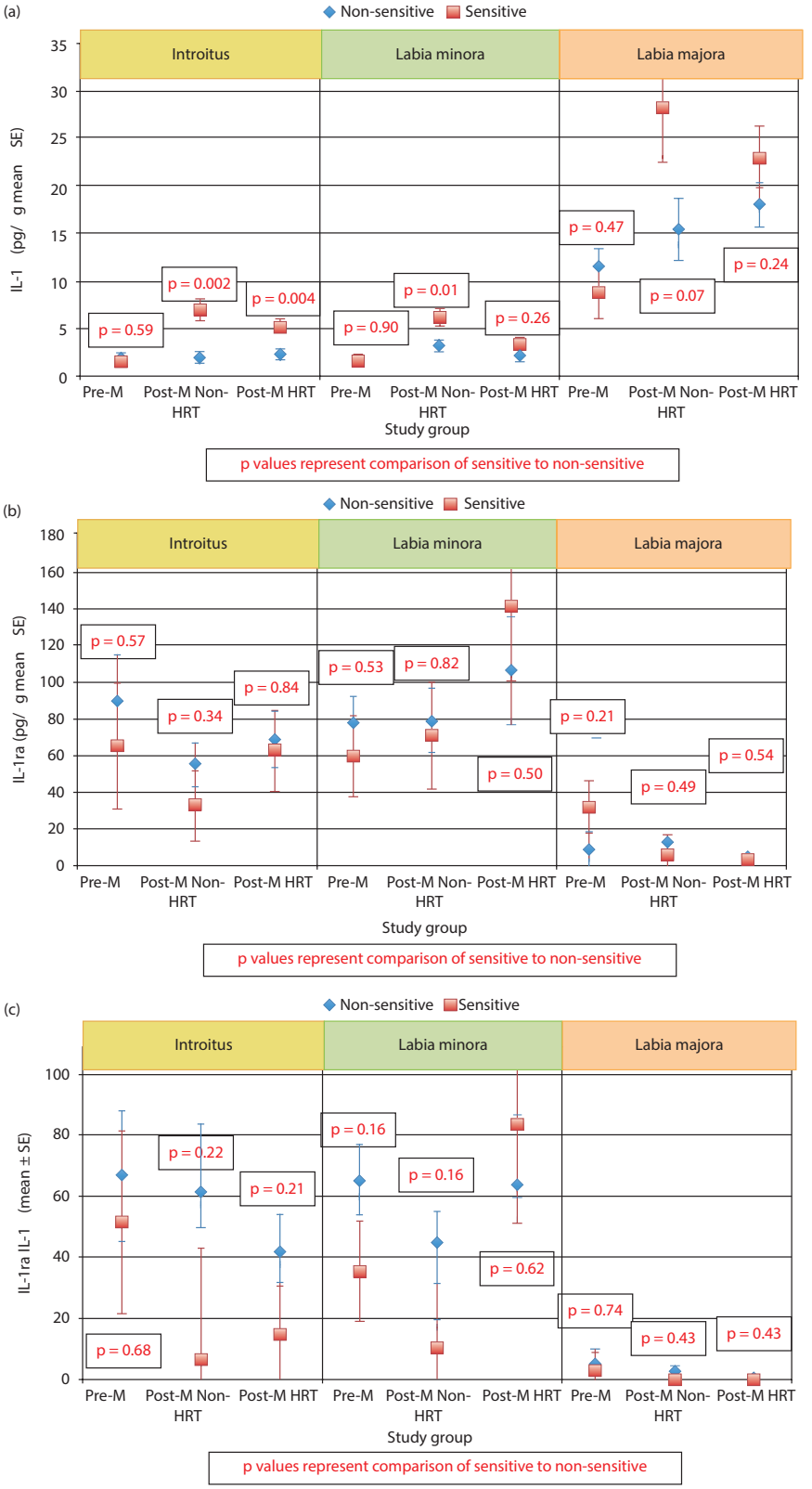

Figure 27.6 Content of IL-1α, IL-1ra, and the ratio of IL-1ra/IL-1α at genital sites among women with sensitive genital skin. In the study to evaluate biomolecular and physical measures of the urogenital skin, sequential tape strips were used to collect material for the quantitative analysis of a variety of biomarkers and cytokines. Results of analyses of (a) IL-1α, (b) IL-1ra, and (c) the ratio of IL-1ra/IL-1α are presented for each group. For each group, the mean value for those who did not have sensitive genital skin was compared to that of those claiming to have sensitive skin using a mixed linear model. (a) Mean IL-1α; (b) mean IL-1ra; (c) mean of the ratios of IL-1ra/IL-1α.

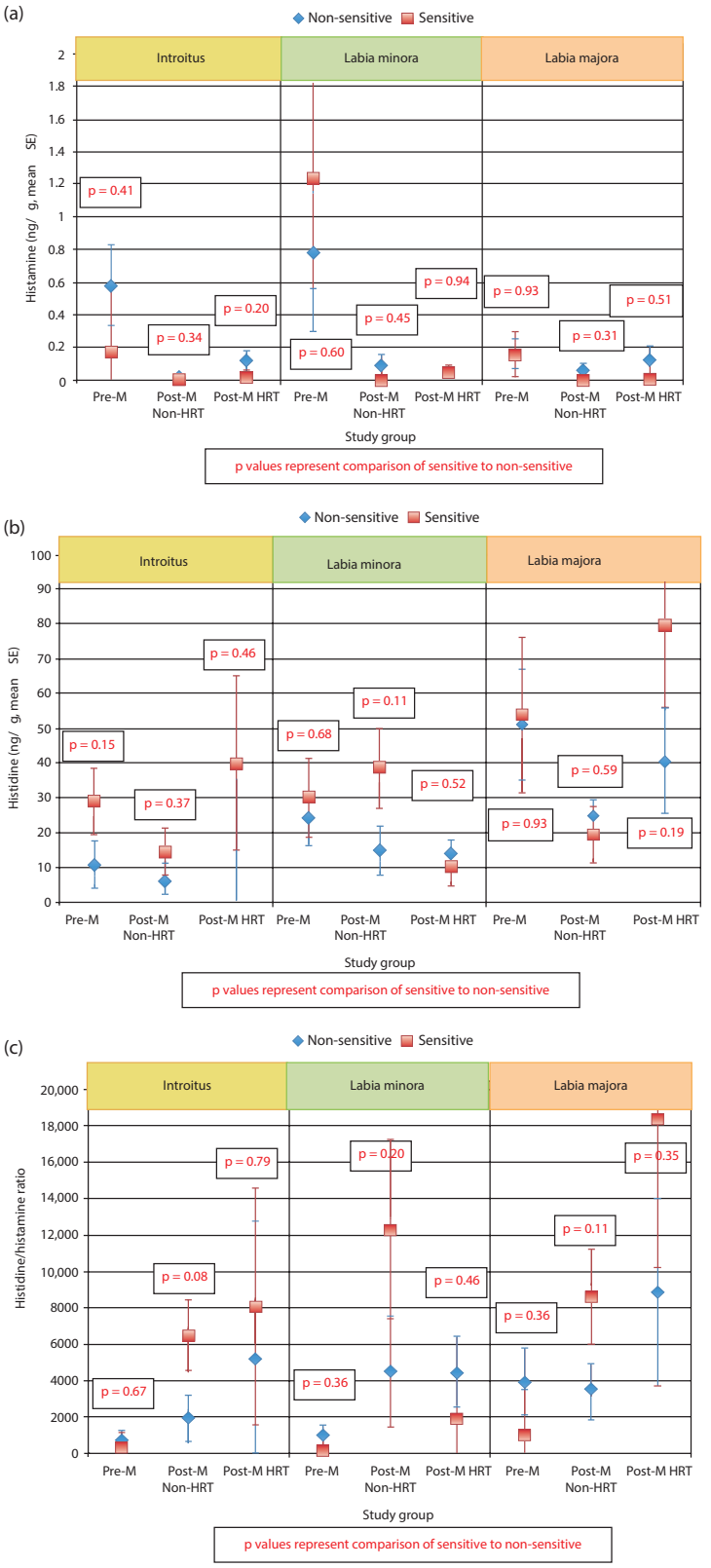

Figure 27.7 Content of histamine and histidine and the ratio of histidine/histamine at genital sites among women with sensitive genital skin. In the study to evaluate biomolecular and physical measures of the urogenital skin, histamine, histidine, and the ratio of histidine/histamine were evaluated. Results of analyses of the Pre-M and Post-M Non-HRT groups are presented for those who did not have sensitive genital skin compared to those claiming to have sensitive skin using a mixed linear model. (a) Mean histamine; (b) mean histidine; (c) mean of the ratios of histamine/histidine.

who had a higher number of complaints of itching (Figure 27.4). This provides an indirect indication that the itching experienced by these women may be caused by other biochemical mediators associated with itch (65) and/or other stimuli, such as dryness. Several roles have been identified for histamine that are related to sexual function (64). Histamine receptors are important in the brain areas involved in sexual arousal (66). As a neurotransmitter, histamine levels are related to sexual desire (67); a decrease in histamine causes a decrease in sexual desire, and an increase causes the reverse. Histamine has local effects on the smooth muscle and blood vessels that are critical to physiological sexual arousal (68). In women, this involves an increase in clitoral cavernosal artery inflow and an increase in clitoral intracavernous pressure, which leads to tumescence and extrusion of the clitoris (67). Engorgement of the genital vascular network increases pressure inside the vaginal capillaries and results in lubrication of the epithelial surface of the vaginal wall (67). Histamine also causes the sexual flush that occurs during arousal. Orgasm is triggered when histamine is released from the mast cells in the genitals. For some women who fail to achieve sexual pleasure and orgasm, the problem may be a result of a biochemical imbalance related to histamine and histidine. Further, histamine may be an important biomarker of genital tissue health with regard to blood perfusion and sexual function.

CONCLUSION

Sensitive skin is a real phenomenon affecting a large proportion of the population, and it is becoming increasingly clear that individuals can have different perceptions about the sensitivity of their skin based on anatomic site. For women, sensitive skin of the genital area can have an adverse impact on daily life and activities. Aging can contribute to the prevalence and symptoms of sensitive skin due to the normal changes that occur in epidermal structure and function. Added to that, aging results in an increased likelihood of incontinence among women and the inevitable onset of menopause.

As the population ages, it will become increasingly important to understand the phenomenon of sensitive skin in order to develop effective therapies for those who suffer from it. We are only beginning to understand the physiological basis for this condition. Painstaking evaluation of the physical and biochemical properties of sensitive skin is a next step in illuminating the mechanisms and causes of this condition.

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Dermatotoxicology of the vulva

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INTRODUCTION

Vulvar toxicology is a unique subject because the vulva contains skin with specialized functions and a unique morphology. The skin of the vulva exhibits a higher degree of hydration, increased permeability, and is prone to irritation as manifested by edema, erythema, and/or corrosion (1–3). It is also the recipient of increased blood flow compared to skin on other sites of the human body (4), which can lead to altered absorption of, and reaction to, topical medications and other products applied to the area. Because of these characteristics that are particular to the vulva, its skin is subject to higher sensitivity to toxicities, leading to dermatitis. On the other hand, despite its increased risk of dermatitis, the vulvar skin is pigmented, located in an occluded area, and structurally unique, thus visually presenting dermatitic symptoms such as erythema in a widely varied fashion amongst different patients. This makes diagnosis via physical examination and visualization difficult and inconsistent, often presenting a conundrum for the physician trying to discover the etiology of the dermatitis and make the correct diagnosis.

PROPERTIES OF VULVAR SKIN

The vulva has unique skin properties that may predispose it to increased irritation and dermatitis. Embryologic developmental differences contribute to the distinct qualities of vulvar skin. The vulvar mucosa is nonkeratinized, originating from the embryonic endoderm, whereas the keratinized cutaneous epithelia of the surrounding mons pubis, labia, and clitoris, is derived from the embryonic ectoderm (5,6). The vulva is subject to increased water loss and permeability to water, suggesting that vulvar skin is a less complete barrier and is more prone to adversely react to certain irritants. The stratum corneum functions to retain water for the skin. The vulvar skin stratum corneum is thinner than other parts of the body, measuring 0.02 µm compared to 11.2 µm on the forearm, supporting the idea of its decreased barrier function. The vulva's increased water loss, and thus permeability to water, is shown objectively by transepidermal water loss (TEWL) measurements by an evaporimeter. Mean TEWL in the vulva is higher at 1.42×10^3 g/m²/h compared to the lower measure of 8.68×10^2 g/m²/h in the forearm (7). However, in other circumstances, the vulva skin has been observed to better adapt than forearm skin to other irritants, such as menses blood (8). Hence, it is important to recall that the unique vulvar skin can show itself to be more or less prone to irritation in different situations.

The amount of skin surface water loss is subject to more "bursts" (or varied increases) in the vulvar skin versus forearm skin. This varied water loss may be affected by occlusion and eccrine sweating on the vulvar skin, as in vulvar skin folds occluding on itself or garment occlusion. This variation can lead to data assessment complications in vulvar skin irritation studies (9). Researchers have tried to control the occlusion factor on the vulva by drying out (via a desiccation chamber to absorb evaporated water) and comparing the capacitance (measure of skin hydration) of vulvar and forearm skin, as measured by a capacitometer. Differences in TEWL and capacitance between forearm and dried vulvar skin were lessened but still apparent, suggesting that occlusion alone does not explain the vulvar skin's higher TEWL and that there are biological differences inherent in the vulva (10).

The vulva's higher capacitance, or skin hydration, leads it to have a higher friction coefficient, µ, which can be measured by the Newcastle Friction Meter. The vulva has a higher friction coefficient at 0.66 ± 0.03 compared to the forearm at 0.48 ± 0.01 (11). This higher friction coefficient leads to increased vulva skin friction irritation from mechanical trauma such as occlusion, clothing, sexual activity, and moisture occlusion from incontinence, which increases skin moisture, resulting in an even higher friction coefficient (11,12). Manufacturers currently do conduct testing models, such as the behind-the-knee test, to predict vulvar tolerance to new products (i.e., sanitary pads or other products that come into contact with the vulva) (13–16). On the other hand, an advantage of vulvar skin is that cold, dry conditions may not affect it as much secondary to its increased hydration and occlusion (15). Notably, the higher incontinence-related friction coefficient comes even more onto the front stage in postmenopausal women who suffer from vulvar skin atrophy in addition to incontinence issues, predisposing them even more to increased vulvar irritation and dermatitis (6). There is a new consensus terminology, genitourinary syndrome of menopause, which more accurately encompasses the postmenopausal physical changes that lead to vulvar symptoms in said patients (17). Vulvar symptoms affecting patient quality of life, such as irritation, itch, dryness, and dyspareunia, continue to be clinically problematic to treat (18). There appears to be a novel treatment approach for severe vulvar itching associated with vulvar irritation: a ventral lateral cordotomy relieved the sensation of itch mediated through the spinothalamic tract (19).

The vulvar skin's higher hydration status (capacitance), higher TEWL, and decreased water barrier make it more permeable to polar irritants like maleic acid and benzalkonium chloride. The vulva has a greater than seven-fold increase in permeability compared to forearm skin. The vulva showed a heightened irritation response compared to the forearm when exposed to the polar irritants maleic acid (20%) and benzalkonium chloride (17%) (1,20). Non-vulvar skin is less hydrated, less permeable to hydrophilic and polar compounds, and more permeable to lipophilic molecules (21). This is the basis for the development of nano-sized drug delivery systems such as

Table 28.1 Unique Vulvar Skin Properties

1. Increased water loss and transepidermal water loss
2. Increased skin hydration capacitance
3. Increased friction coefficient, μ
4. Increased blood flow rate
5. Increased epidermal cell turnover rate
6. Increased skin extensibility

dendritic core-multishell (CMS) nanotransporters (20–30 nm) and solid lipid nanoparticles (SLNs; 150–170 nm) (22). The idea is that skin in much of the rest of the non-vulvar body has hydrophobic-predominant characteristics, and absorption and delivery of hydrophilic drugs may be increased when placed in nano-sized hydrophobic, lipophilic carriers such as CMS and SLN (23–26). However, it is important to recall that the vulvar skin has somewhat opposite characteristics in that it has relatively increased hydration and permeability to hydrophilic compounds, and less to lipophilic ones. Thus, researchers need to bear in mind the unique vulvar skin in the development of nanoparticle drug delivery systems for vulvar skin application, such as antifungals and podophyllotoxin, which can have useful applications in the genital area (26). Clinicians should also consider different exposures in patients from various cultures, who may utilize herbal remedies in the vulvar area. For example, traditional Chinese medicine uses the root of *Sophora flavescens* as an anti-vulvar swelling treatment (27). The vulva may also be subject to unique effects from environmental and product exposures. Allyl bromide is used as a starting material/chemical intermediate in organic synthesis and as an intermediate in the manufacturing of polymers/resins, synthetics perfumes, pharmaceuticals, and agricultural chemicals. Animal studies have shown a marginal increased incidence of squamous cell papillomas of the vulva (28), which should alert manufacturers to take care in selecting the chemical products they include in the production of consumer products that contact vulvar skin.

The vulvar skin has a higher blood flow and epidermal cell turnover rate compared to forearm skin (29). This may aid in its faster healing properties when comparing tape-stripped vulvar and forearm skin (30). Vulvar skin also shows higher extensibility without a comparable increase in elastic fiber network and retraction, which is likely needed in the physiologic changes that are necessary in childbirth (21,31). These unique properties most likely contribute to the vulva's ability to facilitate childbirth and postpartum healing, but may also predispose it to increased susceptibility to irritation. There continues to be the need for ever-vigilant awareness, correct diagnosis, and management of chronic/recurrent vulvar irritation conditions such as lichen sclerosus, lichen planus, and lichen simplex chronicus. These conditions can cause chronic or recurrent vulvar irritation, itching, burning, and pain (32). Additionally, menopausal vulvovaginal atrophy continues to have a large impact on patients' quality of life, including dyspareunia, urinary frequency and urgency, and urinary tract infections (Table 28.1) (5,33).

ASSESSMENT OF VULVAR SKIN PROPERTIES AND IRRITATION

There are various methods of assessing the vulvar skin properties described above. Visual examination and scoring of vulvar irritation is one way, but it may be less sensitive and less able to capture all cases of vulvar skin irritation, especially low-grade dermatitis. The visual scoring system ranges from 0 to 4: normal skin, 0; slight redness, spotty, or diffuse, 1; moderate, uniform redness, 2; intense redness, 3; and fiery erythema and edema, 4 (9,34). This method may not be very sensitive or consistent, as it is operator dependent.

More objective bioengineering instruments have been developed that aid in demonstrating and measuring the unique properties of vulvar skin. Laser Doppler velocimetry can show that blood flow is indeed increased in vulvar skin compared to forearm skin. Monochromatic light is subject to a light frequency change when reflected by moving blood cells, whereas stationary tissue does not show any frequency change. This instrument showed that the basal skin blood flow of vulvar skin was in fact significantly higher than in the forearm (29,34), confirming that this vulvar skin characteristic may aid in its increased healing capacity post-trauma, such as childbirth.

As described before, the vulvar skin has increased TEWL, which is a measure of stratum corneum integrity against water loss. TEWL is measured by an evaporimeter that consists of a hand-held probe that records the amount of water that evaporates from the skin surface while maintaining the skin at a standard temperature. The vulva has increased skin hydration, or skin electrical capacitance, which is an indication of stratum corneum water content. It is measured by a capacitometer, which is a probe applied to the skin with slight pressure for 3 seconds, and the skin capacitance is reported as a digital readout (34).

The behind-the-knee test can assess the frictional effects and mechanical irritant properties of feminine hygiene products that contact the vulvar skin area. Recall that the vulva has an increased friction coefficient and susceptibility to mechanical trauma and skin irritation. Test materials are applied daily to the posterior knee area and held in place for 6 hours by an elastic knee band. Irritation is graded 30–60 minutes after product removal from behind the knee using the four-point visual scoring system. Testing can use dry product on intact skin, dry product on compromised (tape-stripped) skin, wet product on intact skin, and wet product on compromised skin. Studies have shown that two applications of 6 hours each on intact skin are sufficient to ascertain product irritancy level. The test subject's reported sensory complaints, such as pain, stinging, and burning, may be associated with the degree of irritation seen on the objective four-point visual scoring scale (Table 28.2) (13,16).

DERMATITIS OF THE VULVA

Irritant Contact Dermatitis

In terms of overall contact dermatitis of the vulva, a German study in 1998 deemed 24%–38% of noninfectious genital complaints to be vulvar dermatitis (4). Other sources cite an incidence of 20%–30% of vulvar contact dermatitis (4,35,36). Irritant

Table 28.2 Methods of Assessing Vulvar Skin Properties

1. Visual scoring system: skin irritation
2. Laser Doppler velocimetry: blood flow rate
3. Evaporimeter: transepidermal water loss and skin integrity against water loss
4. Capacitometer: skin hydration
5. Behind-the-knee test: frictional and mechanical irritation

contact dermatitis (ICD) is a non-immunologic type of contact dermatitis. There are three types of clinical irritant reactions: acute irritant dermatitis, chronic (cumulative) irritant dermatitis, and sensory irritation. Acute ICD results from exposure to a potent irritant and can be thought of as analogous to a chemical burn. Chronic ICD results from cumulative exposures to weak irritants and can sometimes be confused with immunologically based allergic contact dermatitis (ACD) (36), especially upon visual physical examination. Technology in molecular sciences allows for the testing of mRNA from skin cells via tape-stripping in order to help distinguish between ICD and ACD based on the presence of immunologic factors in ACD and the lack thereof in ICD (37,38). Sensory irritation is characterized by a burning and stinging sensation due to an exposure, but is without detectable skin changes. The vulva can experience any of these three irritant reactions. Some chemicals, such as propylene glycol, can cause irritation (ICD) as well as sensitization (ACD) (35,39). Chronic ICD often involves both endogenous and exogenous etiologies. One endogenous factor is obesity, wherein increased skin folds increase moisture accumulation and the friction coefficient. Another endogenous cause involves the irritation of increased moisture and ammonia exposure with incontinence, which can be further worsened when coupled with vulvar skin atrophy in the postmenopausal patient population (6). Notably, there is evidence indicating that 46% of menopausal and perimenopausal women complain of vulvovaginal irritation symptoms (40). Some exogenous vulvar irritants include certain sanitary napkins (41), soaps, clothing, spermicides, and overly enthusiastic hygienic practices using soaps and antiseptic wipes (4,6,35). There are studies aiming to develop anti-HIV vaginally applied microbicides, and there is hope that these will be an effective method of HIV transmission prevention for women globally. However, with what is known about the unique vulvar skin permeabilities and sensitivities, it is important to keep in mind the variable absorption and dermatologic tolerability of these potentially important topical drugs when used in the vulvovaginal skin area (42,43).

Allergic Contact Dermatitis

ACD is an immunologically mediated inflammatory skin reaction to an allergen in a sensitized person. As mentioned before, it is often difficult to differentiate between vulvar ACD and ICD, especially in light of the vulva's specialized, pigmented skin. In the acute ACD phase, vesiculation and severe pruritus can occur and spread beyond the site of contact. The subacute or chronic phase produces more subtle symptoms, such as less severe pruritus and burning, redness, excoriation, scaling, and pigmentation changes with variable lichenification. ACD histology is similar to ICD, though acute cases may produce increased spongiosis (35).

Although there are not yet any widely used, definitive human predictive ACD tests, there are animal model assays for skin sensitization studies that involve guinea pigs and mice. The guinea pig model involves an induction phase where the test substance is exposed to the same skin area, then there is a rest period of at least 7 days, followed by a challenge phase where a virgin skin site is exposed to the test substance and observed for reaction. In mice, the local lymph node assay (LLNA) is used. The LLNA involves an induction phase followed by injecting the mice with a label and then analyzing the draining lymph nodes for activation. Epidermal Langerhans cells are believed to take up antigen absorbed via the skin, travel to the skin area's draining lymph node, and then present the antigen in order to activate T cells, which then differentiate into allergen-responsive T lymphocytes (44,45).

Increased concentrations of allergenic antigens could potentially penetrate the vulvar skin since it has increased permeability and decreased barrier function (TEWL and capacitance), as discussed previously. This increased exposure to allergens may increase the risk of sensitization and ensuing ACD (21). Because of the vulvar skin's special properties and potentially increased risk of sensitization, ACD information from the skin of other body areas, such as the forearm, cannot be extrapolated to the vulva with the utmost confidence. More conservative quantitative risk assessments (QRAs) may be needed when investigating vulvar ACD (45).

The modified human repeat insult patch test (HRIPT) helps take into account the vulvar skin's increased permeability to allergens. In a standard patch test, potential allergens are applied to normal skin on the back for 2 days under occlusion, with readings taken at days 2 and 4 (46). The original HRIPT had nine 24-hour applications of patches with 24-hour rest periods in between during the induction phase. The modified HRIPT increases the cumulative exposure by 67% by increasing the number of applications to fifteen 24-hour patch applications (24 hours daily for 5 days for 3 weeks, with the important rest periods in between to increase test effectiveness), thereby increasing the test sensitivity for evaluating specialized vulva skin. The 5-day repeated steps mimic the use of some products like feminine hygiene products that contact the vulva skin during the approximately 5 days of menses (47,48).

A modified QRA for the induction of ACD is another systematic method that can be used to evaluate the risk of inducing ACD in more highly permeable vulvar skin. QRA has been applied in order to estimate the risk of ACD induction in chemicals that have been shown to cause dose-dependent and threshold effects. The estimated consumer exposure to the potential allergen is compared to a safe reference dose from a clinically or experimentally derived ACD induction threshold. This reference value is obtained by dividing the experimental threshold dose by sensitization uncertainty factors that extrapolate from experimental to consumer exposure conditions. An uncertainty factors range of 1–10 has been proposed in order to further extrapolate from exposed skin to vulvar skin, again to account for its increased permeability characteristics (21).

In a study of 135 vulvar skin symptomatic patients' patch test results, 47% had at least one positive reaction and 29% had a clinically relevant positive result (39). In another study of 50 women with vulvar skin pruritus, 52% had at least one positive patch test, with 16% having one or more relevant allergic positive reactions. Common allergens included cosmetics, medications, and preservatives (36). Fragrance mix positive patch testing occurred in 11%, with clinical improvement of vulvar dermatitis when perfumed products were avoided, such as scented feminine hygiene products. Another 11% of positive patch tests were to product preservatives formaldehyde and its releasers, such as quaternium-15 and 1,3-dimethylol-5-5-dimethylhydantoin (DMDM) hydantoin, which are found in creams and hygiene products applied in vulvar and other areas (49).

There is an abundance of common vulvar allergens available to patients over the counter. These include topical anesthetics used in vaginal preparations such as benzocaine, topical antibiotics such as neomycin, topical antifungals such as nystatin, and topical steroids, not to mention the preservatives often used in these products, as discussed above (2,50).

The ever-rising popularity of herbal remedies opens the door for a new host of potential vulvar skin allergens. Chamomile sensitized 2.9% of patients, arnica 2.1% of patients, and propolis 2.5% of patients. The extent of sensitization potential may depend on herbal dose, purity, and quality (4). Oral ingestion of herbal products may also affect the vulva upon excretion of said products via urination. A patient was found to have patch-tested vulvar skin ACD from drinking huge quantities of peppermint oil-containing herbal tea daily for 6 years straight. Contact with oral tissue may have been too short in duration, or the metabolization of the substance prior to urinary excretion could have caused symptoms in vulvar but not oral skin areas. Nonetheless, once the patient stopped drinking peppermint tea and avoided all other peppermint-containing products, her symptoms improved (51).

Many other consumer products that contact the vulva may contain potential allergens. Dark clothing, such as underwear, can harbor paraphenylenediamine (PPD)-containing dye and formaldehyde, which are known sensitizers. It is interesting to note that there have been many reports of ACD to the PPD contained in dark henna dyes used for temporary skin tattoos (52–54). Although these henna tattoos are usually placed on non-genital areas, one should keep in mind that there are honored traditional tattoos placed in many different body areas, including genital sites, such as in the South Pacific Islands (55). In modern and permanent tattoos, various ink pigments and ingredients have been known to cause ACD and photoallergic dermatitis, to name a few skin reactions (52,56–58). Patients may choose various sites for pigment introduction, in some cases including the genital areas. In cases of the vulvar skin area, one must bear in mind its unique properties that lead to potentially increased sensitization and ACD, in reaction to the myriad of consumer products and procedures used in, on, and around the vulvar area.

Photoirritation and Photoallergic Dermatitis

Photoirritation, or phototoxicity, is a non-immunologic skin irritation requiring an inciting chemical plus light. The skin reaction resembles a sunburn (59). Photoallergic dermatitis is a subtype of photosensitive dermatitis resulting from ultraviolet (UV)-induced excitation or activation of a chemical applied to the skin after a period of sensitization. These reactions are delayed, manifesting days to years after the UV exposure (60). Given the relatively sun-protected location of the vulva, there are few data available describing these reactions.

CONTACT URTICARIA

Non-Immunologic Contact Urticaria

Contact urticaria syndrome is an immediate contact reaction consisting of inflammatory reactions that appear, usually within minutes, after contact with an eliciting substance. The reaction includes wheal and flare with transient erythema, which may lead to eczema. The most common subtype is non-immunologic contact urticaria (NICU), which occurs without prior sensitization. This reaction remains localized, does not spread to become generalized urticaria, and nor does it cause systemic symptoms. The reaction varies from erythema to an urticarial response, depending on dose, surface area exposed, mode of exposure, and the particular substance (61,62). One can test for a substance's potential for causing such immediate reactions by applying the substance to a guinea pig ear lobe, and if it becomes edematous and erythematous, then the substance is capable of causing a contact urticarial reaction. Edema can be quantified by measuring ear lobe thickness changes with a micrometer caliper. Guinea pig ear lobe biopsies characteristic of NICU demonstrate dermal edema and intra- and peri-vascular infiltrates of heterophilic (neutrophilic in humans) granulocytes (62,63).

In humans, the open test can be used to assess for NICU. A total of 0.1 mL of test substance is applied to a 3×3-cm area of skin on the upper back or extensor surface of the upper arm. The area is observed for 60 minutes, looking for edema, erythema, or small intraepidermal spongiotic vesicles typical of acute eczema, denoting a positive result. If the test is initially negative on non-diseased skin, another testing is done on affected skin (62,64). Unfortunately, thus far, there are scant data regarding vulvar skin reactions of this nature.

Immunologic Contact Urticaria

Immunologic contact urticaria is an IgE-mediated reaction consisting of a local wheal and flare, which in some cases escalates into asthma, allergic rhinitis and/or conjunctivitis, anaphylaxis, and, rarely, death. Diagnosis can be made by using the open test method of skin testing, using extremely diluted solutions under strict protocols and precautions (65). Again, little is documented regarding vulvar skin reactions of this type.

CONCLUSION

The vulva contains skin that has a unique morphology and properties, including increased permeability, hydration, friction coefficient, and susceptibility to irritation from some chemicals and physical trauma. However, it also has an increased blood flow, cell turnover rate, and extensibility, making it an ideal skin to allow for childbirth and healing thereafter. The vulva has a unique response to irritants and allergens. Some substances are more permeable on the vulva (relatively more polar and hydrophilic), whereas they are less so on other skin such as the forearm. Some chemicals induce higher irritation on the vulva, while others induce less irritation compared to forearm skin. Future studies and drug and transdermal drug carrier development should consider the vulva's special characteristics and use appropriate testing methods and targeted biochemical properties in assessing and accessing this unique area of skin.

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Allergic contact dermatitis of the vulva

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INTRODUCTION

The anatomy of the vulvar epithelium, as discussed elsewhere in this text, confers a unique susceptibility to both irritant and allergic reactions in response to environmental exposures. Allergic contact dermatitis (ACD) of the vulva is a common condition in the world of women's health, afflicting unfortunate victims with symptoms of irritation, itch, rash, and pain. The onset of such symptoms can provoke not only confusion and frustration, but also anxiety, shame, and fear. Despite the benign and treatable nature of this condition, there is often a reluctance to seek medical attention, and this leads to underreporting and undue suffering by patients. Even so, the reported prevalence of vulvar ACD is high, serving as a testament to the inherent sensitivity of the region and the wide array of environmental exposures that women face every day. While the pathophysiology of this condition is well understood, and diagnosis is typically clinical, successful treatment can often be elusive, requiring ample time, energy, and strict patient compliance to ultimately resolve the issue and avoid recurrence.

PRESENTATION

Contact dermatitis occurs after exposure to exogenous allergens (ACD) or irritants with direct cytotoxic effects (irritant contact dermatitis [ICD]) and is a common diagnosis in vulvar clinics, with reported prevalence rates as high as 54% in this patient population (1). Contact dermatitis can present in acute, subacute, or chronic forms. Severe, acute contact dermatitis can be very painful, with associated bullous lesions and erosions. More chronically, the patient may present with a milder clinical picture, exhibiting simple irritation and erythema. Conversely, the dermatitis could, over time, demonstrate more prominent eczematous qualities including dry, scaly patches and thick plaques with weeping excoriations, fissures, and potential superimposed infection. Due to the variety of factors previously discussed in this text, the vulvar skin demonstrates increased vulnerability to external agents and is thus prone to the development of contact dermatitis (2,3). As a result, patients may develop such a reaction in the vulvar area despite a lack of obvious sensitivity at other exposed skin sites.

Itching is frequently a major feature of ACD, and this can be somewhat helpful in distinguishing it from ICD, in which pain is a chief complaint. Even so, both symptoms can be present in either disorder, so clinical diagnosis cannot be made simply by the presence or absence of itch or pain. Visually, ACD characteristically demonstrates edema, erythema, and possible vesicular eruptions or bullae with serous weeping and crusting. Since the skin of the vulva is particularly thin, edema may be more striking here than in other involved areas of the body.

Poison ivy is a well-known cause of ACD for many individuals and can present with pruritic vesicles in linear or geometric configurations corresponding to the direction of contact made with the plant. Similarly, the vesicular eruptions sometimes seen in vulvar ACD can assume such geometric arrangements aligning with the direction of allergen spread by the patient's fingers or by contact with the environmental allergen source. For instance, round patches of dermatitis may relate to the circular motion used to apply an offending cream or ointment, or parallel linear streaks of dermatitis may highlight the paths of swiping fingers bearing an allergen.

When chronic, ACD may manifest with scaling plaques and variable amounts of lichenification, erythema, and hyperpigmentation. African–Americans and others of dark complexion are less prone to vesicular responses, with hyperpigmentation often serving as a predominant feature that is able to conceal any existing erythema (4). As such, a lack of these elements in skin of color should not distract from the diagnosis. Beyond appearance, the timing and duration of symptoms are also important to consider. Individuals with recurrent, short bouts of itching, for instance, may be experiencing episodic exposure to an allergen, while those with more constant symptoms could have a stable allergen associated with their clothing or their everyday environment.

Lichen simplex chronicus (LSC) is a condition that can often develop alongside pruritic vulvar contact dermatitis as a direct result of the patient's incessant scratching. Such repeated trauma induces lichenification of the vulvar skin, with a thickened appearance, accentuation of skin markings, and scattered excoriations. Once LSC has developed, it causes pruritus even without an alternative source, thus encouraging further scratching and continued worsening of the LSC in what is known as the itch–scratch cycle. This condition may disturb the appearance of the primary contact dermatitis, turning what may have begun as an erythematous, vesicular eruption into a series of hyperpigmented plaques.

CAUSES

Both ICD and ACD result from the exposure of vulnerable skin to an external agent, and the list of potential allergens is even longer than the lengthy list of known vulvar irritants (see Table 29.1) (5–20). With such a large number of suspects, identifying the responsible agent in ACD can be a difficult task to tackle. Allergens can be found in certain types of creams, detergents, soaps, wipes, perfumes, or other commonly used products. Topical remedies are a prominent source of vulvar ACD, and major culprits include topical anesthetics (e.g., benzocaine), corticosteroids, antibiotics (e.g., neomycin), and herbal extracts (21,22). Reaction to a topical medicament does not necessarily

Table 29.1 Common Vulvar Exposures

Potential vulvar irritants Certain types of:	Potential vulvar allergens Certain types of:
Sexual products: lubricants, condoms, diaphragms, spermicides, arousal stimulants	Fragrance: cinnamic aldehyde, cinnamic alcohol, hydroxy-citronellal, balsam of Peru, eugenol, isoeugenol
Body fluids: urine (ammonia), feces (digestive enzymes), vaginal discharge, sweat, semen	Douches: oil of eucalyptus, oxyquinoline, thymol, fragrance, benzethonium chloride, phenyl mercuric acetate, methyl salicylate
Feminine hygiene products: douches, feminine wipes, sanitary pads/napkins, panty liners, tampons, deodorants, lotions, powders, perfumes, shampoos, soaps, bubble baths, sodium lauryl sulfate	Anesthetics: esters (tetracaine, procaine, benzocaine), amides (bupivacaine, lidocaine, dibucaine), diphenhydramine, crotamiton
Topical medicaments: antifungals, anti-itch creams, antibiotics, Vitamin A&D ointment, tea tree oil, alcohol-based creams or gels, cantharidin, 5-fluororacil, imiquimod, phenol, podophyllin, bichloroacetic acid, trichloroacetic acid	Antiseptics: thimerosal, chlorhexidine, gentian violet, phenylmercuric salts, mercuric chloride, povidone iodine, chlorination and bromination (pools and spas), chlorocresol
Laundry: detergent, bleach, fabric softener	Antibiotics: sulfonamides, polymyxin, neomycin, bacitracin
Physical irritants: tight-fitting clothes, nylon, latex, wash cloths, sponges, hot water, excessive washing, vigorous drying with towel, hair dryer (on hot), shaving and waxing	Antifungals: nystatin, imidazoles (itraconazole, miconazole, clotrimazole, etc.), chlordantoin
	Preservatives: parabens, formaldehyde releasers (imidizolidinyl urea, diazolidinyl urea, quaternium 15), stearyl alcohol formaldehyde, bronopol, kathon, propylene glycol
	Rubber (pessaries, diaphragms, condoms, gloves, etc.): latex, thiurams, mercaptobenzothiazole
	Spermicides: oxyquinoline sulfate, quinine hydrochloride, hexylresorcinol, nonoxynol, phenylmercuric butyrate, phenylmercuric acetate
	Corticosteroids: all of them
	Emollients: propylene glycol, glycerin, lanolin, jojoba oil
	Nail polish: sulfonamide, formaldehyde resin, toluene
	Sanitary wipes: fragrance, methacrylates, acetyl acetone, formaldehyde, dyes (e.g., colored toilet paper)
	Body fluids: saliva, seminal fluid
	Metal (jewelry, buttons, etc.): gold, nickel, palladium
	Plants: urushiol (poison oak/ivy/sumac), peppermint oil

Source: Adapted from Braitman M. *AMA Arch Dermatol Syphilol* 1952; 65(6): 727; Salim A, Powell S, Wojnarowska F. *J Obstet Gynaecol* 2002; 22(4): 447; Margesson LJ. *Dermatol Ther* 2004; 17(1): 20–7; Schlosser BJ. *Dermatol Clin* 2010; 28(4): 697–706; Trager JD. *J Pediatr Adolesc Gynecol* 2005; 18(4): 275–80; Epstein E. *Obstet Gynecol* 1966; 27(3): 369–70; van Ulsen J et al. *Contact Dermatitis* 1987; 17(2): 115–6; Vermaat H et al. *Contact Dermatitis* 2008; 58(6): 364–5; Eisner P, Wilhelm D, Maibach HI. *J Am Acad Dermatol* 1990; 23(4 Pt 1): 648–52; Giroux L, Pratt MD. *Am J Contact Dermat* 2002; 13(3): 143–5; Guillet G, Dagregorio G. *Contact Dermatitis* 2004; 50(5): 318–20; Wilhelm D et al. *J Reprod Med* 1991; 36(8): 556–60; Williams JD, Frowen KE, Nixon RL. *Contact Dermatitis* 2007; 56(3): 164–7; Bauer A, Geier J, Elsner P. *J Reprod Med* 2000; 45(8): 649–54; Coopman S, Degreef H, Dooms-Goossens A. *Br J Dermatol* 1989; 121(1): 27–34; O'Gorman SM, Torgerson RR. *Dermatitis* 2013; 24(2): 64–72.

indicate allergy to the product's active ingredient, as sometimes allergens might unknowingly be part of preservative systems or other inactive components. Examples of such unnoticed offenders include foaming agents such as sodium lauryl sulfate, parabens found in topical antibiotics, and the stabilizer, ethylenediamine, previously used in antifungal creams of the 1970s and 1980s. Scents like "fragrance mix" and balsam of Peru have also been incriminated as inducers of ACD (23).

The anesthetic benzocaine can be considered a "dirty" allergen, as it is known to cross-react with a variety of other compounds including aniline dyes, sulfa drugs, para-aminobenzoic acid, and paraphenylenediamine. With this in mind, a history of sulfa or hair dye allergy can be useful in suggesting possible ACD in patients with vulvar symptoms who are using a benzocaine-containing product (24,25). Several over-the-counter products, including yeast infection treatments and various hemorrhoid and wart preparations, contain benzocaine, meaning patients have free access to this common allergen and are frequently applying it to the vulvar region.

Many individuals exhibit allergy to inorganic compounds in their environment, including metal. Nickel allergy is a common example of such, and atopic reactions can certainly present in the vulvar region after exposure to nickel-containing products like razor blades, jewelry, and buttons on clothing. Contact can even occur by finger transmission after handling these items or other external nickel sources. Surprisingly, nickel may even be found in some toilet papers made from certain recycled paper (21,26), a fact that highlights how allergens can unknowingly make their way into our everyday lives. Other culprits may more readily be identified, such as those exposures that are specific to the vulva. Examples include certain types of tampons, moist wipes, sanitary pads, over-the-counter creams intended for vulvar symptoms or yeast infections, and sexual products like spermicides, lubricants, condoms, and sex toys (5–7,27,28). Colored dyes can elicit ACD through overt exposure with lotions or underwear, or more discreetly through contact with colored wipes or toilet paper (8).

While topical corticosteroids are regularly used in the treatment of various vulvar dermatoses, it is important to consider their propensity for inducing ACD themselves (Table 29.2). For patient's suspected of having a corticosteroid allergy, positive patch test rates as high as 10.7% have been reported, with some subjects adversely reacting to several different steroids (29). In 1989, Coopman et al. (22) classified corticosteroids into four groups based on patch test results and chemical structure: (A) hydrocortisone type; (B) triamcinolone acetonide type; (C) betamethasone type; and (D) hydrocortisone-17-butyrate type. Others have since expanded upon these initial listings, and group D was later subdivided into two groups, D1 and D2, based on the presence or absence of a C16 methyl substitution or halogenation on the C9 of the B ring. Corticosteroids within the same group demonstrate high cross-reactivity with each other, as do compounds in group D2 and groups A and B. Groups C and D1 do not tend to cross-react with steroids in other groups and are thus less prone to causing ACD (22,30–32).

Table 29.2 Corticosteroid Allergy Cross-Reactivity

Corticosteroid group	Examples
A	Hydrocortisone (succinate, phosphate, acetate), methylprednisolone (succinate, phosphate, acetate), fludrocortisone, cortisone, cortisone acetate, tixocortol pivalate, prednisone, prednisolone acetate, fluorprednisolone, cloprednol, fluormetholone, fluormetholone acetate, isoflupredone acetate, meprednisone, medrysone
B	Desonide, budesonide, amcinonide, triamcinolone, triamcinolone alcohol, triamcinolone acetonide, flunisolide, acetanide, fluocinomide, halcinonide, fluocinolone, mometasone, flucloronide, procinonide, formocortal
C	Fluocortolone, flucortin butyl, paramethasone, desoxymethasone, dexamethasone (acetate, sodium phosphate, disodium phosphate, isonicotinate, metasulfobenzoate), betamethasone, betamethasone sodium phosphate, beclomethasone hydrochloride, diflorason diacetate, halomethasone
D1	Alclometasone dipropionate, flucortolone caproate, beclomethasone dipropionate, clobetasone-17-butyrate, clobetasol-17-propionate, betamethasone (valerate, dipropionate), diflorasone diacetate
D2	Methylprednisolone aceponate, prednicarbate, fluticasone propionate, mometasone furoate, hydrocortisone (aceponate, buteprate, 17-butyrate, 17-propionate, 17-valerate)

Source: Adapted from Eason EL, Feldman P. *CMAJ* 1996; 154(8): 1173–6; Jacob SE, Steele T. *J Am Acad Dermatol* 2006; 54(4): 723–7; Morren MA, Dooms-Goossens A. *Clin Rev Allergy Immunol* 1996; 14(2): 199–208; Torres MJ, Canto G. *Curr Opin Allergy Clin Immunol* 2010; 10(4): 273–9.

PATHOPHYSIOLOGY

As previously established in this text, some women self-declare as having sensitive genital skin, and this intrinsic vulnerability might increase the risk of a number of pathologic processes, including heightened immunoreactivity to external exposures. Unlike ICD, which is a condition resulting from exposure to substances with direct cytotoxic effects on the epithelium, ACD is a type IV delayed hypersensitivity reaction involving antigen-presenting Langerhans cells stationed within the epidermis. These dendritic cells interact with antigens at the skin surface, sampling and processing them for transport to nearby lymph nodes. Within the lymph nodes, antigens are presented to T lymphocytes, inducing antigen-specific T-cell proliferation and ultimately resulting in the production of inflammatory cytokines. As this immune process requires time to unfold, it may take 48–72 hours after allergen exposure for physical symptoms to appear. Considering this significant delay, it is not hard to see why confident identification of the responsible allergen is often difficult to achieve.

Histopathologically, acute ACD demonstrates prominent spongiosis with a predominantly perivascular dermal infiltrate of eosinophils, lymphocytes, and histiocytes (33). Eosinophils and lymphocytes additionally exhibit exocytosis upwards into spongiotic foci within the epidermis (see Figure 29.1). Sub-acute ACD displays moderate spongiosis, acanthosis, and a denser lymphohistiocytic infiltrate within the dermis. When chronic, spongiosis becomes much less prominent, often appearing only focally with scant inflammatory infiltrate. Epidermal acanthosis becomes the main feature, complimented by hyperkeratosis and scattered areas of parakeratosis. As with the macroscopic appearance of the condition, the overlap with ICD is extensive, and histologic differentiation is often not possible (and usually not clinically necessary).

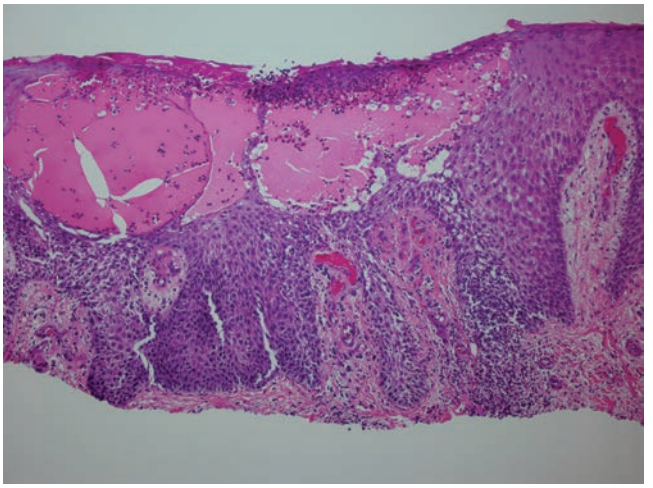

Figure 29.1 A hematoxylin and eosin (H&E)-stained histologic section of vulvar allergic contact dermatitis demonstrates epidermal spongiosis with mild acanthosis and scattered intraepidermal vesicles containing eosinophils and serum. There is an underlying superficial perivascular and slightly interstitial infiltrate comprising lymphocytes and numerous eosinophils.

DIAGNOSIS

Differential Diagnosis

The frequently eczematous appearance of chronic contact dermatitis must be distinguished from a slew of other vulvar dermatoses, some of which may hold worse prognoses and require more urgent treatment. Conditions on the vulvar differential include seborrheic dermatitis, vulvar psoriasis, LSC, tinea cruris, lichen planus, lichen sclerosis, and atopic/irritant dermatitis. More worrisome possibilities—such as extramammary Paget disease or squamous cell carcinoma *in situ*—should also be considered if the affected area is localized and the clinical picture consistent. As lesions may be more vesiculoerosive in cases of acute contact dermatitis, the differential should expand to include blistering disorders like bullous lichen planus, pemphigus vulgaris, bullous pemphigoid, Hailey–Hailey disease (benign familial pemphigus), erythema multiforme, herpes simplex, erosive lichen planus, and candidiasis.

Making the Diagnosis

While Occam's razor is a general principle in the art of medicine, it is always possible that multiple conditions may be contributing to a patient's presentation. This is important to consider, as effective treatment may necessitate identification

of all underlying processes and every irritating environmental exposure. For example, a patient with lichen sclerosis may be treating herself with a topical steroid that is inducing an ACD on top of her underlying disease. She may also be utilizing an over-the-counter antifungal cream to combat yeast infection while on the topical steroid. This patient may additionally scrub her vulva daily with an abrasive washcloth and a caustic soap filled with fragrances and foaming agents like sodium lauryl sulfate. With this example in mind, it is easy to imagine how complicated a case of vulvar symptoms can be. Though cases are not always this clouded, it is exceedingly common for patients to present with no idea about what exposures and behaviors might be contributing to their symptoms. In such cases, the clinician must act much like a detective to obtain the appropriate information and accurately identify and rank the numerous possible suspects.

In pursuing the diagnosis, a thorough patient interview is imperative. The patient must be questioned about all possible vulvar exposures, with particular focus on those that correlate with the onset of symptoms. As previously discussed, there are a wide variety of products that can cause vulvar ACD and must be reviewed with the patient, including certain types of sanitary pads, topical creams, wet wipes, laundry detergents, soaps, lubricants, powders, ointments, dyes (found in underwear or colored toilet paper), abrasive wash rags, excessively hot water, and more. The questioning should also extend beyond the vulvar region, as the patient may inadvertently be transferring allergens with their fingers from the surrounding environment or from other areas of the body, such as the axilla (some deodorants) or face (certain makeups), or from jewelry (nickel). Even the patient's significant other should be probed, as fragrant body sprays and washes or other common offenders can easily be transmitted during sexual activity.

Sometimes, the initial interview may be relatively fruitless, with the patient only able to recall a few specifics about the products she is exposed to. Other times, the result might be a list of possible suspects that is so long and so broad that determining the specific culprit seems an overwhelmingly difficult task. In such cases, it is necessary to employ an initial filter through which the list may be significantly narrowed. Other than statistics (determining which products are most known to cause ACD), patch testing is one commonly used method of achieving this goal and identifying possible allergens. In patch testing, the physician utilizes a number of different transdermal patches, each containing a specific antigen. The patches are applied to the patient's skin and left in place for several days. The skin is then monitored for local allergic response, with tests best read at 48, 72, and 96 hours. The differential reaction of the patient's skin to each patch helps identify any contact allergies, and this information can be useful in pinpointing the exposure on the suspect list that might be inciting the patient's vulvar dermatitis.

Depending on the study, the detection rate of one or more clinically relevant contact sensitivities varies among women presenting with vulvar pruritus, but it seems to be somewhere around 40%–50% (23,34,35). This suggests clinical utility for patch testing in the work-up of this condition, but allergies can be missed if testing is too narrow in scope. Recommended series include the 50-patch North American Contact Dermatitis Group series, the corticosteroid series, and potentially a preservative and medicament series including medications commonly used on the vulva. Considering the well-known cross-reactivity of various steroids, most cases of corticosteroid-induced ACD can be detected by patch testing with just three steroids: tixocortol pivalate (group A), budesonide (group B), and hydrocortisone 17-butyrate (group D2).

Positive patch tests, while informative, can be misleading and must be interpreted with caution. For example, some preservatives are found in higher concentrations within their respective patch than they are within the actual medications in which they are used. Thus, real-world application of a product might not reach the threshold necessary to cause an allergic response, even if the patient had a positive patch test to a preservative component within that product (36). Additionally, a positive patch test may not be clinically relevant (may not indicate the cause of a patient's vulvar ACD), so the astute clinician should not stop with the first positive result. For instance, one study found nickel to be the most commonly detected allergy in patients with vulvar symptoms, but this was almost never determined to be clinically relevant. By contrast, topical anesthetics, antibiotics, and fragrances were less commonly detected on patch testing but were almost always deemed clinically significant to the patient's symptoms (37).

Patch tests can be used not only to identify particular allergens, but also to determine if the correct diagnosis is, in fact, irritant in nature. For instance, one study used patch testing to investigate 30 cases of vulvar dermatitis that were thought to be allergic reactions secondary to the use of feminine hygiene sprays (38). Despite this notion, only four of the patients had positive patch test results (to various contents of the sprays, including benzethonium chloride, chlorhexidine, isopropyl myristate, and perfume). The experimenters proposed that the majority of these cases were likely ICD in response to the fluorinated hydrocarbons used to propel the contents. They believed patients were increasing their exposure by holding the bottle too close to the vulvar skin when discharging.

In a case of vulvar symptoms, the extent of the patient's rash might be helpful in predicting the usefulness of patch testing, as one study demonstrated a positive patch test rate of 19% in dermatoses confined to the vulva, while 43% of patch tests were positive in patients who had rash involving both the vulvar and perianal skin (39). Other variables may also be useful in predicting the likelihood of positive contact allergy in a patient presenting with vulvar pruritus, including severe pruritus on a self-report scale, sexual inactivity, and use of multiple topical treatments (34). A patient with a history of biopsy-proven vulvar dermatitis is also more likely to return a positive patch test result, though such invasive testing should certainly not be utilized simply to determine if a noninvasive patch test would be worthwhile.

Because the differential can contain more concerning diagnoses such as squamous cell carcinoma, basal cell carcinoma (40), or infection, biopsy and culture might be indicated if the clinical picture fits. Biopsy can be definitive in making the final diagnosis and ruling out the more worrisome possibilities, but should only be utilized after exhausting all less-invasive diagnostic and treatment options (or if clinical suspicion for malignancy is high). As previously mentioned, ICD and ACD can appear histologically similar, so this distinction may not be a guarantee, but the importance of excluding serious diagnoses is paramount. Even with a perfect biopsy, background inflammation can cloud interpretation of the sample. If the diagnosis remains uncertain after the initial biopsy, it may be appropriate to repeat the biopsy once the background inflammation has subsided with treatment, particularly if a suspicious lesion remains (9).

Secondary infection with bacteria, viruses, or fungi can occur, and clinical manifestations of such include fissuring, crusting, and pustules. Bacterial and fungal cultures can be performed on contents collected from unroofed pustules, as can potassium hydroxide microscopy for fungal elements. With vesicular eruptions, a Tzanck smear may be indicated to rule out possible herpes. Appropriate oral antimicrobial therapy should follow if infection is suspected. While topical options may be available, these may further contribute to allergic reaction and should thus be avoided.

MANAGEMENT

Effective treatment of vulvar contact dermatitis is often challenging, sometimes requiring a multidisciplinary approach involving gynecology, dermatology, psychology/psychiatry (for emotional and sexual support), and possibly physical therapy (if secondary spasms of the pelvic floor muscles are an issue) (41). The first and often most difficult step for the patient is complete elimination of all possible external offenders in order to determine which habits and practices or products might be contributing to the condition. This may require dramatic modifications to the patient's lifestyle, including changes in daily routine, sexual practices, and shopping habits. To demand so many sacrifices in the patient's everyday life can be overwhelming and can induce significant distress, potentially serving as a potent barrier to patient compliance. To avoid this outcome, anxiety should be anticipated and addressed as much as possible at the start of treatment in order to allow the best chance for symptom resolution.

Vulvar Skin Care Guidelines

The vulvar skin care guidelines were established to provide a general outline that would enable an individual to effectively decrease vulvar contact with known allergens and irritants, including chemical products, friction, occlusion, and natural moisture. Advice is wide in scope, calling for alterations in personal hygiene, birth control, bathing, laundry, and clothing. Loose-fitting clothes are recommended to avoid excessive friction and occlusion, with particular avoidance of tighter apparel, like pantyhose, being advised. Pure cotton underwear is preferred over those made with synthetic material, and, in fact, no underwear should be worn when sleeping, as this facilitates ample aeration and decreased occlusion throughout the night. Until the particular allergen can be distinctly identified, patients should be advised to discontinue use of all fragrant products, including soaps, detergents, lotions, and dryer sheets, and they should also take care to avoid dyes when possible.

Though the patient may find comfort in a steaming shower, excessively hot water can be a significant irritant and should be avoided when showering or bathing. Gentle washing of the vulva is preferred to avoid damaging the skin, and this should be done with the hand alone and not with a rag or sponge. There should be no soap used on the vulva, only water, and the area should be gently patted dry with a towel or dried with a hair dryer on its cool setting. As shaving can irritate and damage the sensitive vulvar epithelium, this practice should be ceased. Trimming or clipping of the area is a better alternative, as the blades do not have as direct contact with the skin as with a traditional razor. If the patient refuses this recommendation, it can still be beneficial to recommend using a razor made with titanium as opposed to one that may contain nickel (given the possibility of nickel allergy).

While artificial lubricants are commonly used in sexual practice, there are plenty of natural substances that can serve the same role without the propensity for irritation. Lubricated condoms should be avoided, and artificial products should be substituted with more natural lubricants like coconut oil, olive oil, or vegetable oil. Zinc oxide ointment or petrolatum jelly can be applied to the vulva to shield from common environmental exposures like sweat, blood, and urine. Powders like Gold Bond® or Zeasorb® are useful for those who struggle with excessive dampness in the vulvar region, and they can be sprinkled once or twice daily in the underwear for increased moisture absorption. As always, fragrant options like baby powder should be avoided, as should those containing cornstarch.

While these guidelines are broad in scope and will undoubtedly result in the elimination of a number of benign vulvar exposures that are not causing harm, the notion is that the offending agent will almost certainly be amongst the horde. Once this notion is confirmed by clinical resolution of the contact dermatitis, products and exposures can be reintroduced one at a time on a weekly or biweekly basis to allow for recognition of symptom recurrence and easy correlation with a specific allergen or irritant.

Medical Intervention

While the appearance of vulvar contact dermatitis can be dramatic, the symptoms—burning, itching, and weeping—are often the main source of patient distress. With this in mind, patient satisfaction will best be achieved with adequate symptom control as the chief priority. Furthermore, symptom abatement will facilitate a better emotional state for the patient—a necessity if the patient is to effectively enact and maintain the dramatic lifestyle changes that are vital for cure.

Incessant itching is a common and often maddening complaint for many patients with ACD. As over-the-counter antihistamines can block the underlying immune process causing itch, these medications can be beneficial in ACD and should be utilized as indicated (42). Non-sedating options—like loratadine (Claritin®), fexofenadine (Allegra®), or cetirizine (Zyrtec®)—are best used in the morning and afternoon, while sedating antihistamines—including hydroxyzine (Vistaril® and Atarax®) or diphenhydramine (Benadryl®)—can be used at night to facilitate sleep. Mitigating itch is important for patient satisfaction and is also vital in the healing process, as repetitive scratching will only further damage the epithelium and will propagate the itch–scratch cycle of comorbid LSC, if present.

For pain control, non-steroidal anti-inflammatory drugs or acetaminophen should be recommended as first-line agents, as this circumvents the addition of a topical medication that may serve as an irritant or allergen. Application of cold compresses can suppress both itch and pain, but it is important to avoid excessive cold that can lead to frostbite. Though more time consuming, sitz baths may also be significantly comforting and can be utilized one to two times a day, as desired. Liberal use of topical petrolatum or zinc oxide may soothe the vulvar skin while additionally serving as a barrier to further exposures.

If pain is not adequately curbed with the above interventions, prescription topical anesthetics like lidocaine or combined lidocaine/prilocaine can be effective. While topical anesthetics are actually a major source of ACD, this most commonly occurs with ester anesthetics like benzocaine, and less

often with amides like lidocaine or prilocaine (21,23,29). The benzoic acid group is perhaps the key culprit, as other benzoate-containing anesthetics like amethocaine (tetracaine) and procaine (Novocain®) are also known to cause contact dermatitis (24). Even so, allergic reactions and symptoms like stinging and burning still do occur with amide anesthetics, so avoidance of all topical anesthetics is preferred if pain can be controlled through other methods.

If pain is persistent, systemic, neuropathic pain medications have been used with benefit. These include drugs like anticonvulsants (e.g., pregabalin and gabapentin) and tricyclic antidepressants (e.g., nortriptyline, amitriptyline, and desipramine) (43,44). Gabapentin is a relatively safe medication, and can be started at 300 mg daily and titrated over the first week up to 300 mg three times a day (TID). The target range is 300–1200 mg TID, so the dose can be increased if necessary until pain control is obtained. The tricyclic class carries more risk, including anticholinergic, antihistamine, and anti-α1 adrenergic effects. As such, tricyclics may be considered as second-line agents to anticonvulsants for pain management.

As a tricyclic, amitriptyline should be titrated up from a low starting dose in order to minimize the risk of side effects. Beginning at 5 mg daily is reasonable, with a gradual increase to a target of 150 mg. As amitriptyline is known to cause sedation, its less-sedating cousin, desipramine, may be a viable option for those experiencing this problem. The therapeutic range for desipramine is 125–150 mg, and gradual up-titration is likewise recommended (43). Duloxetine and venlafaxine are examples of selective serotonin and norepinephrine reuptake inhibitors (SNRIs), which have similarly demonstrated efficacy in treating vulvar pain. Some providers even combine a SNRI with an anticonvulsant for increased benefit (43). While SNRIs tend to be pricier and are more predominantly used in depression, they serve as another viable option for pain if tricyclic antidepressants are not doing the trick. As a testament to this, the Food and Drug Administration has actually approved duloxetine for the treatment fibromyalgia and neuropathic pain. A cited effective dose for this purpose is 60 mg once daily (45).

In addition to symptom control, the skin barrier insufficiency and underlying inflammation of vulvar ACD must be addressed. In addressing the first of these issues, the previously outlined vulvar skin care guidelines should go a long way to preventing further irritation and allowing for healing. In a postmenopausal patient with tissue atrophy secondary to low estrogen, replacement via topical, intravaginal (tablets or an estrogen-releasing ring), or oral estrogen preparations can help refortify the thinned skin barrier (41). Emollients are also beneficial, as they soften and attract water to the stratum corneum while simultaneously decreasing transepidermal water loss (TEWL) (46).

Occlusive emollients (e.g., petrolatum, mineral oil, lanolin, beeswax, vegetable oils, silicones, and ceramides) decrease TEWL, while humectants (e.g., sorbitol, glycerin, sodium lactate, urea, and propylene glycol) are hygroscopic substances that serve to attract water to the stratum corneum from the atmosphere and from the deeper skin layers (46). For maximum benefit, many products (e.g., Cetaphil® Cream, Aveeno® Moisturizing Cream, and Eucerin® Original) combine humectants with occlusive emollients. Liberal application multiple times a day is recommended, as benefits are only reaped while the emollient is on the skin.

In general, if topical medications of any kind are to be used on the vulva, ointments are preferred over creams, as they are better absorbed, less irritating, and also act as an emollient. While topical steroids can be the source of allergic symptoms in some individuals, they may also be the key to relieving them. Particularly in those with more severe manifestations, such as vesicular eruptions or thickened plaques, attempting treatment with topical steroids can be useful to curbing the underlying inflammation. The steroid should be applied twice a day, and the selected potency should correspond to the severity of disease. Over-the-counter hydrocortisone 1% is the weakest of choices, and often patients have already exhausted this option and are in need of something stronger by the time they seek out help. The rest of the spectrum consists of low-potency hydrocortisone 2.5%, a step up to mid-potency triamcinolone acetonide 0.1%, and high-potency clobetasol propionate 0.05% or halobetasol 0.05% as final resorts. Other options are also available at each potency level.

A common reason for treatment failure is selection of a steroid that is too weak and/or applied too infrequently, and this is partially due to the unique adaptability of the vulvar skin (41). In fact, this adaptability is not consistent throughout the vulvar region, and steroid potency may need to vary depending on the specific location of the lesions being treated. The epithelium of the vestibule is particularly resistant to steroids and may require high-potency medications, while the surrounding skin of the labia majora and perianal/perineal areas is more sensitive and better suited for lower-potency steroids (41). No matter what medication is initially selected, steroid potency and frequency of application should be decreased in correlation with disease severity in order to prevent excessive skin thinning.

Systemic steroids may be needed to treat vesiculoerosive disease or other particularly severe cases of ACD. A common regimen includes 40–60 mg (or 0.5–1 mg/kg) of oral prednisone daily, given as a 14- to 21-day taper. An alternative is to administer 1 mg/kg of triamcinolone acetonide as a one-time intramuscular injection. While this latter option is simpler for the patient and may achieve better compliance, it forgoes the ability to discontinue treatment if adverse effects arise. Intralesional injection of steroids can be useful for thick lesions and patches of deep inflammation that remain unresponsive to topical treatments (41). Triamcinolone acetonide 10 mg/mL can be employed as a 1-mL injection to help thin out a persistent plaque, and another injection may be administered at a future date if necessary. For more of an anti-inflammatory effect, the triamcinolone can be diluted with saline and given as a 3.3-mg/mL injection. This can be repeated every 6 weeks as long as local adverse effects like hypopigmentation and atrophy do not arise.

While corticosteroids are not required by all patients with vulvar ACD (sometimes symptoms are mild and exposure avoidance is all that is needed), they are a common component of ACD treatment for many patients, and, in such cases, anticipation and prevention of common side effects are imperative. As steroids are immunosuppressant agents, the risk of infection increases with use, both locally with topical preparations and systemically with oral or injectable treatments. Yeast infections of the vulva and vagina are particularly prominent consequences in women. Prophylaxis may be recommended in this population, typically with oral fluconazole 150 mg once a week. Topical antifungals are reasonable alternatives to systemic therapy, but they are cumbersome for the patient and may induce ACD. As such, they are not the ideal mode of prophylaxis.

Due to the frequently chronic nature vulvar dermatitis, and considering the side effects of long-term topical steroid

use, some have sought an alternative option for the treatment of such patients. One study investigated the efficacy of a topical medication formulated from natural active ingredients extracted from plants (47). The product, known as Zantogin®, contains 18β-glycyrrhetinic acid, levomenol, zanthalene, curcumin, tea tree oil, and lactic acid. When compared with a placebo treatment (containing only tea tree oil and lactic acid), Zantogin® resulted in complete symptom relief in 85% of treated patients, with only 15% requiring supplemental (average of three applications over 60 days) mometasone furoate 0.1% to maintain good control. In comparison, 90% of subjects in the placebo group required additional mometasone furoate 0.1% for adequate symptom control, with an average of 16 applications per patient over 60 days. Zantogin® and other similar formulations may thus be viable options for the treatment of chronic vulvar dermatitis in order to decrease long-term use of topical corticosteroids while still effectively mitigating inflammation and itch.

CONCLUSION

ACD is a prominent entity in clinical practice, representing one of the most common reasons for why women present with vulvar pain and pruritus. While the natural history of this condition is benign, the negative impact on quality of life can be drastic. Because of the sensitive nature of vulvar symptoms, patients are often unwilling to offer up complaints on their own. For providers caring for these patients, it often takes a thorough interview and physical examination to uncover the problem, and a non-judgmental disposition and good patient rapport are helpful to encourage further discussion.

The primary goal of ACD treatment is to identify and eliminate the responsible environmental exposure(s) eliciting symptoms. While this formidable undertaking is pursued, relief can be obtained through mitigation of inflammation—utilizing corticosteroids and other means—and restoration of the compromised vulvar epithelial barrier. Successful resolution and subsequent prevention of ACD often requires the patient to make major adjustments in their lifestyle, but the end result is typically well worth the sacrifices.

For practitioners, realizing the prevalence of vulvar ACD will go a long way to facilitating improved recognition of affected individuals. A good understanding of the underlying pathophysiology will enable providers to offer proper education and counsel to their patients dealing with this common condition. Combined with a basic grasp of vulvar ACD treatment principles, clinicians can make huge strides in relieving the suffering of many women to come.

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Bioengineering methods for the vulva

Sibylle Schliemann, Britta Opper, and Peter Elsner

INTRODUCTION

Noninvasive bioengineering methods permit the sophisticated detection and quantification of subclinical changes in skin physiology. Some methods have become standard in specialized fields such as skin pharmacology, cosmetology, and dermatological research. However, their application can also be beneficial when studying the female genital area. Human vulvar skin is an example of specialized skin, comprising keratinized epithelium and nonkeratinized mucosa, accompanied by considerable underlying age- and hormone-related changes throughout life. Exposure to humidity, occlusion, friction, and a particular microbial environment, coupled with the lack of ultraviolet light exposure, contribute to the vulvar skin's unique functional characteristics, such as its less-complete water barrier function as compared to other body regions (1–3). Garments, shower gels, soaps, moisturizers, deodorants, sanitary pads, as well as condoms may induce subclinical skin irritation or even apparent contact dermatitis (4).

Therefore, enhanced susceptibility of the vulva to irritants might be assumed, but, surprisingly, this has not been ascertained in general by bioengineering clinical studies (2,5). In contrast to apparent conditions such as acute allergic contact dermatitis, lichen sclerosus, or psoriasis, clinical assessment of low-grade vulvar irritation is often difficult due to considerable interindividual variability of normal vulvar skin, which can often include some degree of erythema, even in unaffected women. In addition to simple clinical scoring systems such as that of Frosch and Kligman (which has been used for a long time for the quantification of inflammatory responses and irritation in many experimental settings) (2,6–8), noninvasive bioengineering methods allow researchers to monitor subclinical changes; for example, the inflammatory state and skin blood flow, barrier function, and stratum corneum hydration.

In general, when applying bioengineering methods to female genital skin, a convenient measuring environment free of disturbance is a prerequisite. A trusting relationship between the patient and the investigator must be established in order to minimize artifacts caused by emotional stress. Indeed, even "training" of volunteers may be necessary to achieving reproducible measurements (9). In order to avoid typical pitfalls, it is necessary to become familiar with the technical background of the devices used and perform the procedures in a standardized manner (10). Area recognition is a problem in all noninvasive measurements used on genital skin. Dansyl chloride 1% in petrolatum as a fluorescent marker can be helpful in this regard (7).

COMMON BIOENGINEERING TECHNIQUES

Erythema Quantification—Skin Color Reflectance

The color of the skin, and of any object, depends on the wavelength of the light and the optical characteristics of the surface. Different chromophores, mainly hemoglobin and melanin in healthy skin, absorb different wavelengths of light. Detailed insight into the complex optical principles of the skin and chromophores is provided by Pierard (11) and by Kollias (12). Measurement of skin color reflectance is a suitable method for erythema quantification in addition to clinical assessment. It has been applied frequently in the grading of contact dermatitis and irritant and allergic patch test reactions (13). Its value has also been proven in studies on the vulvar skin with respect to erythema quantification in irritant contact dermatitis (7). Skin color reflectance is especially suitable for serial measurements and can also be used for ethnic skin (14,15). However, the sensitivity of an experienced dermatologist's eye may still be superior to instrumental erythema quantification (12).

In contrast to the spectrophotometric method, which uses broadband (scanning) or selected wavelengths, the Minolta Chroma Meter (Minolta Chroma Meter CR-300®, Minolta, Osaka) is a tri-stimulus colorimeter that follows the recommendations of the Commission Internationale de l'Eclairage. Color is expressed in a three-dimensional coordinate system, in terms of three units: L* (luminance/brightness) (white–black), a* (red–green), and b* (yellow–blue) (Figure 30.1). a* represents the red–green axis with +100 expressing full red and –100 expressing full green (13). The Chroma Meter is equipped with a polychromatic xenon flashlight for the illumination of the skin area and is easy to handle. Prior to measurement, the instrument must be calibrated. As the genital skin color is influenced by the modulations of cutaneous blood flow caused by temperature, orthostatic effects, emotional status, and the intake of drugs or caffeine, measurements should always be performed in a standardized and reproducible setting, following the guidelines thoroughly (13,16). In order to obtain reliable results, the probe should be held to the skin without exerting pressure. Taking the arithmetic means of repeated measurements for analysis is advisable. Baseline L* values of healthy, unaffected vulvar skin were shown to be significantly lower, indicating a higher absorption of light, whereas a* values were significantly higher compared to forearm skin, due to higher basal blood flow at the vulva. After induction of experimental irritant contact dermatitis, the a* values increased significantly in both sites, but less on the vulva, whereas the L* values remained unchanged at the vulva, but decreased at the forearm (7).

Cutaneous Blood Perfusion—Laser Doppler Flowmetry

The laser Doppler flowmetry (LDF) is an excellent noninvasive technique for monitoring cutaneous blood perfusion. As an early indicator of inflammation and changes in the

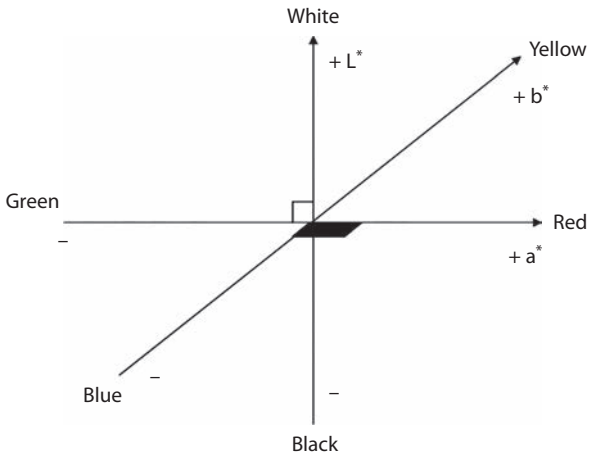

Figure 30.1 The Commission Internationale de l'Eclairage system: guideline for the measurement of skin color and erythema. (Adapted from Fullerton A et al. *Contact Dermatitis* 1996; 35: 1.)

microcirculation, LDF has been applied in many fields of clinical medicine and dermatology in healthy skin, as well as in inflammatory diseases (17) and for research purposes in the vulvar skin (5,8,18,19). Monochromatic, coherent light is emitted onto the skin and reflected at different wavelengths by the tissue and by the moving red blood cells in small vessels. The reflected light is detected photoelectrically and a dimensionless output signal is generated, which is proportional to the red blood cell flow. The signal is then processed by a personal computer, and the perfusion level can be displayed and calculated in a color-coded manner on the screen. Areas of interest can be defined and analyzed separately. By using a laser Doppler perfusion imager (LDPI), the disadvantage of placing the probe directly on the skin can be avoided. Furthermore, larger areas of up to 12 cm^2 can be mapped (18). However, in the genital area, scanning larger areas is difficult, as the vulvar skin is not flat and therefore not parallel to the probe, which can lead to artifacts (18). The laser Doppler technique has been used to quantify the irritant response of the vulva to sodium lauryl sulfate (SLS) in an experimental setting. By using measuring intervals of 45 seconds with a sampling rate set at one measurement per second, a higher baseline but a lower blood flow increase of the vulvar skin was detected as compared to the forearm skin after exposure to SLS. The sensitivity for detecting changes of the relative blood flow was higher compared to visual scoring (7,8). In lichen sclerosus lesions, the perfusion was found to be elevated and even increased after mechanical alteration due to scratching, mast cell degranulation, histamine release, and reactive vasodilatation (20). In epithelial tumors, such as the vulvar squamous cell carcinoma, increased cutaneous perfusion was detected using LDPI, which was attributed to neoangiogenesis with a lack of autonomic control (21). This method is relatively time consuming and easily influenced by environmental and individual-related factors (22). Constant measurement conditions, such as room temperature and relative humidity, must be maintained, as well as rest periods for the subjects (at least 20 minutes) prior to the measurements. Recently, laser Doppler Imaging has been shown to be useful in the diagnosis of vulvar vestibulitis (23) and in vestibulodynia (24).

Transepidermal Water Loss

Disturbance of the epidermal barrier function, which is maintained mainly by corneocytes and stratum corneum lipids, occurs with increased transepidermal water loss (TEWL). This phenomenon occurs early in irritant reactions and precedes visible skin changes. Accordingly, TEWL is a very sensitive parameter and has become one of the most important bioengineering considerations. Measurement of TEWL has been used in several studies on the vulvar skin, mainly to quantify irritant contact dermatitis (2,25,26). Different methods for TEWL measurements are available. In general, the more common open-chamber devices, such as the Tewameter® (Courage & Khazaka, Cologne) and the Evaporimeter® (Servo Med, Stockholm), have become much more established as compared to closed-loop systems (27). The open-chamber methods utilize a cylindrical probe that is integrated into a hand piece and equipped with a pair of sensor units (hygro sensors coupled with thermistors). When placed onto the skin, the probe measures the continuous water vapor gradient from the skin surface. Ideally, the probe should be handled in a horizontal plane position, which is difficult to achieve on the vulvar skin. In contrast, closed systems are designed to be applicable in different positions (27). However, the main drawback of these methods is the tendency to occlude the skin, thus causing artifacts. Furthermore, continuous measurements are not possible with these methods (28).

Baseline values of TEWL were found to be significantly higher on vulvar compared to the forearm skin (29). Age-related differences were observed between pre- and post-menopausal women, as TEWL was significantly lower in postmenopausal compared to premenopausal women (30). In general, significant intra- and inter-individual variations of TEWL are well known, and not only in the genital area. As the water evaporation from the skin is also influenced by the thermoregulative requirements of the individual and sweat gland activity, it is of utmost importance to exclude disturbing variables by thoroughly following the guidelines of the European Society of Contact Dermatitis regarding the measurements of TEWL (28). TEWL can only be measured after an appropriate waiting period in order to allow the postocclusion water loss to subside (9).

Skin Hydration Measurement

Skin dryness is related to the water content of the stratum corneum. The stratum corneum hydration interacts with the barrier function, permeability, and mechanical properties of the skin and is related to the water-binding capacity of the stratum corneum lipids (31). Objective quantification of skin hydration by bioengineering tools has gained wide popularity, as it provides fundamental information on skin function and is comparatively easy to perform. Three electrical methods for skin hydration measurements are currently used, based on capacitance, impedance, and conductance measurements (32). The Corneometer® (Courage & Khazaka, Cologne) is based on a capacitance measurement. Two metal plates with an electric field in between are integrated onto the electrode surface. Capacitance is the capability to store the electrical charge that is built up by an electron excess at one plate and an electron deficit at the other plate. It is influenced by the dielectric constant of the material between the plates, which changes with water content. The device estimates the water content in the epidermis up to an approximate depth of between 60 and 100 mm (31). The Corneometer CM 825® is the most recent version. The Skicon® principle is based on the conductance measurement of a fixed

high-frequency current of 3.5 MHz with a probe consisting of two concentric electrodes (I.B.S., Hamamatsu). It measures more superficial depths as compared to the Corneometer. The Nova Dermal Phase Meter® (Nova Technology Corporation, Gloucester, MA) is an impedance-based capacitance instrument (32). Fluhr and colleagues (33,34) have undertaken comparative and systematic studies of five different instruments.

In order to gain accurate and reliable results with any of these devices, a considerable number of individual and environmental factors must be recognized. Dependence on the position and pressure exerted on the probe must be considered. Because of occlusion, values can increase in repeated measurements. Thus, waiting periods of at least 5 seconds are recommended. In addition, environmental conditions must be considered; constant room temperature and relative humidity should be maintained (32).

Capacitance measurements with the use of the Corneometer have had widespread applications, as has the measurement of TEWL, in studies of vulvar skin physiology and experimental contact dermatitis (2–8,25,26,29). Baseline capacitance values of unaffected, healthy skin were found to be significantly higher at the vulva as compared to the forearm. However, the reactivity of female genital skin after exposure to typical detergent irritants such as SLS was not higher as compared to that of the forearm (30). Age-related differences were detected in pre- and post-menopausal vulvar skin. The dehydrating capacity of SLS was less pronounced in postmenopausal as compared to premenopausal women (29).

Skin Surface pH

In general, the pH value reflects the free hydrogen ion concentration of aqueous solutions. However, as the skin is not an aqueous solution, the surface pH, which is recorded in a semihydrophobic milieu, most likely represents the combined acidity of exposed corneocytes, lipids, and water-soluble compounds (35). The surface pH, which reflects the term "acidic mantle of the skin," is influenced by many exogenous and endogenous factors, such as free fatty acid presence on the surface, desiccation, sweating, water content, bacterial count (1), and environmental factors such as temperature and air humidity. Its role has become more understood in recent years. Surface pH has been shown to be regulated by the generation of free fatty acids (36) and itself contributes to the regulation of epidermal permeability barrier homeostasis, stratum corneum integrity (37), and antimicrobial defense (36). In healthy skin, pH values range between 4.5 and 6.0, turning alkaline in the presence of ammonia, which is the degradation product of sweat with bacteria. While pH values between 4.0 and 5.0 are supposed to prevent the occurrence and growth of microorganisms, elevated values can promote bacterial colonization (38). The pH of the vulva was described as being more acidic, ranging from 3.8 to 4.2 during the menstrual cycle (35). The vulvar pH changes with age were recently described by Farage et al. (39). However, in other bioengineering studies, significant differences between the baseline pH values of the vulva and the forearm were not confirmed (7); in fact, the values obtained on vulvar skin tended to be even higher (25). The stratum corneum pH is altered by inflammation, dryness, and irritant-induced skin changes (7). After standardized trauma with tape stripping, the vulvar skin surface pH decreased immediately, but recovered more quickly than that of the forearm skin (26). The glass electrode technique using a pH-Meter® (Courage & Khazaka, Cologne) has gained widespread acceptance for the measurement of skin surface pH (38). The device must be calibrated prior to measurements using standard buffers and must be rinsed with distilled water after each measurement. It must be realized that a surplus of water on the electrode as well as an electrode that is too dry both affect the results. In addition, no residues of cosmetics must be left on the skin (35).

MEASURING MECHANICAL PROPERTIES

In vivo quantification of mechanical skin properties remains difficult. Several techniques have been developed for this task, including tensile, torsional, indentation, suction, and vibration tests, which makes it difficult to compare results (40). The Cutometer® (Courage & Khazaka, Cologne) is a suction device that applies a vacuum on the skin surface in a test area of only 3 mm^2 by using a hand-held probe. The method is suitable for monitoring therapy and/or progression of connective tissue diseases such as scleroderma, and has been used in cosmetology for efficacy quantification of antiaging products (41,42). When comparing the elasticity parameters of the forearm and the vulvar skin, the ratio between viscous deformation (Uv) and elastic deformation (Ue) and the biological elasticity (i.e., the ratio between immediate recovery [Ur] and total deformation [Uf]) were both significantly lower in the vulvar than in the forearm skin. Age-related differences were similar at both sites (43). The frictional properties of the vulvar skin are of interest due to their relationship with eventual frictional trauma and resulting lichenification. Using a Newcastle Friction Meter (Design Unit Department of Mechanical Engineering, Newcastle University, Newcastle-upon-Tyne) with an annular Teflon ring rotating at a constant velocity, the friction coefficient of the vulvar skin was found to be higher than on the forearm skin, due to the higher hydration levels of vulvar stratum corneum (30).

CONCLUSION

In conclusion, the detection and investigation of clinical and subclinical vulvar changes, such as in irritant contact dermatitis, can be accomplished by using noninvasive bioengineering methods in order to monitor early inflammatory changes. LDPI and the measurement of color reflectance can be recommended initially in order to assess irritant reactions on vulvar skin, and combinations of different methods might be useful (7).

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Vulvar therapies

Evidence vs. testimony

Natalie Moulton-Levy and Howard I. Maibach

INTRODUCTION

Management of vulvar conditions requires special consideration, as there are unique emotional, psychological, and physiologic components that clinicians must address. Thus, currently accepted therapeutic techniques for vulvar disease are specific, reflecting the necessary modifications of treatments for standard dermatologic diseases. This chapter describes the vulvar lesions encountered most commonly and discusses their evidence-based therapies. Unfortunately, the number of published randomized clinical trials (RCTs) for the management of vulvar disease is limited.

VULVODYNIA

The cause of vulvodynia is multifactorial. As such, most effective treatments are interdisciplinary and highly patient specific. There are few clinical trials (with inadequate numbers of participants) demonstrating the efficacy of therapies to treat this disorder; placebo-controlled studies are yet to be performed.

Vulvar pain syndromes can be emotionally devastating. It has been suggested that there is a psychological component to vulvodynia; however, many patients are reluctant to seek psychological help. It is of utmost importance for the caregiver to provide emotional support and education about the disorder (1). Patients may also benefit from support group participation.

Medical therapy for patients with all subtypes of vulvodynia consists of treatments generally used for treating neuropathic pain. Several reports, including a non-controlled retrospective study (2), suggest that oral tricyclic antidepressants, specifically 100–150 mg of amitriptyline or desipramine, may be effective in reducing pain. The retrospective study showed that 58% of patients "responded well" to treatment and 20% were "cured" after 6 months. As some patients do not wish to take a psychiatric drug, it is important to explain that the medication is being used for its neuromodulating effect. (Though tricyclic antidepressants are commonly used to treat neuropathic pain, the Food and Drug Administration (FDA) has not cleared these agents for pain indications.) In order to minimize potential adverse side effects, clinicians often prescribe tricyclic antidepressants at an initial dose of 5–10 mg daily, with the dose increasing gradually to 150 mg per day, as tolerated by the patient, or until the symptoms have been controlled. The average time required for effective treatment is 7 months, after which the treatment can be discontinued or tapered. Side effects of tricyclic medications include drowsiness, fatigue, mouth and eye dryness, constipation, increased appetite, and urinary retention. Within the tricyclic antidepressant class, desipramine has one of the best side-effect profiles: it is less sedating, has lower anticholinergic effects, and leads to less weight gain. This agent, however, is more likely than amitriptyline to produce tremulousness. Desipramine can be prescribed in the same dosages as amitriptyline, but should be taken at night. In addition, there have been reports of the efficacy of treating this condition with non-tricyclic antidepressants, such as selective serotonin reuptake inhibitors and venlafaxine (2).

For women who cannot tolerate tricyclics or whose pain does not improve, gabapentin may be an acceptable alternative (2). Patients can start with low doses and increase the dose gradually to 900–3600 mg per day, divided into three or four dosages. Limited non-controlled case reports demonstrate gabapentin's efficacy in treating vulvodynia; however, many clinicians report successful treatment with gabapentin. Side effects include drowsiness, fatigue, dizziness, nausea, vomiting, and ataxia.

Lidocaine (5% ointment) is the topical therapy that is used most commonly. Long-term overnight topical treatment may minimize pain (3). Lidocaine ointment may cause erythema and numbness. Other topical treatments that might be beneficial include 2% amitriptyline with 2% baclofen (4), applied one to three times daily; side effects include contact dermatitis, dry mouth, drowsiness, and constipation. Additional topical treatments include estradiol cream (0.01%, twice a day for a minimum of 4–8 weeks) (4), capsaicin (4), and cytokines (5). Note that estradiol may cause vaginal bleeding.

Neuromuscular dysfunction can contribute to pain. Pelvic floor muscle rehabilitation combined with biofeedback has been beneficial in relieving pain by up to 40%–60% in several non-controlled clinical trials (2). If pelvic floor abnormalities are identified by surface electromyography, regularly exercising the muscles twice daily for 8–12 months has been shown to be beneficial, with improvement noted after several months (6). Unfortunately, therapists and physiatrists skilled in this type of training are not widely available.

Trigger-point injections of 0.2–0.3 mL of 3 mg/mL triamcinolone acetonide may be of great benefit in treating patients with localized pain (5). An additional injection after 4–6 months may provide permanent pain relief. Intralesional interferon-α (IFN-α) injections have been reported to be beneficial (7). Treatment consists of 1 million units of IFN-α injected three times per week for 4 weeks circumferentially at the vestibule periphery. Side effects such as fever, malaise, and myalgias can be reduced by pretreatment with acetaminophen or ibuprofen. Patients also sometimes experience pain at the site of injection, which may be minimized by pretreatment with a topical anesthetic. Improvement 1 year after the therapy is variable.

Some researchers believe that the pathophysiology involves an adverse reaction to *Candida*. Therefore, treatment

for this subtype can include antifungal medication, even in patients with negative cultures. This treatment regimen proved beneficial in a RCT (8). The most common regimen is fluconazole 150 mg orally once weekly for 2 months and then once every other week for 2–4 months (8).

Severe or refractory vulvar vestibulitis that has failed medical treatment for 6 months can be treated surgically with vulvar vestibulectomy (9). Many surgeons remove all areas of the vestibule, including areas that do not exhibit pain, because vestibulectomy failures result in recurrences in the remaining vestibule tissue. Surgical excision has been curative or produced significant improvement of symptoms in 66%–85% of patients (9). However, hematoma, wound dehiscence, poor healing, symptom recurrence, or worsening of pain can occur after vestibulectomy. Flash lamp-excited dye laser treatment has been somewhat successful in reducing the need for resective surgery (4).

High oxalate levels may cause vulvar irritation, contributing to the pain of vulvodynia. A low-oxalate diet with calcium citrate supplementation to inhibit absorption of oxalate can reduce pain symptoms (10). However, other studies have failed to detect increased oxalate levels in patients with vulvodynia and have shown no correlation between oxalate levels and symptom improvement (4).

ECZEMATOUS AND PAPULOSQUAMOUS VULVAR DERMATOSES

Contact Dermatitis (Irritant and/or Allergic)

Contact dermatitis can be either irritant (non-immunologic) and/or allergic (immunologic). Lesions occur on areas of the vulva that contact environmental irritants or antigens. It is essential to restore the normal skin barrier and protect the skin from additional injury. Treatment begins with the identification and withdrawal of the offending substance. To prevent recurrence, careful documentation of possible irritants or allergens is necessary. Women with vulvar dermatoses should be patch tested to define or rule out disease-causing agents (11).

After irritant withdrawal, symptoms of non-immunologic contact dermatitis should disappear rapidly. However, if the lesions are of allergic etiology, signs and symptoms can persist for days after the discontinuation of the allergen. Though clinical improvement is apparent and supported by clinical trials, there has been no RCT evaluating treatment for contact dermatitis of the vulva.

Common habits can cause mucocutaneous irritation, and behavior modifications are necessary to reduce risk of vulvar irritation and ensure successful management. Modifications include, but are not limited to, use of cotton underwear, lubrication with sexual contact, washing with mild soap, keeping the vulva clean and dry, and avoidance of cosmetics, perfumes, or other caustic substances in this sensitive area. Aluminum acetate in water (e.g., Burow's solution), topical creams (such as Sorbolene or aqueous cream), sitz baths with mild soap, and lubricants (such as petroleum jelly) are helpful in some cases. Secondary bacterial or *Candida* infections require specific treatment.

Antipruritic medications, such as antihistamines, are not of great therapeutic benefit except as soporific agents. Drugs with antihistamine and sedative properties, such as doxepin (10–20 mg at night), can be helpful in controlling nocturnal scratching (12).

Topical corticosteroids can be helpful in cases of irritant contact dermatitis that are unresponsive to conservative therapy. These agents may reduce inflammation in allergic contact dermatitis, but typically are not used for long-term treatment. Ointments are preferred to creams or lotions, which can be dry and irritating. Topical corticoids are most effective when applied and covered with a barrier, such as plastic wrap, a gauze dressing, or petroleum jelly.

Pharmacologic treatment consists of mid- to high-potency topical corticosteroids, such as triamcinolone, betamethasone, and fluocinolone (2), usually for 14 days or until symptoms have resolved. At this point, a weaker corticosteroid, such as 1% hydrocortisone, can be continued for an additional 2–3 months. This cycle can be repeated if disease activity flares. In cases of mild disease, low-potency steroids are safer and are typically preferred. Use low-potency topical steroids, such as hydrocortisone 2.5%, on thinner skin and for patients who prefer to use a topical preparation regularly. Alternatives include intralesional triamcinolone injections every 3–6 months. Brief courses of systemic corticosteroids are reserved for severe or recalcitrant dermatitis. Adequate dosage and an adequate taper length are important points to consider. Treatment with topical corticosteroids should be limited, as long-term use may induce telangiectasias, skin friability, striae formation, and easy bruising. Caution must also be taken to avoid rebound inflammation upon withdrawal from long-term, high-potency corticosteroids. See Chapter 29 for a more thorough discussion of contact dermatitis of the vulva.

Atopic Dermatitis

Endogenous atopic dermatitis is not curable but, typically, is readily treatable. Though there are clinically effective treatment options, no randomized or controlled trials have been performed. Primary treatment is aimed at avoiding exacerbating factors, which, in limited cases, can control symptoms effectively.

Moisturizers can be helpful in rehydrating the skin and helping to relieve symptoms. Symptomatic benefit may be obtained from wet Burow's solution compresses applied for 30 minutes several times daily. Mild topical corticosteroids such as 0.5%–1% hydrocortisone cream applied several times daily can further aid healing and alleviate irritation in mild to moderate atopic dermatitis (13). Strong topical corticosteroids may be needed to control severe acute disease. To prevent side effects, highly potent corticosteroids should be used for only short periods. Oral corticosteroids are used occasionally to treat chronic atopic dermatitis, but should not be used regularly.

Topical tacrolimus (14) and pimecrolimus (15) have been shown to be more effective than placebo in the treatment of generalized atopic dermatitis. Tacrolimus is a macrolide immunosuppressant with multiple immune-modulating effects, including suppression of proliferating T lymphocytes and inhibition of interleukin-2. These topical agents have been found in clinical experience to be an effective new therapeutic regimen for vulvar disease, but data specific to the vulvar area are lacking.

The immunosuppressant azathioprine is a purine analogue that has been shown by double-blind, placebo-controlled clinical trials to be effective as a monotherapy for generalized atopic dermatitis (16). It is thought to act through the inhibition of DNA and RNA synthesis (17). For severe or refractory vulvar disease, azathioprine is used typically as a corticoid-sparing adjunct. Side effects include gastrointestinal discomfort. Rare but severe complications include renal impairment, liver disease, and bone marrow suppression; clinicians should monitor

the patient's complete blood count every 2 weeks, and it is advisable to check liver and renal function tests periodically. This drug should not be prescribed to pregnant women, as both the drug and its metabolites cross the placenta and are potential teratogens. Azathioprine has not been studied for specific use in the vulvar region and should be used with caution.

Psoriasis

Treatment of psoriasis is aimed at symptom relief and minimizing Köebner's phenomenon. After psoralen and long-wave ultraviolet radiation (PUVA) treatment for extensive, generalized disease, psoriatic vulvar plaques may remain due to inadequate phototherapy in this region (18). Thus, vulvar psoriasis may require separate treatment. This disorder often requires more aggressive and prolonged treatment than dermatitis.

For cases of limited disease, clinicians can attempt initial treatment with a low-potency topical corticosteroid, such as 1% hydrocortisone cream. However, when used as monotherapy, such drugs are seldom effective for disease control. Many cases can be treated successfully with a 14-day course of mid- to high-potency topical corticosteroid. Intralesional corticosteroids may be an alternative (13). Systemic steroids often produce a rebound flare-up of the disease and should be avoided.

Randomized, placebo-controlled studies have proven both topical tacrolimus and pimecrolimus to be successful for treating generalized disease, but not for vulvar psoriasis. Clinically, tacrolimus has been effective in treating psoriasis of the vulva.

Tazarotene, a retinoid, and calcipotriene, a topical vitamin D_3 analogue, are used to treat generalized psoriasis without the adverse effects of steroid treatment. These have not been studied specifically for use in vulvar disease.

Weak tar preparations, such as 3% liquor picis carbonis in aqueous cream, are possible alternatives. Generally, however, tar preparations are irritating to the vulvar skin and should be avoided.

Seborrheic Dermatitis

Treatment of seborrheic dermatitis is similar to that of contact dermatitis. Exacerbating factors, such as excessive sweating, emotional distress, and tight clothing, should be minimized. Hydrocortisone cream is the most effective medical therapy (18). Acute episodes may be treated with sitz baths or topical aluminum acetate solution. Antibiotics should be administered for secondary infection.

Lichen Sclerosus

Effective treatment of lichen sclerosus will control symptoms, minimize scarring, and allow for early detection of malignant change. As a result of compelling data from clinical trials, treatment recommendations have changed recently. The current recommended and accepted treatment for all forms of lichen sclerosus is the potent topical corticosteroid ointment clobetasol propionate (19,20). One RCT comparing clobetasol, testosterone, progesterone, and petroleum jelly showed higher rates of symptom control with clobetasol (75%) (21). Clobetasol 0.05% gel or cream provides rapid symptomatic improvement in over 90% of treated women. It also reverses some of the histological changes and is effective in long-term disease control. The medication should be applied once or twice daily (22), and treatment typically lasts 3 months (23). The dose should be tapered gradually and then used only when symptoms recur, typically fewer than once or twice per week. There is some evidence that lichen sclerosus of the vulva may be treated with long-term maintenance therapy (24). The patient should be advised that this therapy is not curative and recurrence is likely.

Intralesional triamcinolone 5–20 mg/mL injected once a month has shown promise in the treatment of plaques of lichen sclerosus. Ideally, these are performed after topical anesthetic using a 30-gauge needle and are repeated every month for a maximum of 3 months. A biopsy should always be performed initially on such hyperkeratotic plaques to rule out vulvar intraepithelial neoplasia (VIN) (25).

If lesions recur, re-treatment may be necessary. Potential side effects include cutaneous atrophy or adrenal suppression but, in practice, these complications are rare. The modified mucous membranes of the labia and clitoris are relatively resistant to corticosteroid-induced side effects such as telangiectasia and atrophy, so long-term therapy seems to be safe (26). There is anecdotal suggestion that intralesional injections of triamcinolone every 3–6 months may be an appropriate alternative therapy (27).

In the past, androgens and progesterones have been used widely. Androgenic side effects are common and include clitoral enlargement, hirsutism, amenorrhea, increased libido, and voice changes (28). Side effects of progesterone include changes in vaginal discharge. Placebo-controlled trials have demonstrated that testosterone (29) is no more effective in the treatment of lichen sclerosus. Clinical trials have also indicated that prednisolone is not an effective treatment (30).

Surgical therapies, such as excision followed by skin grafting, vaginoplasty, and vulvectomy, have been used for the treatment of lichen sclerosus; however, there are no data proving their effectiveness. Surgical treatments are associated with a high recurrence rate and surgery is not currently recommended in the absence of VIN or malignancy (30). In contrast, surgical intervention is always necessary in the case of lichen sclerosus complicated by malignant disease. In severe cases with extensive fissuring and scar formation, surgical correction may be considered. Topical steroids postoperatively may help prevent recurrence. Other ablation techniques include cryotherapy (31) and laser therapy (32). These have not been investigated, recurrence rates are high, and there can be significant post-procedural discomfort, resulting in limited use of these therapeutic modalities. Scarring and stenosis are unlikely to improve with treatment, and some women might require enlargement of a narrowed introitus because of difficulties with micturition or sexual intercourse.

Photodynamic therapy (PDT) with topical 5-aminolevulinic acid and argon laser light has been reported to result in clinical improvement (33).

Several studies (34,35), including a placebo-controlled trial (34), showed some efficacy of systemic retinoids for the treatment of lichen sclerosus; however, there are many intolerable and potentially harmful side effects. There is no evidence demonstrating the effectiveness of topical retinoids, and clinical use is unlikely because these drugs cause severe skin irritation. There are various reports of other systemic treatments, including methotrexate and methylprednisone, but the literature is limited. Nonetheless, these agents might be considered in severe and unresponsive cases (36).

Case studies have demonstrated the efficacy of treating anogenital lichen sclerosus with low-dose PUVA (37), as well as with PUVA cream photochemotherapy (38). It has been

postulated that radiation suppresses collagen synthesis and induces collagenase activity, leading to softening of sclerotic skin plaques.

Topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, are also promising agents for treating lichen sclerosus. There have been multiple RCTs indicating the efficacy of these drugs in generalized disease. Case reports demonstrate treatment success specifically with genital lesions (39,40); however, further investigation is necessary at this time (36).

Lifetime risk of developing squamous cell carcinoma in the affected area is approximately 4% (41). At a minimum, patients should have yearly follow-ups to monitor for malignancy. Clinicians should advise patients to return sooner if they notice any growth or ulceration. Any erosions, ulcers, and hyperkeratotic or erythematous areas should be evaluated with biopsy.

Associated symptoms such as dyspareunia should be treated with lubricants and postmenopausal vulvovaginal atrophy should be treated with topical estrogens (26).

There is debate as to whether asymptomatic patients should be treated, and this decision should be based on each individual case. Treatment may prevent disease progression and, possibly, malignant transformation. This, however, must be considered in the context of the multiple disadvantages to long-term therapy. Regardless of the treatment decision, all patients should have long-term follow-up.

Lichen Planus

Few data support the efficacy of any specific therapy for vulvar lichen planus. Typically, vulvar lesions of lichen planus are treated with a potent topical corticoid cream such as betamethasone valerate 0.1% ointment twice daily for 4–6 weeks. For hypertrophic or erosive disease, a superpotent topical corticosteroid is advised (cloetasol 0.05% ointment twice daily for 3 month). Intralesional corticosteroids are used for refractory disease, typically at doses of 10 mg/mL, using 0.5–1 mL depending on the extent of the disease. Intramuscular triamcinolone (1 mg/kg) is favored by some due to the fact that the vulvar area might be too inflamed initially for topical or intralesional applications of treatments (42).

Antihistamines are also helpful in treating pruritus. Generally, systemic steroids are reserved for severely symptomatic disease (43); upon discontinuation, oral steroid dosages must be tapered.

There have been reports indicating the value of vaginal suppositories in the treatment of this disease (44); 25 mg hydrocortisone suppositories intravaginally twice daily for 2 months resulted in improvement in 16 of 17 women in one series.

Oral and topical retinoids have proven effective for generalized disease and there have been some reports of the success of these agents with vulvar disease (45). However, the data are too few to make any conclusive recommendations regarding the use of these agents. Additionally, topical retinoids cause significant irritation and may worsen lesions.

Griseofulvin has been reported in one case series to be efficient in managing patients with vulvar disease. However, a subsequent study failed to reproduce these results (43). Small studies have shown cyclosporine to be effective in the treatment of severe disease (43). Cyclosporine acts by suppressing proliferating T cells and inhibiting lymphokine production. Side effects of this powerful drug can be severe, and include nephrotoxicity. It is essential to monitor the renal function of patients taking this drug every 2 weeks (16).

Oral or topical dapsone may be effective in chronic, recalcitrant cases. An uncontrolled case series demonstrated the efficacy of the drug, particularly when used in conjunction with oral corticosteroids. The exact mechanism of action is unknown, but is believed to be anti-inflammatory, possibly through alterations of neutrophil function (16). Rarely, dapsone has been associated with hemolytic anemia or agranulocytosis. During therapy, complete blood count should be measured regularly; most advise monitoring liver and renal function, as well. Before initiating the therapy, a glucose-6-phosphate dehydrogenase (G-6-PD) screen is recommended, as G-6-PD deficiency is a contraindication to drug use.

Recent studies have also shown topical tacrolimus 0.1% ointment to be effective in treating erosive vulvar lichen sclerosus (46). A more recent retrospective series investigating topical tacrolimus therapy demonstrated symptom control and clinical improvement in 94% of patients (47). Stinging can occur upon application, but this can be minimized by the concomitant use of a topical steroid and liberal emollients. Pimecrolimus has also been used successfully in vulva lichen planus (42).

In cases where there is inadequate response to topical therapy, a 6-month trial of oral antibiotics may be added, due to their anti-inflammatory effect. If there is inadequate response, oral prednisolone may be helpful. It is, however, prudent to consider alternative systemics, such as azathioprine, methotrexate, and hydrochloroquine (42).

There have also been case studies demonstrating the use of PUVA cream phototherapy in genital lichen planus (40). At present, however, data are limited.

Surgical methods of treatment include excision, cryotherapy, and carbon dioxide laser. Blunt dissection may be performed with the addition of potent topical steroids in the postoperative period (43).

As with lichen sclerosus, these patients should be monitored regularly because of an increased risk of developing vulvar malignancy (43).

BENIGN VULVAR NODULES OR TUMORS

In most cases, excision of solid lesions is diagnostic as well as therapeutic. Pigmented vulvar lesions include lentigo and nevi. Approximately 2%–5% of melanomas, but only 0.1% of nevi, are located on the vulva, supporting theories that vulvar nevi are at increased risk of malignant transformation (48). As such, detection and careful evaluation of vulvar nevi are critical. The benign lesions of seborrheic keratosis do not require treatment. However, surgical removal can be performed at the patient's request, often for cosmesis.

In the case of acrochordons (fibroepithelial polyps) and hidradenomas, simple excision is curative. There is no evidence that patients with these lesions are at increased risk of malignancy (48). Achrocondon is usually asymptomatic, but repeated trauma and irritation can cause it to become ulcerated. If the lesion is in a troublesome location, such as the panty line or groin fold, it can be removed in an outpatient setting with local anesthesia and simple electrocautery or scissor excision.

Fibroma and related fibromyoma should be removed for diagnostic purposes to exclude a rare leiomyosarcoma or sarcoma. Lipomas usually do not require surgical excision unless they become painful or are cosmetically unacceptable to the patient. Painless, firm Bartholin's masses, especially postmenopausal, should be excised to rule out Bartholin's gland malignancy (13).

INFECTIOUS DISEASES

Bacterial

Abscesses and Cellulitis

Vulvar sites that are often affected by abscesses or cellulitis include the hair follicle, apocrine glands, Skene's glands, and, most commonly, Bartholin's glands. The infection is usually polymicrobial in nature, with both aerobic and anaerobic (*Bacteroides* species and other colonic and vaginal bacteria) flora. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are encountered frequently.

The treatment of Bartholin's gland infections depends on the patient's symptoms. Asymptomatic women less than 40 years of age do not need treatment. Therapy for symptomatic cellulitis, with or without an abscess, consists of broad-spectrum antibiotics and warm sitz baths. In the case of isolated abscesses without evidence of cellulitis, antibiotics are not necessary (49). Spontaneous rupture and drainage of an abscess sometimes occurs, but recurrence is likely. Definitive treatment involves surgical drainage with a Word catheter, marsupialization, or excision. The former two treatments are office-based procedures and can be performed using local anesthesia.

The treatment of choice for a symptomatic abscess is a Word catheter, which provides a convenient and highly successful method of creating a fistula from the duct of the gland to the vestibule. Most cases resolve after a few days of drainage and the catheter often falls out within a week. Ideally, the catheter should remain in place for 4–6 weeks, during which time an epithelial sinus will form. Sitz baths two to three times daily after the procedure may help with discomfort, keep the area clean, and hasten the healing process.

If the abscess is too deep, Word catheter placement is impractical, and other options must be considered. Simple incision and drainage is an easy procedure but is discouraged because of the high risk of abscess recurrence, which has been reported to be as high as 13% (49). Also, incision and drainage may complicate later attempts at Word catheter placement or marsupialization. Nonetheless, if a Word catheter proves ineffective, incision and drainage is an acceptable option before proceeding to surgical excision. The incision for abscess drainage should be made on the mucosal rather than the cutaneous surface. If the abscess recurs, more definitive therapy in the form of marsupialization or complete excision of the gland may be required, but these procedures are not the initial treatment of choice.

Marsupialization is a more complex procedure involving incision and drainage followed by suturing the walls of the cyst to the skin. As with Word catheters, postoperative sitz baths can be beneficial. The recurrence rate following marsupialization is approximately 5%–15% (49). Complications include dyspareunia, hematoma, and infection. There is a report of sepsis after marsupialization of a Bartholin's gland abscess by Miller (50). Pregnant women should be considered high risk and managed accordingly.

Excision of Bartholin's gland and duct is another option. Though some clinicians routinely suggest excisional surgery following the first infection, surgery is more commonly reserved for the patient with persistent infection or multiple abscess recurrences. Some experts advocate for excision and biopsy for gland enlargement in women more than 40 years of age in order to evaluate for possible Bartholin's gland adenocarcinoma (13). Excision should be performed only in the absence of active infection. This is not an office procedure, as regional block or general anesthesia is necessary. Associated complications include intraoperative hemorrhage, hematomas, scarring, and dyspareunia.

Necrotizing Fasciitis

The presence of cellulitis, deteriorating vital signs, and a deep, spreading, painful erythema, especially in the postpartum or postoperative patient, should raise concern for necrotizing fasciitis. Necrotizing fasciitis is a rapidly progressive infection commonly caused by mixed aerobic–anaerobic bacteria. Unfortunately, antibiotic treatment usually proves ineffective. Necrotizing fasciitis is a surgical emergency requiring immediate and extensive surgical debridement of the necrotic fascia to prevent septic shock and fatal complications. Patients may require several debridements, and skin grafts are often needed to repair large defects. Due to the emergent nature of this condition, women presenting with vulvar cellulitis and with risk factors for necrotizing fasciitis (obesity, diabetes mellitus, corticosteroid use, or immunosuppressed states) should be hospitalized for treatment with intravenous broad-spectrum antibiotics, including a penicillin, and surgical treatment (51).

Treponema pallidum (Syphilis)

For over 50 years, administration of penicillin G to patients with syphilis has resulted in resolution of lesions and decreased transmission rates, and has prevented sequelae of the disease effectively. On the basis of the clinical results, penicillin is accepted as the treatment of choice for syphilis. No comparative trials have been conducted to determine the optimal dose, preparation, or length of therapy. The efficacy of most treatment recommendations is based on experience with the disease supported by case studies, clinical trials, and clinical experience. Data are not reinforced by results from RCTs, but at this time, conducting such a trial would most likely be of little additional benefit.

Parenteral penicillin G is the preferred drug for the treatment of all stages of syphilis (52) (treatment for tertiary syphilis will not be discussed further). For primary and secondary syphilis, the recommended treatment regimen is a single dose of benzathine penicillin G, 2.4 million U intramuscularly. If non-treponemal titers do not decrease four-fold within 6 months of treatment, the patient should be retreated with benzathine penicillin G, 2.4 million U intramuscularly weekly for 3 weeks.

Treatment alternatives for penicillin-allergic patients include doxycycline (100 mg twice daily for 14 days), tetracycline (500 mg four times daily for 14 days), erythromycin (30–40 g given in divided doses over a period of 10–15 days), or penicillin desensitization. Tetracycline can cause gastrointestinal side effects; the other agents may increase the patient's compliance.

Some data demonstrate the efficacy of ceftriaxone for the treatment of early syphilis. However, the optimal dose and duration of therapy have not been defined clearly. The current recommendation is 1 g daily either intramuscularly or intravenously for 8–10 days.

Small studies, including one randomized comparative pilot study, indicate that azithromycin as a single oral dose of 2 g or two doses 1 week apart may be effective in treating early primary syphilis (53). This treatment is an attractive future alternative because it is administered orally. Recent reports have documented strains of *Treponema pallidum* with functional resistance to azithromycin (54).

Because they currently lack recommendation by the Centers for Disease Control and Prevention (CDC) and their efficacy is supported by limited data, clinicians must follow patients receiving ceftriaxone and azithromycin closely.

Regardless of the drug used for treatment, patients treated for syphilis may develop the Jarisch–Herxheimer reaction, an acute febrile reaction starting within 24 hours of treatment initiation. This condition is characterized by fever, headache, and myalgias. Patients should be informed about this possible adverse reaction.

Parenteral penicillin G is the only documented efficacious treatment for syphilis during pregnancy. Thus, penicillin-allergic pregnant women with syphilis in any stage should be desensitized and treated with penicillin. Tetracycline and doxycycline should not be used during pregnancy. Erythromycin should not be used because it does not cure the infected fetus reliably. The Jarisch–Herxheimer reaction may induce early labor or cause fetal distress; however, this concern should not delay or prevent therapy.

Haemophilus ducreyi (Chancroid)

Successful treatment for chancroid cures the infection, resolves the clinical symptoms, and prevents transmission to others. Recently, *Haemophilus ducreyi* has shown resistance to many pharmacologic agents, such as trimethoprim–sulfametrole, penicillin, and tetracycline, some of which have been used traditionally for its treatment. Worldwide, there have been reports of isolates with intermediate resistance to ciprofloxacin, ceftriaxone, and erythromycin. Current regimens accepted by the World Health Organization (WHO) and CDC are as follows: oral erythromycin (500 mg three or four times a day for 7 days), oral azithromycin (1 g single dose), intramuscular ceftriaxone (250 mg single dose), oral ciprofloxacin (500 mg twice a day for 3 days), oral ciprofloxacin (500 mg single dose), and spectinomycin (2 g single dose intramuscularly) (52,55).

Intramuscular azithromycin and ceftriaxone allow for single-dose therapy. For ciprofloxacin, there is some debate concerning the duration of therapy; the WHO recommends a single 500-mg oral dose and the CDC recommends 500 mg daily for 3 days. A recent double-blind RCT showed comparable cure rates (56). The WHO and CDC also differ in their recommendations of the frequency of dosing of erythromycin. The WHO recommends 500-mg treatment four times per day, whereas the CDC recommends the same dose three times per day. Both regimens appear effective.

With treatment, buboes smaller than 5 cm typically resolve in 1–2 weeks. Larger buboes, as well as fluctuant buboes, should be aspirated or incised and drained for symptomatic relief and to avoid spontaneous rupture, chronic ulceration, and tissue loss. Partners should be examined and treated and sexual contact should be avoided until treatment is complete and lesions have resolved. Pregnant women should be treated with either erythromycin or ceftriaxone regimens.

Patients with HIV infection have reduced healing and persistent infection and, therefore, should have careful follow-up.

Donovanosis (Granuloma Inguinale and Calymmatobacterium Granulomatis)

Few trials report appropriate antibiotic choice or duration of therapy for the treatment of donovanosis. However, current CDC recommendations are as follows (52): oral trimethoprim–sulfamethoxazole 800 mg/160 mg twice daily or oral doxycycline 100 mg twice daily. Alternatives include ciprofloxacin 750 mg twice daily, erythromycin base 500 mg four times a day, and azithromycin 1 g once per week. Regardless of antibiotic choice, treatment should be continued for at least 3 weeks or until the lesions have healed. Larger lesions may require longer periods of treatment. Some clinicians recommend adding an aminoglycoside, such as gentamicin 1 mg/kg intravenously every 8 hours, if improvement is not apparent within the first few days of therapy.

Patients should be seen regularly until symptoms resolve. Follow-up is essential, as patients may relapse 6–18 months after seemingly effective treatment.

Pregnant and lactating women should be treated with erythromycin, with consideration given to the addition of gentamicin. Azithromycin may prove efficacious in this population, but there currently are no published data.

Lymphogranuloma Venereum (C. trachomatis Strain)

Oral doxycycline (100 mg twice a day for 3 weeks) is the drug of choice for this genital infection. Oral erythromycin (500 mg four times a day for 21 days) is an appropriate alternative (52). Azithromycin (1 g once weekly for 3 weeks) appears effective, although there are no supporting clinical data. Successful treatment provides symptomatic relief, cures the infection, and prevents continued tissue damage. Scarring, which results from tissue reaction, is unaffected by antibiotic treatment. Buboes can persist, as they are not affected by antibiotic therapy. Persistent buboes may require aspiration or incision and drainage.

Patients should be followed clinically until signs and symptoms have resolved. Pregnant and lactating women should be treated with erythromycin.

FUNGAL DISEASES

Candidiasis

Multiple double-blind, randomized studies have proven the efficacy of both oral and topical antifungals for the treatment of candidiasis. Administration route is largely dependent on patient preference. Topical antifungals include butoconazole, clotrimazole, miconazole, nystatin, terconazole, and tioconazole. Table 31.1 (57–75) summarizes topical treatments tested in RCTs. Cure rates are over 80%, with symptomatic resolution in 48–72 hours and mycological cure within 4–7 days (76). Oral azoles (fluconazole, itraconazole, and ketoconazole) also achieve high cure rates; however, fluconazole is currently the only FDA-approved agent (77). Itraconazole has been found to be as effective as fluconazole. Oral agents may be preferable because of convenience and the avoidance of skin sensitization that has been associated with topical antifungals. Side effects of fluconazole are mild and infrequent, but include gastrointestinal intolerance, headache, and rash (76). There is increased hepatotoxicity with concomitant use of fluconazole with other hepatotoxic drugs, most notably statins. Oral azoles should not be used during pregnancy. One RCT has shown boric acid to be as effective in treatment as nystatin; however, this agent can cause skin irritation, is toxic if ingested, and should not be a first-line therapy (78).

Candida vulvitis can be classified into complicated and uncomplicated forms (56). Uncomplicated infection, which affects 90% of patients, is caused typically by *Candida albicans* and responds to a short-course oral or topical antifungal. There are currently many effective single-dose oral regimens, such as a one-time dose of fluconazole 150 mg. The rare infection with

Table 31.1 Randomized Clinical Trial-Supported Topical Medications Proven to be Beneficial for Uncomplicated Vulvovaginal Candidiasis

Treatment	Placebo controlled?	Comment	Reference
Butoconazole 2% cream 5 g for 3 days	Yes	Also compared to clotrimazole and miconazole	(57)
Butoconazole 2% cream 5 g, once	No	Compared to miconazole	(58)
Clotrimazole 1% cream 5 g for 7–14 days	No	Compared to terconazole	(59)
Clotrimazole 100 mg vaginal tablet for 7 days	No	Compared to clotrimazole 14 days and miconazole, also to oral fluconazole	(60–62)
Clotrimazole 100 mg vaginal tablet, two tablets for 3 days	No	Compared to tioconazole, itraconazole, and oral fluconazole	(63–65)
Clotrimazole 500 mg tablet, once	Yes	Also compared to oral fluconazole	(65–70)
Miconazole 2% cream 5 g for 7 days	Yes	Also compared with terconazole	(71)
Nystatin 100,000 unit tablet for 14 days	Yes	Has also been compared to intravaginal imidazoles	(72)
Tioconazole 6.5% ointment 5 g, once	No	Compared to terconazole	(73)
Teraconazole 0.4% cream 5 g for 7 days	No	Compared to clotrimazole	(74)
Teraconazole 0.8% cream 5 g for 3 days	No	Compared to tioconazole	(73)
Teraconazole 80 mg suppository for 3 days	Yes	Also compared to miconazole and oral fluconazole	(71,75)

azole-resistant *C. albicans* requires higher doses of fluconazole. Ketoconazole is effective in treating uncomplicated candidiasis; however, hepatitis is a rare but serious side effect and the risks outweigh the benefits of its use in treating candidiasis.

Complicated candidiasis, seen in approximately 10% of cases, requires antimycotic therapy for 10–14 days (77). Microbial infections with *Candida* species other than *C. albicans*, particularly *Candida glabrata*, are less susceptible to azoles and azole therapy is unreliable. *C. glabrata* and the other non-*C. albicans* infections frequently respond to topical boric acid 600 mg/day for 14 days or to topical flucytosine.

Recurrent vulvitis, defined as four or more episodes per year, is usually due to azole-susceptible *C. albicans* (77). Clinicians should assess patients for possible risk factors, such as uncontrolled diabetes mellitus, immunosuppression, or chronic antibiotic therapy. Multiple studies have demonstrated the effectiveness of a 6-month period of antifungal maintenance suppressive therapy after an initial 2-week induction regimen, resulting in negative cultures. Typically, induction is achieved with an oral azole. Acceptable maintenance therapies include oral fluconazole (150–200 mg weekly), oral ketoconazole (100 mg daily), oral itraconazole (100 mg every other day), or daily therapy with any topical azole (52). Two small RCTs provide insufficient evidence about regular prophylaxis with intravaginal imidazoles (79,80).

VIRAL DISEASES

Herpes Simplex Virus

Randomized trials (81,82), including one placebo-controlled trial for acyclovir (83), show effective clinical management of disease with three oral antivirals—acyclovir, famciclovir, and valacyclovir—each of which is an acyclic nucleoside analogue. These drugs result in clinical improvement, but do not eradicate latent virus, nor do they affect the frequency or severity of recurrences after discontinuation. More recently, a mucoadhesive tablet of acyclovir was approved for recurrent herpes labialis infections. Topical antivirals offer little benefit and are not recommended.

Effective treatment will decrease shedding, as well as the length and severity of the symptoms of initial episodes of genital herpes of both types 1 and 2. According to the Sexually Transmitted Diseases Guidelines, primary infection should be treated with acyclovir 400 mg TID, acyclovir 200 mg five times daily, famciclovir 250 mg three times a day (TID), or valacyclovir, 1 g twice a day (BID) (52). Treatment should last for 7–10 days. Following the course of medication, treatment is extended if healing is incomplete. Studies comparing these agents have shown equal efficacy.

Antiviral therapy for recurrent genital herpes can be administered either episodically or continuously for disease suppression. Effective episodic treatment of recurrent herpes is most effective if initiated within 1 day of lesion onset, or during the prodrome, if possible (52). Episodic treatment decreases the time to active disease resolution and duration of shedding by 1–2 days (84). Each of the recommended drugs has been shown to be effective in RCTs (85–87). Recommended regimens include acyclovir (400 mg three times a day for 5 days or 800 mg BID for 5 days), famciclovir (125 mg BID for 5 days), or valacyclovir (500 mg BID for 3–5 days or 1 g daily for 5 days) (52). A RCT indicated that a 3-day course of valacyclovir 500 mg twice daily is as effective as a 5-day course (88). Though these drugs are equally efficacious, acyclovir is the least expensive, and cost should be considered when choosing agents for prolonged therapy. Clinicians should counsel patients about how to identify recurrences and should provide a supply of antiviral medication for future use.

Herpes simplex virus suppression is indicated in patients with more than six outbreaks per year (52). Recommended treatment options include acyclovir (400 mg twice daily), valacyclovir (500–1000 mg once daily), or famciclovir (250 mg twice daily) (52). Valacyclovir 500 mg once a day might be less effective than other dosing regimens in patients with more than 10 episodes per year (52). Daily suppressive therapy decreases symptomatic recurrence by up to 70%–80%, increases quality of life, and decreases transmission to uninfected partners (84). Therapy with 500 mg of valacyclovir once daily for 8 months can reduce disease transmission by up to 48% (84). Nonetheless, clinicians should advise patients that suppressive therapy reduces, but does not eliminate, viral shedding (89). There has been no increase in side effects noted with long-term therapy. Safety has been documented with daily acyclovir therapy for as long as 6 years and for 1 year with valacyclovir or famciclovir (84). For many patients, the frequency of recurrences diminishes with time. Because of this fact, periodic discussion regarding the discontinuation of suppressive treatment is advised.

It is critical for clinicians to provide education and counseling to infected individuals and their partners. Education

should include an explanation of the natural course of the disease, asymptomatic viral shedding, sexual and perinatal transmission, and methods to reduce transmission. Counseling may help, because some patients are troubled more by the psychological manifestations of the disease than the physical symptoms. Initial counseling can be provided at the first visit; the patient may benefit from direction to websites or printed materials for further support.

For HIV-positive patients, lesions may be larger and more painful, with longer healing times and more recurrences. Higher medication doses and longer treatment times may be necessary. Episodic or suppressive antiviral therapy should be considered (52).

Genital Warts (Condyloma Acuminata Caused by Human Papilloma Virus)

Sixty percent of condylomata acuminata are estimated to resolve spontaneously within 2 years; nonetheless, patients frequently request treatment (52) for various reasons, including cosmesis and symptom relief. Despite the fact that there is such a high rate of spontaneous resolution, the natural course of the disease varies; the condition may remain unchanged or warts may increase in size or number. Counsel patients that although the lesions may not be present, the virus may always be present in the genital tract, and that recurrences are common, generally in 6 months after treatment (90). It is unknown whether treatment reduces transmission, as there is no established laboratory marker of infectivity. Existing data indicate that currently available therapies for genital warts may reduce but probably do not eradicate infectivity (91).

There is a variety of treatment options that have been proven in RCTs to be safe and effective. Some treatments have been used for a long time and have shown promise in years of clinical practice. There are other new treatment options, the efficacy of which is supported by research data, but their long-term safety and efficacy have not been demonstrated in practice.

Treatment options may be either physician or patient applied. In the case of patient-applied treatment, if possible, the health care provider should apply the initial treatment to demonstrate correct application techniques. The two recommended patient-applied treatments are podofilox and imiquimod, the efficacy of which has been supported by data from RCTs.

Podofilox is a purified podophyllin resin available in a 0.5% solution. The medication should be applied to visible warts twice daily for 3 days, followed by 4 days without therapy, a cycle that can be repeated as necessary, up to four times (52). There are eight randomized, placebo-controlled trials and many more RCTs supporting the use of podophyllotoxin that report clearance rates of up to 77% within 6 weeks of treatment (90). Recurrences have been reported for up to 34% of patients followed in clinical trials (92). The safety of podofilox during pregnancy has not been established.

Imiquimod is an immunomodulator with a mechanism of action that is not understood completely, but studies indicate that the chemical induces cytokines, such as IFN-α, thus activating antiviral activity. The 5% cream should be applied at bedtime, three times a week for up to 16 weeks. At 6–10 hours after application, the treatment area should be washed with soap (52). Imiquimod has been studied in a number of clinical trials, five of which were placebo controlled (93,94). Imiquimod is currently a FDA-approved treatment for genital warts and has up to a 70% clearance rate (90), without recurrence in up to 37% (94). Most studies indicate that this drug is less effective in men than in women (90). Side effects include skin irritation and erythema.

Polyphenon E ointment contains a concentrate of catechins, which are natural substances extracted from green tea leaves. Topical polyphenon E has been shown to be effective in the treatment of external genital and perianal warts. In one study, up to 53% of patients showed complete clearance of all baseline and new anogenital warts (95).

Four recommended provider-administered treatments include cryotherapy, podophyllin resin, acetic acid, or surgical removal. Cryotherapy with liquid nitrogen or cryoprobe can be repeated every 1–2 weeks (52). Non-placebo-controlled clinical trials show efficacy similar to that of bi- and tri-chloroacetic acid, better treatment success than with podophyllin, and possibly less efficacy than electrosurgery (96). The practitioner should attempt to freeze the lesion itself, avoiding the surrounding skin. Complications include burning and ulceration, which usually resolve in 7–10 days with little or no scarring. Recurrences rates may be 40%–75% (90).

Podophyllin has not been investigated in a placebo-controlled trial; however, there are many data comparing podophyllin to the various other treatment options, and there is consensus that efficacy in clearing lesions is similar (91). However, the recurrence rate can be as high as 60%. Provider-administered podophyllin resin is most effective for lesions that are 2 cm or less in diameter (52). A 10%–25% solution can be applied to visible warts weekly, as necessary. If regression is not achieved after four applications, an alternative therapy should be considered. Transmucosal systemic absorption does occur, and this solution should not be applied intravaginally. Complications include a subjective burning sensation or actual ulceration, which can affect as many as 30% of patients (91). Washing the area 1–4 hours after treatment will minimize the severe irritation associated with prolonged exposure. Neurologic, hematologic, and febrile complications and death have been associated with topical podophyllin. Podophyllin is cytotoxic and is contraindicated during pregnancy.

An 80%–90% solution of bi- or tri-chloroacetic acid is an effective treatment for small lesions, as shown by two RCTs comparing it with cryotherapy (91). Treatment may be repeated weekly for up to 4 weeks. Some recommend applying petrolatum ointment, talcum powder, or bicarbonate of soda to skin that is in contact with the treatment area to avoid extensive irritation. The solution can be washed off 6–8 hours after treatment, and a sitz bath with baking soda may relieve some discomfort. Overall, this regimen has a better side-effect profile than podophyllin and can be used safely by pregnant women.

Genital warts can be excised by tangential scissors, shave excision curettage, or punch biopsy, and treatment can be repeated as necessary. RCTs demonstrate no difference in the results achieved by laser and surgical excision or between the clearance rates as compared with podophyllin. However, surgical excision is more effective in preventing recurrence than podophyllin (91).

Alternative surgical techniques include loop electrosurgical excision procedures (LEEP) and laser surgery with a CO_2 laser. Electrosurgery uses thermal coagulation to destroy genital warts. Randomized trials showed a slightly greater efficacy of electrotherapy compared with cryotherapy, but this difference did not persist after 3–5 months of follow-up. One

placebo-controlled trial found electrosurgery to be only slightly more effective in clearing lesions than placebo (91).

Laser therapy uses focused, infrared light energy to vaporize genital warts. In general, laser therapy is reserved for larger lesions and the lesions must be destroyed down to the base to minimize recurrence rates. Some authors suggest that the clearance of warts is better when laser therapy is performed under colposcopic examination. Recurrence rates in a randomized controlled design ranged from 60% to 80% (97).

Several other promising treatment options exist for genital warts. Topical IFN can be used to treat recurrent or resistant genital warts. Treatment efficacy has been supported by three placebo-controlled clinical trials and a trial with podophyllotoxin, which showed wart clearance to be increased substantially. IFN-α and -β can be used as adjuvants to surgery (98,99). Side effects are generally limited to burning and itching. Systemic IFN has been studied in RCTs with inconsistent results. This drug causes immunosuppression and its risks outweigh the benefits of its use as a treatment of genital warts.

The antiviral cidofovir has been reported to be effective in limited case series. One study has shown a 65% response rate (90). Typically, this drug is used as a 1% gel applied for 5 days straight, followed by 1 week rest, for up to six cycles. Four hours after application, the area must be washed. In a placebo-controlled trial, 47% of cidofovir-treated patient achieved complete remission compared with none of the placebo controls (100). Another placebo-controlled trial in HIV-positive patients showed similar results (101). In HIV-infected patients, one randomized (but not placebo-controlled) study showed the efficacy of cidofovir combined with electrosurgery, with a significant reduction of recurrence in patients treated with both cidofovir and electrosurgery in comparison to patients treated by surgery alone (102). These data are based on few subjects and further investigation is necessary; however, cidofovir remains a promising option for the future.

Another clinically effective, patient-applied treatment is 5-fluorouracil (5-FU) 5% cream. Small clinical trials support its efficacy as a monotherapy (103) and 5-FU with adrenaline gel has been tried and proven to be effective by a randomized, double-blind, placebo-controlled study (104). Associated side effects include erythema, edema, and skin ulceration. Though initial studies produced positive results, with the limited available data and with the potential toxic effects of the drug, this is not currently considered as a first-line therapy.

Immunomodulation with the human papilloma virus (HPV) vaccine is a more recent advance in the treatment of viral infections. Current research focuses on the development of prophylactic vaccines to prevent HPV infection and therapeutic vaccines to increase host immunity against HPV infection (105).

Less commonly employed therapies include topical or systemic retinoids and intralesional or systemic bleomycin. Both of these therapeutic options have significant adverse side effects and should be limited to use in refractory cases (105).

Molluscum Contagiosum

Lesions of molluscum contagiosum often involute spontaneously, without scarring. Despite this, the lesions are often treated to prevent patient discomfort, as well as autoinoculation and transmission.

Mechanical treatments such as curettage, cryotherapy, and electrosurgery achieve moderate to high initial success rates with variable recurrence rates (106), but can result in pain and mild scarring. Case reports show that CO_2 laser therapy may be an effective alternative (107), although keloid formation is possible after treatment (108). Curettage allows for the added benefit of confirmatory diagnosis. However, the success of physical ablation treatments has not been evaluated adequately and placebo-controlled studies are lacking.

Chemical therapies include trichloroacetic acid, 5-FU, bleomycin (106), cantharidin, phenol, salicylic acid, lactic acid, nitrates, and strong saline solution (109). Tretinoin cream may be useful as an adjuvant therapy (109). Randomized controlled trials have proven the success of podophyllotoxin as a treatment for molluscum contagiosum; however, these results are yet to be reproduced in a study with female participants (110). Local use of cytotoxic agents may result in skin reactions, pain, or adverse systemic effects (106).

Immunomodulators may be of benefit in treating molluscum contagiosum, especially in severe or treatment-resistant cases. In the past, IFN was used to treat molluscum contagiosum; however, results for genital lesions are variable (106). Imiquimod is currently used to treat genital molluscum contagiosum and its efficacy is supported by multiple studies (111,112), which show total clearance rates of 53%, with additional subjects showing substantial reductions in lesion size. Recurrence rates were as low as 7% after 12 months (111). Treatment typically lasts from 4 to 16 weeks. Advantages include its ease of application. There are few local side effects, including erythema, pruritus, and erosion; typically, tissue damage is less than the damage resulting from ablation.

Currently, cidofovir is being used for treating molluscum contagiosum (113), as are they are for other Poxviridae (114). Studies show promising results of treating HIV-infected patients with advanced molluscum contagiosum with topical and intravenous cidofovir (115). Any added benefit in this population may be due to antiviral effects.

Patients should be educated that, after treatment, the condition may recur due to re-inoculation from sexual partners.

Ectoparasitic Infections

Scabies (*Sarcoptes scabiei*)

The CDC-recommended treatment regimens for scabies include permethrin, lindane, and ivermectin (52). Effective alternatives include crotamiton, precipitated sulfur, and possibly benzyl benzoate (116). Even if they are asymptomatic, household contacts and sex partners from the previous month should be treated as well. Bedding and clothing must be decontaminated and sexual contact should be avoided until partners are cured (52). A few small studies have shown permethrin to be more effective compared with lindane and crotamiton in terms of clinical, parasitic, and subjective cure (116). One larger trial showed no difference between permethrin and lindane (117). Despite conflicting data, permethrin is the first-line treatment for scabies in adults and children over 2 months of age (52), a recommendation most likely based on clinical practice and reviews. Table 31.2 (117–124) summarizes RCT-supported treatments for scabies.

Permethrin 5% cream should be applied once to affected areas and washed off 8–14 hours later (52). Advantages include a limited side-effect profile and safety for use by pregnant women and children. Adverse reactions include burning, stinging, and exacerbation of recurrence of pruritus (125). Permethrin is more expensive than lindane and crotamiton, and cost should be considered when choosing therapy. There have been a few documented cases of permethrin-resistant scabies (126), and the number of such cases may be much higher.

Table 31.2 Randomized Clinical Trial-Supported Treatment Options for Scabies

Treatment	Placebo controlled?	Comments	Reference
Permethrin	No	More effective when compared with crotamiton and lindane; larger study showed no difference when compared to lindane	(117–121)(119) (largest, 476 subjects)
Crotamiton	No	Comparison with lindane showed no differences; see comments for permethrin	(118,119)
Lindane	No	See comments for permethrin and crotamiton	(117,118,120–123)
Ivermectin	Yes	Showed no difference when (the only oral agent) compared with benzyl benzoate or lindane	(123)
Sulfur	No	More effective when compared with benzyl benzoate	(124)
Benzyl	No	See comments for sulfur benzoate	(124)

Lindane 1% should be applied once and washed off 6–8 hours later; some clinicians recommend a second application 1 week later. Generally, lindane is an appropriate alternative treatment for scabies; however, there have been reports of possible resistance (52), and there are multiple possible adverse side effects. Convulsions may occur if applied after a bath or in patients with extensive dermatitis (127). Lindane has also been associated with the development of aplastic anemia (128,129) and brain tumors in children (126), though data are few. Accidental ingestion can lead to lindane-induced central nervous system toxicity, manifested by headache, nausea, vomiting, tremors, convulsions, respiratory failure, coma, and death (130). It is possible that these toxic side effects are due to overexposure or improper use. Lindane should not be used by patients with seizures or neurologic disease (125), pregnant or lactating women, or by children under 2 years of age (52). Exercise caution when prescribing this drug for any child weighing less than 50 kg (110 lbs) (131). Because of its multiple and potentially lethal side effects, the FDA in 2003 issued a public health advisory concerning the use of topical lindane for the treatment of scabies and lice (131). Despite this advisory, due to its low cost, ease of administration, and high efficacy, the use of lindane will likely continue. Thus, to reduce the incidence of toxicity, clinicians must warn against overuse and educate patients about proper product application techniques.

Crotamiton 10% lotion/cream should be applied once and reapplied 24 hours later, without washing between applications. The patient may bathe 48 hours after the final application (52). Some health care providers suggest a 5-day application (125,132). In non-randomized trials, cure rates have been as high as 70% (133), although the only RCT studying crotamiton found it to be no more effective than lindane (118). Some health care providers do not recommend using crotamiton because of the lack of toxicity data (133). There have been cases of crotamiton resistance (134).

Ivermectin, the only oral scabies treatment (100–200 mg/kg, and repeated 2 weeks later) is very useful for severe infection (52). Studies have shown cure after a single dose, even for immunocompromised patients (135). A review of published clinical trials showed no consensus regarding the most effective dosing regimens (136). Although one small randomized, placebo-controlled trial demonstrated the effectiveness of this drug (137), subsequent RCTs have shown that ivermectin is more beneficial than benzyl benzoate or lindane (116).

Epidemics occurring in nursing homes or hospitals must be controlled by treating the entire population at risk. In such epidemics, if topical agents fail, ivermectin may be considered (138). Tolerance is typically good; however, one study demonstrated increased mortality with ivermectin treatment among elderly, debilitated persons (139), but the authors failed to address the effect of confounding factors on the results. Therefore, the validity of this study is questionable (116). Case reports suggest its usefulness in severe infection, although a single oral dose might be inadequate in this scenario (126,140). Anecdotally, topical ivermectin has been used with success (133). Common side effects include headache, abdominal pain, and vomiting. Notably, ivermectin is not recommended for pregnant or lactating patients and its safety for children weighing less than 15 kg (33 lbs) has not been determined (52).

Sulfur is the oldest known treatment for scabies. Currently, a 6% ointment of precipitated sulfur applied for 3 consecutive nights is used as an alternative treatment for pregnant women and children under 2 months of age (52), or in situations in which other options are intolerable. This drug was shown to be more effective than benzyl benzoate in one RCT (124). Its advantages include its low cost, but it is difficult to apply and can cause skin irritation.

Benzyl benzoate 10%–25% in a lotion is applied for 24 hours on 3–5 consecutive days to treat scabies (126). Though it has been used for decades, its effectiveness has not been proven. Studies show it to be less effective than sulfur (124) and it has not been compared with permethrin (116). However, according to recent reports, benzyl benzoate may be helpful in certain cases of crusted scabies or in recurrent disease (133). Its disadvantages include skin irritation and a high treatment failure rate, possibly due to incorrect application. It should not be used by pregnant and lactating women, infants, and young children less than 2 years of age. Because of the lack of supporting data and the ease, effectiveness, and availability of other options, this treatment is used rarely.

Malathion, an organophosphate acetylcholinesterase inhibitor, was once used to treat scabies. This agent has not been investigated in RCTs (116). A lack of data, its bad odor, and the need for a long treatment period have caused this drug to fall out of favor.

More recently, topical spinosad 0.9% topical suspension has been found to be effective in scabies infection. Spinosad is derived from soil bacteria and has ovicidal activity. Spinosad is indicated for the treatment of head lice infestations in patients aged 6 months and older. Common side effects include skin irritation.

As rash and pruritus may persist for up to 2 weeks after treatment, clinicians should re-evaluate patients with scabies after 2 weeks. Some health care providers recommend retreatment after 2 weeks for patients who remain symptomatic, whereas others advocate for retreatment only if live mites are seen. Patients with initial treatment failure should be retreated with an alternative therapy (52).

Pediculosis Pubis (*Phthirus pubis*)

Currently, the CDC recommends treatment with permethrin, lindane, and pyrethrins with piperonyl butoxide. Other options include malathion and, possibly, ivermectin. Most of these preparations were discussed in the previous section and will be described only briefly here.

Permethrin 1% cream should be applied to the affected areas and rinsed off after 10 minutes (52). Higher cure rates are reported after a second application 1 week after the first (126). Permethrin is usually the first line of treatment, although resistance increases with time, which may present a problem (126).

Lindane 1% shampoo is also used topically, applied to the affected area, and washed off after 4 minutes. Lindane may have neurologic and hematologic side effects and should not be used by children or pregnant and lactating women (52).

Another effective treatment is natural pyrethrins with piperonyl butoxide applied to the affected area and washed off after 10 minutes (52). A second application 1 week later increases the cure rate (126). There are various vehicles available, including liquids, gels, and foams. Pyrethrins can provoke respiratory distress in patients allergic to ragweed (126).

Malathion, a 0.5% lotion, should be applied and left in place for 8–12 hours, then washed off (90). As stated previously, malathion is not used frequently.

Oral ivermectin has been used in trials (132,141), but is not currently recommended for lice. A 0.8% ivermectin lotion was successfully applied to 25 patients with head lice. As with scabies, recent household contacts and sex partners must be treated, bedding and clothing must be decontaminated, and sexual contact should be avoided. If lice are seen at follow-up in 1–2 weeks, the patient should be retreated.

Although indicated for head lice, topical spinosad 0.9% suspension has been used with success in cases of pubic lice (142).

VULVAR NEOPLASM

Vulvar Intraepithelial Neoplasia

Surgical treatment for frankly invasive vulvar carcinoma is clearly indicated; however, no commonly accepted treatment for VIN exists. The goal of treatment is to minimize symptoms and halt progression to invasive cancer while attempting to preserve anatomy and sexual function. Options include topical agents, wide local excision, laser therapy, and skinning vulvectomy. Management is individualized based upon biopsy, extent of disease, and symptoms. Table 31.3 (21,143–153) summarizes vulvar neoplasm treatments supported by non-RCTs.

Lower-grade VIN may be managed best with conservative, nonsurgical treatments that preserve vulvar anatomy. Several chemotherapeutic agents appear promising, but are yet to be proven by RCTs.

Imiquimod is currently FDA approved for the treatment of genital warts is being used currently to treat HPV-associated VIN. In a few small non-controlled studies, topical 5% imiquimod cream three times weekly was found to clear VIN II/III (143,154). Studies have shown at least a 75% overall response rate (154). Efficacy, however, may be limited when dysplasia extends into the ducts of glands or into hair follicles (145). Invasive carcinoma must be ruled out prior to therapy, as invasive disease has been found after treatment with imiquimod. Further studies investigating its efficacy are warranted.

In a case series, topical 5% 5-FU showed response rates of 50%–60% (144). However, 5-FU causes chemical desquamation that can result in significant discomfort, inflammation, and painful ulcerations. There has been one case report of the successful treatment of extensive VIN III with topical 1% cidofovir. Further investigation is necessary to determine the role of these drugs in the treatment of VIN.

Cidofovir is an acyclic nucleoside analogue with broad-spectrum antiviral activity. In one study, 12 women with VIN III were treated with cidofovir 1% every other day for 4 months. Out of the 10 women who completed follow-up, only three failed to respond. The others had 50%–100% resolution. Side effects include ulceration at the application site. While this may be an option for treatment of VIN, further investigation is necessary before this will be a recommended treatment option for this condition (155).

One small randomized, double-blind, crossover study evaluated topical IFN-α in 18 patients with VIN III. The study compared IFN-α versus IFN-α with nonoxyl-9 and showed a 67% response rate in all patients, independent of the addition of nonoxyl-9 (146). Although the results appear promising, the efficacy cannot be determined until a placebo-controlled trial with more participants is performed.

For low-grade VIN, surgery may be unnecessary. However, untreated VIN III lesions have a high incidence of conversion to invasive squamous cell carcinoma; typically, surgery is the best management (143). Surgical excision can be diagnostic as well as therapeutic, offering an advantage over ablative

Table 31.3 Non-Randomized Trial-Supported Treatment for Vulvar

Neoplasm stage	Primary treatment	Additional therapies
VIN	Local excision (143), skinning vulvectomy (144), laser (145), LEEP (145)	Promising topicals: imiquimod (21,143), 5-FU (144), IFN-α (146), PDT (147)
Stage I	If 1 mm: local excision with wide or radical margins (148) If 1 mm: add lymphadenectomy (149)	Laser/LEEP (145)
Stage II	Three-incision conservative or radical vulvectomy with bilateral inguinofemoral lymphadenectomy (149)	Laser/LEEP (145)
Stage III	Three-incision radical vulvectomy with bilateral inguinofemoral lymphadenectomy (149) If greater than or equal to one positive lymph node, add postoperative groin and pelvic irradiation (150)	Primary chemoradiation therapy (151), preoperative chemoradiation (152), preoperative radiation (153)
Stage IV	Radical or en bloc vulvectomy and lymphadenectomy, remove metastases (149) If greater than or equal to one positive lymph node, add postoperative groin and pelvic irradiation (150)	Primary chemoradiation therapy (151), preoperative chemoradiation (152)

Abbreviation: VIN: vulvar intraepithelial neoplasia; 5-FU: 5-fluorouracil; IFN-α: interferon-α; LEEP: loop electrosurgical excision procedure; PDT: photodynamic therapy.

or medical management options. This is important because of the frequency of undetected coexisting invasive squamous cell carcinoma. In a case series of patients treated with excision, more than 20% had underlying invasive disease, the majority of which was more than 1 mm (143,156). Local excision with 5-mm margins is sufficient treatment in unifocal disease with disease-free biopsy margins and no evidence of stromal invasion (143). Although excision through the depth of the epidermis is satisfactory, removing some underlying dermis may be of added benefit to rule out invasive disease (144). Disfigurement is a disadvantage; however, excision and close follow-up reduce the chance of development of invasive cancer. Nonetheless, in a 15-year follow-up study of patients after surgical excision, recurrence or persistence occurred in 48%, and disease progressed to frankly invasive carcinoma in 7% (157). Despite the widespread use of surgical treatment, there are no systematic reviews or RCTs showing the effects of the surgical treatment of VIN.

Several non-controlled studies support the use of laser therapy (excision and vaporization) as an alternative treatment for multiple small lesions (144,145). Laser excision has a cure rate of up to 87% (141,157). The cure rate after one treatment with laser vaporization is up to 75% (143,145,158). Most other cases achieve disease control with a second or third treatment (144,145). Some patients who received additional treatment developed invasive squamous cell carcinoma subsequently (143). A retrospective cohort study showed a significant increase in disease recurrence or persistence with laser vaporization as compared to local excision (157); subsequent smaller uncontrolled studies have had varied results. It is essential to rule out invasive cancer before using laser vaporization, as this modality involves tissue ablation. Superficial laser treatment may be more appealing cosmetically than the other surgical techniques—for example, clitoral involvement—in which case precision minimizes deformity and sexual dysfunction (156). In areas with hair, dysplastic cells are deeper and superficial treatment is not appropriate; in this case, the laser causes scarring and deformity. Recurrence is common in these regions; thus, standard surgical excision is preferable (148).

Skinning vulvectomy is recommended for more extensive lesions. Skin is removed subepidermally, allowing for preservation of subcutaneous tissue. Closure is either by reapproximation or with a skin graft (148).

Electrosurgery has been used with success and, when compared to laser therapy, appears to be as efficacious in clearing disease, but further study is necessary (145,159). Because of the availability and better success of other options, electrosurgery is currently not recommended. Cryosurgery, which has been used in the past to treat VIN, can have up to a 90% recurrence rate (160); however, data have been derived from studies with few participants.

In uncomplicated cases, an alternative to standard therapy is PDT (161). Topical 5-aminolevulinic acid can be applied to the vulvar lesion and activated with light. Multiple non-controlled studies show similar efficacy rates to conventional treatment options in clearing all grades of VIN. The advantages of PDT include a short healing time and minimal disfiguration (147). However, PDT can be associated with significant patient discomfort, including burning sensations and pain; in addition, recurrence of VIN is common after this treatment (144), and response rates in multifocal lesions and lesions with increased pigmentation and hyperkeratosis are lower (147). Nonetheless, PDT deserves further investigation.

Invasive Vulvar Neoplasm

There are several histologic types of invasive vulvar carcinoma, including squamous cell carcinoma, Paget's disease, basal cell carcinoma, melanoma, Bartholin's gland carcinoma, and sarcoma. Treatment for all of these types is similar.

Surgery is the primary treatment for invasive vulvar cancer. Historically, en bloc vulvectomy was the standard of care. This procedure includes vulvectomy and inguinal and upper femoral node dissection. However, en bloc vulvectomy results in severe genital disfigurement and is accompanied by a high incidence of treatment-related complications, including 1%–5% mortality rates (162). Currently, more conservative surgical techniques are preferred and are equally effective in limited, non-aggressive disease. Farias-Eisner et al. (163) reported similar survival rates when comparing patients with stage I and stage II disease after treatment with conservative versus radical vulvectomy. Nonetheless, in advanced, aggressive disease, radical vulvectomy may be necessary.

Alternatives to surgery include radiotherapy and/or chemotherapy.

Chemotherapy alone is of limited efficacy in vulvar cancer, but the combination of chemotherapy and radiotherapy appears effective (153). Radiation (150) and chemoradiation (152) can also be adjuvants to surgery. For patients with any stage of vulvar carcinoma who are unable to undergo surgery, radical radiation (153) alone may enhance survival.

Local surgical excision with wide or radical margins is the treatment of choice for stage I vulvar carcinoma (148,149). With less than 1 mm stromal invasion, fewer than 1% of cases are complicated by inguinofemoral lymph node metastases, and this procedure alone is adequate (144). Mohs microsurgery allows for complete removal of the primary lesion.

For more invasive stage I lesions (1 mm), the risk of nodal metastasis is 8% and additional unilateral lymphadenectomy is suggested (153). Ansink and van der Velden (164) authored a systematic review of two non-randomized, case-controlled, observational studies investigating the effect of surgical treatment in early squamous cell carcinoma of the vulva (cT1-2N0M0 tumors). With lateralized, node-negative disease, radical local excision with complete ipsilateral lymphadenectomy appears effective. Both studies reported similar recurrence rates in local excision as compared with radical vulvectomy (165,166). One non-randomized, case-controlled study supports ipsilateral dissection being as effective as bilateral dissection (165). Alternatively, for central lesions, bilateral lymphadenectomy is indicated (144). When resecting nodes, it is imperative to take both iliac and femoral nodes; one study found that leaving the femoral nodes resulted in a 4% groin recurrence rate (152). Though not first-line treatments, LEEP and CO_2 lasers may be acceptable alternatives to conventional surgery (145).

Three-incision conservative or radical vulvectomy with bilateral inguinofemoral lymphadenectomy is used to treat stage II disease (144). Five-year survival rates are 80%–90% (137). Survival and disease-free intervals are similar for modified radical vulvectomy and en bloc radical vulvectomy (167). Both LEEP and CO_2 laser treatment may be acceptable alternatives (145).

For stage III vulvar cancer, radical vulvectomy with inguinal and femoral lymphadenectomy is the currently accepted first-line therapy (144). In a randomized trial, participants with two or more positive nodes who underwent radical vulvectomy and bilateral inguinal and femoral groin node dissections

showed significantly better survival with postoperative groin and pelvic irradiation than with pelvic node dissection (150). Therefore, if nodes are positive, it is currently accepted practice to add pelvic and groin irradiation. A study investigating the role of radiation alone showed recurrence rates of 10% in patients with stage III/IV disease (150), proving that radiation alone is an unacceptable alternative for surgery. It is, however, an appropriate therapy for patients who are unable to tolerate or are unsuitable candidates for surgery (150). Preoperative radiation therapy may improve operability and decrease the extent of surgery required (153). Chemoradiation as a pretreatment before surgical excision may lessen the tumor burden, allowing for more conservative excision. In a Phase II study by the Gynecologic Oncology Group and Moore et al. (152), over 97% of patients treated with combination therapy were free of disease. Alternatively, chemoradiation can be used as a primary treatment of vulvar cancer (151). Trials have resulted in complete response rates of 53%–89% and disease-free survival rates of 47–84%, with a median follow-up of 37 months (153).

Chemotherapeutic agents with demonstrated effectiveness in combination with radiation include 5-FU, cisplatin, mitomycin C, bleomycin, and methotrexate (144). The disadvantages of combination therapies include multiple complications due to each individual intervention, as well as the risk of cumulative toxicity.

The surgical management of stage IV vulvar cancer involves radical or en block vulvectomy and lymphadenectomy and removal of metastases (144). With two or more positive nodes, surgery followed by radiation provides better survival rates than postoperative pelvic node dissection (140). Preoperative radiation (153) or chemoradiation (152) may decrease the tumor size and the extent of surgery required. Chemoradiation (151) alone is an acceptable alternative to surgery. For those who are intolerable of or unsuitable for surgery or chemotherapy, radical radiation therapy alone may increase survival (153).

Close follow-up is necessary to detect recurrence. Without nodal involvement, the 5-year survival rate after radical local excision is up to 75%. Inguinal recurrences may require vulvectomy. Radiation or chemoradiation may be used with or without surgery for palliation.

There is no standard treatment for metastatic disease. If distant metastases are present, salvage cytotoxic chemotherapy with cisplatin, methotrexate, bleomycin, mitomycin C, and cyclophosphamide may be appropriate (144). Prognosis is poor.

Verrucous carcinoma is a squamous cell carcinoma variant that is treated with wide local excision (168). If node positive, lymphadenectomy should be performed as well. Radiation is contraindicated because it may induce anaplastic transformation and increase the likelihood of metastases (169).

CONCLUSION

The vulva is a physiologically unique area and requires unique therapeutic consideration. Therapies that are used to treat general disease may not have the same effect when used to treat the vulvar area. It is important to address the need for specific treatment options for this area.

This chapter reviews current therapies for common vulvar conditions. Though these disorders are encountered commonly in the population, there are few convincing data supporting therapeutic regimens. Most of the recommended treatment options are based on clinical experience and case reports, with few supportive clinical trials. There are alarmingly few RCTs proving treatment safety or efficacy or determining optimal doses, preparations, or lengths of therapy. Existing studies have small participant populations and are methodologically imperfect. As a result, few conclusions can be made safely.

With women comprising over half of the U.S. population, it is essential that we gain understanding about the specific nature of the vulva and how this affects the ways that we treat the disease processes that are specific to this area. Further research is needed in order to appropriately elucidate the safety, effectiveness, and physiologic mechanisms of available vulvar therapies.

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PART 3

Genital Alterations and Classifications

Female genital alterations
A sociological perspective

Samar A. Farage

INTRODUCTION

In the last 30 years, female genital mutilation has become a topic of worldwide discussion and debate both as a health issue and a human rights violation (1–5). In 1996, the World Health Organization estimated that approximately 100 million women have undergone different forms of genital alterations in over 60 developing countries (6). Three types of such alterations are recognized widely by authorities as constituting genital mutilation. The first type, called *Sunna* circumcision, involves the removal of the prepuce with or without the excision of part or all of the clitoris. The second type of mutilation involves partial or total removal of the clitoris as well as scraping off of the labia majora and minora. The third type, and the most extreme form, consists of infibulation or pharaonic circumcision, which removes the clitoris, adjacent labia, and then sews the scraped sides of the vulva, leaving a small opening for urine and menstrual blood (6).

Calling these forms of alteration "mutilation" has become a political issue. Some researchers have argued that using the term "mutilation" to refer to the traditional forms of female cuttings is a value-laden approach that condemns the cultural context of these practices. Some also question the appropriateness of the use of the term "female circumcision" on the grounds that the severity of the harm done to women is underplayed by such comparison to male circumcision (5,7). Thus, this chapter avoids using these value-laden terms and uses the neutral phrase "female genital alterations" (8). This terminology permits the exploration of practices of genital alteration regardless of country, rationale, or even degree of technological sophistication. In addition, because of the political connotations of "female genital mutilation," the sociological and medical literature on the topic has focused on practices in Africa and Asia and almost entirely overlooked the history and current prevalence of female genital alterations in the West.

Female genital alterations began in Western countries in around the 1820s and were mainly justified as a cure for the "diseases" caused by excessive masturbation and nymphomania. The advent of such surgical alterations was linked to a transformation of masturbation from a sin, condemned by the Church for centuries, into a medical condition. This chapter discusses the distinct forces that converged to create a new illness called "postmasturbatory disease," which comprised such different manifestations as epilepsy, syphilis, fatigue, and dementia thought to be caused by masturbation. The extraordinary obsession with masturbation during the 19th century that led to female genital surgeries cannot be understood without considering the strange confluence of economic, cultural, religious, and medical ideas.

THE MASTURBATION SCARE

Masturbation was not an object for prescientific or Galenic medicine, which reigned supreme from the 2nd century AD until the late Middle Ages. For 1500 years until the 17th century of Western history, the precepts guiding medical practices were based on the Galenic conception of the body as a flux of fluid humors: black bile, yellow bile, blood, and phlegm. Maintaining good health required the balance of these humors in their correct proportions; disease was signaled by either an excess or deficiency in these fluids (9).

Hence, masturbation was considered quite therapeutic in certain cases, because it led to the evacuation of excessive seed in the body (10). Therefore, medieval physicians such as Avicenna, Albert the Great, and Riverius recommended the "friction of the genitals" for health purposes (11,12). This understanding of masturbation implied that it was not a moral issue within premodern medical thought. Even though some premodern physicians such as Boorde and Boerhaave in the 17th century warned of the debilitating psychological and physical effects of masturbation, they did not speak of it as a moral issue. Hare documents the debilitating effects ascribed by Boerhaave in his *Institutes of Medicine* (1701): "the semen discharged too lavishly occasions a weariness, weakness, indisposition of motion, convulsions, leanness, dryness, heats and pains in the membranes of the brain, with a dullness of the senses, more especially of the sight, a tabes dorsalis, foolishness and disorder of the kinds" (13). However, we can see no specific mention of masturbation per se (although it was included under sexual activity) until the beginning of the 18th century, and no belief that it was specifically harmful. This would change profoundly in the modern period as a consequence of the influence of church edicts against masturbation.

Masturbation was always a subject of discussion in religious circles; the church had condemned it as a minor variant of the illicit sexual activities that were explicitly outside the realm of procreation and, therefore, were against nature (11,14,15). The church doctrine on masturbation was unequivocal: any kind of masturbation was forbidden and the physician who recommended it for health was no less a sinner than the person who engaged in it; in the fourth Lateran council of 1215 under Innocent III, it was stated that "since the soul is much more precious than the body, we forbid any physician under pain of anathema, to prescribe anything for bodily health of sick persons that may endanger their souls." From the beginning of the Middle Ages, the position of the church evolved from a complex argument based on a stridently debated distinction between nocturnal emissions and voluntary pollutions. Its most vehement interdictions were aimed at the latter

rather than the former, which were classified as a mere venial sin. In contrast, voluntary pollution was considered a mortal sin or a sin against nature because it provoked sexual pleasure without carnal union (15).

This claim was backed by the authority of two Biblical texts. The first from Genesis invoked the crime of Onan, who was punished by God for "spilling his seed" (Gen: 38; 6–10). The second is found in the first letter of St Paul to the Corinthians (6; 9–10), who insisted that those guilty of "mollities" would be banned, along with fornicators and sodomites, from the Kingdom of God. The condemnation of the Church was not restricted to the bare act itself, but extended to the lascivious thoughts that accompanied it. Thus, for example, thinking of the Virgin Mary aggravated the mortal sin into a "horrendum sacriligium," and imagining oneself in the company of a married woman was equivalent to adultery (14).

Hence, before the 18th century, the medieval physician and the medieval priest viewed masturbation differently. Before the second half of the 18th century, none among the theologians and jurists who condemned masturbation as a sin against nature based his verdict on medical grounds. On the other hand, few if any medieval doctors spoke of masturbation as a sin, much less as a mortal one (16).

The publication in 1710 in England of *Onania, or The Heinous Sin of Self Pollution and its Frightful Consequences in Both Sexes Considered, with Spiritual and Physical Advice to Those Who Have Already Been Injured by This Abominable Practice and Seasonal Admonition to the Youth of the Nation of Both Sexes*, was a signal event in the West. Its authorship and date of publication are still subject to dispute according to most commentators, though the scholarly consensus seems to vacillate between John Marten and the priest Becker. Though written from within the Christian perspective (11,17), it marked the merger between the once distinct medical and religious positions on masturbation. By insisting that masturbation had reached epidemic proportions, the author aimed at fostering "Virtue and Christian Purity and to Discourage Vice and Uncleanliness." The book was extremely popular; it began as a 60-page pamphlet, and by the 16th edition had grown to 194 pages, accompanied by a 142-page supplement comprising letters from sufferers, repented sinners, and supporters.

The book is divided into three sections: causes, consequences, and diseases caused by self-pollution. Masturbation was not only condemned as a sin, but by tracing its consequences upon both the body and the soul, the author inserted the moral consequences into the medical outcomes. For example, masturbation was linked to stunted growth, phimosis and paraphimosis, strangury, priapism, gonorrhea, ulcers, thin and waterish seed, fainting fits, epilepsy, consumption, loss of erection, premature ejaculation, and infertility. The book is notable for not only raising the specter of masturbation as a medical and moral issue, but also for describing the ill effects of masturbation on women. Hence, masturbation was believed to cause the relaxation of private parts and "retentive faculty" leading to infertility, because male semen could no longer be held within the woman.

Moreover, according to the author of *Onania*, women who masturbated were prone to hysterical fits, barrenness, imbecility, fluor albus (leucorrhea), multiple miscarriages, and infertility. In addition, masturbators suffered physical transformations: "meager jaws, pale looks, feeble hams, legs without calves, their generative faculties weakened if not destroyed … dryness, emaciation, spirit sunk, body wasted, strength decayed" (14). Moreover, their entire progeny and the very future of the human race apparently lay in the balance: "from the wretches that survive, children may be expected so sick and weakly that they are a misery to themselves, a dishonor to the Human race and a scandal to their parents" (18).

The remedies for this "heinous sin" were both physical and moral. While the recommendations of marriage repentance and renunciation were the usual fare of moral injunctions, the author distinguished himself as a clever marketer by hawking 10-shilling "strengthening tinctures," 12-shilling "prolific powders," and "Aromatik Snuff" (18). After the publication of *Onania*, the term "onanism" made its appearance for the first time in the encyclopedia, defined roughly as the involuntary efflux of semen (synonyms were "mastupratio, manstupratio, and manustupratio"). By tying together the medical and moral reflections on masturbation, *Onania* provided a fecund frame for the proliferation of moral anxieties and the multiplication of medical interventions around "nature's handmaiden."

The repercussions of this pamphlet were felt on the European continent and absorbed within the burgeoning spirit of the French Enlightenment. However, it was the book written in 1758 by the Swiss physician Samuel August Tissot that raised masturbation to the position of a "colossal boogey" (13). In this book, published in Latin as *Tentamen de Morbis ex Manustrupatione* and translated into French in 1760 as *L'Onanisme ou Dissertation Physique sur les Maladies Produites par la Masturbation*, Tissot departs from the English *Onania* and its moral–theological overtones (19). Instead, Tissot makes much of his scientific grounding by asserting that 1 oz of sperm is equal to exactly 40 oz of blood. Hence, at this purported ratio of exchange, it was not surprising that Tissot considered sperm a very valuable fluid, calling it a "precious liquid." This idea was echoed almost 100 years later by Dr. George Calhoun of the USA, who stated, "The production of semen takes place much more slowly than that of any other secretion in the human body. This is owing to the route that semen has to take. If all seminal canals were extended in one line, it would be about 5208 ft long … the immense length shows that it is difficult for the semen to reproduce but that its excessive loss must be attended with disastrous consequences on the whole organism" (14).

Tissot's scientific aims extended to the mental effects of masturbation. Following the third law of Newton on action and reciprocal reaction, Tissot theorized that orgasms were spasms of extreme nervous activity that necessitated an equal and opposing depression of the nerves. This dampening of the nervous activity caused permanent derangement when it occurred too frequently, making the individual more susceptible to apoplexy, paralysis, insanity, and other nervous diseases (17). This idea contributed to the 19th century notion of "masturbatory insanity" caused by permanent brain damage due to constant irritation.

Therefore, according to Tissot, masturbation denuded the body of blood and, thus, gave rise to grave physical and mental consequences. Included among these were weakening of the digestive system, loss of or excessive appetite, vomiting, indigestion, breakdown of the respiratory system, and general debility and lassitude, as well as damages to the faculties and memory. The consequences to women were even more grave, because masturbation led to hysteria, "vapeurs affreuses," incurable jaundice, stomach cramps, prophase and ulceration of the womb, and clitoral rashes, for example. The young were particularly vulnerable, as the loss of "precious

liquid" stunted their natural physical development and contributed to feeblemindedness (14,17).

By providing a pathological model of masturbation rooted in the seemingly scientific and secular domain, Tissot's book sparked the 19th century medico-scientific masturbation phobia in the USA. Masturbation was transformed from one of the many forms of seminal and excretory loss into a sexual practice potentially fatal to individuals and society alike (20,21).

THE MANAGEMENT OF SEXUALITY AS A PROBLEM: POSTMASTURBATION DISEASE

The drastic cures and genital alterations that were developed for the first time in the 19th century emerged as a response to the masturbation scare. However, this development cannot be understood fully without understanding how sex became an object of political intervention (22). Historians of the 19th century have pointed out that the health of the nation-state depended on a micro-regulation of individual bodies as well as the management of populations (23–27). As evidenced by the medical journal *The Lancet* in 1819, doctors thought of themselves as being "… responsible for the employment of [their] peculiar authority in promoting the purification and well being of human society" (28).

This political regulation of sexuality as a paradigmatic instance of health management emerged at the confluence of five distinct (yet related) forces:

1. Changes in medical authority
2. Changes in body perception
3. The invention of childhood sexuality
4. The new demands of the industrialized economy
5. A renewal of religious fervor and Victorian cultural ideals

Changes in Medical Authority: The Physician/Priest and the New Body

It is now well known that since the beginning of the 19th century, the moral authority of the physician in the USA grew to encompass that of the priest. As noted by the social historian Englehardt, "The cycle of sin, confession, penance, and redemption was transferred from the confessional to the consulting room" (29,30). In this new role of physician/priest, doctors not only attempted to cure diseases, but also enforced the standards of a puritanical sexual morality well into the middle of the 20th century (31). By being able to tie the scientifically established consequences of masturbation to morally freighted proscriptions against it, doctors were able to give a new legitimacy to the idea of postmasturbatory diseases. From then on, such diseases would constitute the locus for the definition of normal sexuality and the massive political efforts to control people. Although the moral injunction against masturbation was venerable, the addition of the scientific standing of medicine in the early 19th century provided decisive weight to the political management of sexuality.

For example, the nerve theory of Haller and Cullen, the discovery of tissues as the site of disease by Bichat and Broussais, the confirmation of the mechanical nature of respiration and circulation first suggested by Harvey, and the entitative nature of disease agents established by Mortgagni constituted some of the diverse strands that led to the emergence of scientific medicine (32).

Changes in Body Perception

The explanations offered for postmasturbatory diseases since the early 19th century under the light of scientific medicine were based on a new concept of the human body as being analogous to a machine (33,34). The older understanding of the body as composed of fluid humors was replaced by a structural and functional view, which implied that the body was reducible to a machine composed of nerves, fibers, muscles, and glands. This conception of the body was not only promulgated by the physicians, but also adopted by their patients, who would routinely speak of themselves using terminology such as "depleted energy," "nervous excitations," and "muscular fatigue" (32). A substantial current within the new scientific medicine was the belief that sexual excess threatened the loss of vital energy. This theme, which drew from the theories of energy conservation in physics of the mid-19th century, entailed that each person was invested with a finite quantity of energy and its misuse would lead to physical degeneration and mental depravity (35). This energy model of the body would be instrumental in the creation of a new "spermatic economy," in which sperm—like money and labor force—had to be used optimally (36).

The Invention of Childhood Sexuality

The idea of childhood sexuality did not exist before 1700. Neither priest nor physician paid any attention to the sexual behaviors of children. In the beginning of the 18th century, both the moralist and the medic began to censure childhood sexual activity as both sinful and/or pathological. By the 19th century, masturbation among children was considered a social evil and a threat to the polity as a whole; it became the first building block in the invention of childhood sexuality (37–39). Just as sexuality in general was considered a problem to be managed, childhood sexuality in particular would give rise to the concerted and institutionalized effort to control children. For example, whether through schools, churches, or new forms of parental supervision, the child was thought of as a distinct social entity in need of specialized attention (40). This belief gave rise to the vast industry of child-rearing techniques premised on regulating childhood sexual behavior and instilling childlike obedience to authority (26,38,41). As the flow of semen coincided with the onset of puberty, it was widely believed that any loss of semen at this age would stunt development and growth (20). As the well-being of a child became linked to his or her sexual propensities and behaviors, parents became willing agents to the nostrums of the 19th century medical establishment that recommended chastity belts, toothed rings on the penis, strait jackets, surgeries, and other such procedures (42,43).

The Demands of an Industrialized Economy

The onset of widespread industrialization in the USA beginning in the mid-19th century led to a heightened attention to the idea of labor force. The requirement of a hard-working pool of labor for the emerging factories promoted the ideas of labor productivity, work ethic, and the bourgeois character, who exercised financial thrift and sexual continence. The capitalist economy based on maximizing efficiency in the use of resources demanded maximum productivity with minimum waste. Furthermore, the fruits of industrialization were well understood to be the consequence of the interdependence arising from the division of labor. In this sense, the economic strength and political order of a nation depended crucially on the self-discipline of people imbued with a strong sense of civic

responsibility (16,20,44). This generalized schema had its counterpart in the "spermatic economy"; sperm, like money, had to be invested fruitfully. Therefore, such acts as masturbation and frequenting prostitutes were seen as wasting the potential to accumulate precious capital. As masturbation was a solitary vice performed alone, it was condemned as antisocial and narcissistic.

The self-absorbed masturbator was considered the exemplar of those who refused to contribute to the well-being of the nation (20,44,45). The idea of climbing the social and economic ladder that was held as ideal in the 19th century American society required the laboring classes to mimic the sexual self-control or sublimation that contributed to the success of the middle classes (46,47). The professional and gentlemanly class differentiated itself by adhering to the repressive demands of continence to fuel their economic prowess. In a similar vein, the moral–medical attacks on prostitution and nymphomania were justified by the argument that such practices were unproductive and bore no useful fruit (15). Thus, prostitution and the regulation of women's sexuality received major impetus from the consideration of sexuality in economic terms (48). The wastefulness inherent in the commerce with oneself or others thus became a major front in the creation of sexuality as a problem to be managed. It was precisely this mentality that would later fuel the eugenic movement in the Anglo-American world.

Victorian Ideals and Religious Fervor

The division of labor required by the new industrial economy redefined the ideals of masculinity and femininity (33). The separation of work from home life cemented the division between the roles of men and women, mainly in the middle classes (49). In this newly defined role, women were confined to the home and thought to be frail, passive, and passionless (50–52). By the middle of the 19th century, men were thought of as producers whereas women were considered to be reproducers. This growing sexual division of labor was underscored by medico-scientific theories that posited the naturalness of this divide by arguing that women's passive nature left them ill-equipped for the competitive world of education, work, and politics. Women's delicate nervous system, monthly "illness," smaller brain, and specific reproductive organs all made them unhealthy to vote, work, go to college, or participate in the public arena (53).

The Victorian ideal of a woman as nurturing, affectionate, intuitive, moral, domesticated, and dependent was assumed to have a biological basis in the smaller and, therefore, more sensitive nerves that made women more prone to anxiety, neurasthenia, hysteria, and irrationalities (54–57). Medical prejudice considered women prisoners of their reproductive organs and thought that a woman's uterus and ovaries controlled her body and behavior from puberty to menopause.

So deep was this medical idea rooted in the Victorian ideal that even as late as 1870, a physician is on record as stating, "It was as if the Almighty, in creating the female sex, had taken the uterus and built up a woman around it" (47). Thus, any exposure to sexual excesses was considered detrimental to their sexual purity and effectiveness as mothers (47,54). Indeed, a curious reversal of sexual identity was ascribed to masturbation. It was believed that men would become more effeminate while women would become more masculine (as agitating the clitoris would render it more penis-like) if either engaged in acts of "self-help" (33).

Another current feeding the Victorian ideal of the passionless woman was the rise of the Evangelical movement in the USA between 1790s and 1900s. Within this movement, rooted in Protestantism, there was no distinction between mortal and venial sins. Accordingly, all sexual acts were sins per se, unless for the purpose of procreation. Promoting of Christian values and virtues contributed to the transformation of women from sexual into moral beings responsible for the upbringing of future generations (51). In this role, churchmen such as Rev. John Todd (1800–1873) used their pulpits to bully women into exercising sexual restraint as proof of their moral and noble character. Pulpits—no less than manuals, pamphlets, and exhortations—were used to spread the masturbation phobia throughout the 19th century (36,58). This combination of moral, economic, and medical factors that gave rise to sexuality as a problem created the conditions for an intensive and unprecedented investigation into techniques and methods to control the sexual behavior of men, women, and children (37,59). Notably, women were the principal experimental guinea pigs for the rash of surgical techniques, instruments, and devices aimed at controlling sexual energies (60–62).

TYPES OF FEMALE GENITAL ALTERATIONS

The application of surgical procedures to the genitalia of men, women, and children is a predominantly 19th century phenomenon in the West. Male circumcision has an ancient and largely religiously inspired history (60,63). However, genital surgeries on females and children are almost exclusively a product of the 19th century. Moreover, the use of instruments and devices to restrain sexual activity in the general population (as opposed to monks) gained much in inventiveness and intensity of pain during this period. While the abovementioned factors contributed to the acceptance of genital surgeries and related devices, three rationales were given during the 19th century for their specific use (64–69).

First, as masturbation was linked to a wide and seemingly limitless range of diseases, from epilepsy to rheumatism and insanity, the medical establishment focused much of its curative efforts on the genitalia. This therapeutic rationale was foremost among the justifications for genital surgical interventions and the invention of new methods for sexual restraint (70). For example, according to the 1848 report on the Massachusetts Lunatic Asylum, approximately 32% of admissions were for self-pollution (71). Further, it was a routine matter to castrate such inmates in droves to prevent masturbation and, thus, to cure them of insanity. Women in particular were "castrated" by removing their ovaries to cure them of psychological disorders (72,73).

The second dominant rationale was that of public health or sanitary injunctions. According to this line of reasoning, both doctors and public health officials were concerned with maintaining the general health of the population; they were involved in cleaning up pollution whether caused by industry or the self (74). This large-scale effort to sanitize cities and bodies would also encourage putting self-polluters into insane asylums and then using them as a captive population for experimenting with advances in genital surgeries and devices of restraint. Even private entrepreneurs got into the sanitary game. Wellness centers sprung up all over the country, a good example of which is the Kellogg Center for Clean and Healthy Living (75). Not only were Kellogg's corn flakes sold as a healthy non-stimulant designed to dampen all sexual passions, but his centers were

hotbeds for restraining techniques (41,76). Sylvester Graham, a Presbyterian minister, invented the Graham cracker, which, together with a mild vegetarian diet, was intended to reduce sexual cravings, while C.W. Post marketed his Postum cereal as the "Monk's Brew."

Lastly, a general rationale often mentioned was the need to eradicate childhood sexuality. It is notable that a vast proportion of the surgical interventions and instruments was applied to the bodies of young children, both boys and girls. For example, the antimasturbation school bench was designed to force students to keep their legs apart and prevent them rubbing their genitals; long coats were forbidden and strenuous gymnastics, boxing, and other vigorous sports were recommended to channel the energy of the young into productive activities (43).

PROCEDURES OF THE 19TH AND 20TH CENTURIES

Methods to control female sexuality included relatively pain-free interventions such as hydrotherapy, dietary prescriptions, and educational exhortations. However, the use of inventive restraints of various kinds flourished during this period as a preferred method of controlling women's bodies (48). For instance, the Moody Girdle of Chastity of the mid-19th century is exemplary. It "… consisted of a cushion made out of rubber or some other soft material and suitably covered with silk, linen, or soft leather. This cushion or pad formed the base into which was fixed a kind of grating and this part of the apparatus rested upon the vulva, the pad being large enough to press upon the mons veneris …" (43).

Dietary measures, hydrotherapy, educational exhortations, and even physical restraints seemed too slow in their effects on stopping masturbation. Surgery was a much quicker procedure and was often described as affording immediate relief and preventing the further development of illnesses and deterioration of patients (77).

The onset of surgical genital procedures can be attributed to the medical work of Dr. Marion Sims, the "father of gynecology" and the "architect of the vagina." By the mid-19th century, the traditional art of obstetrics expanded to include the new science of gynecology (36). Procedures that explored the interior of the female anatomy were the brainchild of Dr. Sims in the USA. It was he who invented the vaginal speculum and systematized the use of uterine sound and curette, as well as cervical dilators. Around this time, the first specialized medical journal in the USA was devoted to obstetrics. Descriptions of ovariotomies, hysterectomies, and the repair of vesicovaginal fistulas conducted under the most primitive conditions were featured routinely in its pages. Dr. Sims performed surgeries to repair vesicovaginal fistulas and applied his techniques, without the use of anesthesia, first on slave women in Alabama. Later, during the mid-19th century, he exported these techniques to upper-class women in New York.

While Dr. Sims was engaged in his surgical experiments in the USA, Dr. Isaac Baker Brown introduced clitoridectomies in England as a cure for epilepsy, syphilis, insomnia, unhappy marriages, and even insanity. He was the president of the Medical Society of London and was considered an authority on the nervous diseases of women. As a consequence, his work on scissoring the clitoris became the model for this surgical intervention. Dr. Brown believed that all feminine weaknesses could be cured by the excision of the clitoris. According to him, the peripheral excitement of the pubic nerve, which ends in the clitoris, led to disease that could be divided into eight progressive stages of degeneration: hysteria, spinal irritation, hysterical epilepsy, cataleptic fits, epileptic fits, idiocy, mania, and death. Hence, restlessness, loss of appetite, back pain, and distaste for marital intercourse were considered signs that demanded clitoridectomy (78–80). In cases in which he avoided excising the clitoris, he would damage the vulva and the clitoris by applying caustic substances to cause painful sores.

It is interesting to note that by the 1860s, the work of Dr. Brown was castigated by the medical community in England and he was removed from his position in the obstetrical society. In England, the practice of clitoridectomies declined rapidly in the face of the vociferous criticism that centered on its brutality. Nevertheless, Dr. Brown's inventiveness found a fertile home in the USA. The evangelical impulse that gained ground quickly gave his techniques a moral legitimacy. What was then viewed with disfavor in England became the procedure of choice for the moral correction of women and girls in the USA.

By the 1880s, with the increasing association of masturbation and insanity, female castration or oophorectomy became widespread (81). This procedure was the 1882 invention of Dr. Robert Batty of Georgia and was called normal ovariotomy (73,82). The vogue of female castration received encouragement under the eugenic movement and lasted well into the 1940s. Indeed, the eugenic movement inspired not only castration, but also the rampant use of sterilization as a cure for insanity and general debility (13,83).

The prevalence of genital surgeries as legitimate medical procedures can be gauged by the establishment of the Chicago-based Orificial Surgery Society in the late 1880s (43,65). During its uninterrupted and popular run until the 1920s, the Society, which was composed of prominent medical experts, oversaw the regular publication of a professional journal and textbooks. The Society was anchored by the belief that the lower orifices were responsible for moral, religious, and emotional well-being. For example, as a disorder in the sphincters could cause nervous irritation, the Society recommended dilation, amputation, and related operations on women and men. Between approximately 1850 and 1950, the USA was the site for a sustained rash of surgical procedures performed on the genitalia of men, women, and children (60,84). Whereas the last recorded castration was performed in 1946, the last medically justified clitoridectomy occurred in Kentucky in 1953 in a 12-year-old girl (58). The call for developing new and better, improved techniques still was voiced in the late 1950s (85). In retrospect, it can be seen that the advent and flourishing of genital surgeries for over a century was a complex response to the masturbation scare.

CONTEMPORARY FEMALE GENITAL ALTERATIONS IN NORTH AMERICA

Even though the scare died down after the Kinsey Report of 1948, which normalized masturbation and even considered it a healthy release or an expression of self-love, genital surgeries for medical reasons did not end completely (15). Female circumcision continued to be encouraged in the postwar years for cleanliness, hygiene (18), frigidity, cancer, urinary tract infections, prevention of sexually transmitted diseases such as AIDS and HIV (35), and genital anomalies. One gauge of the latter is that approximately 2% or approximately 80,000 live births in the USA annually are subjected to modifications of genitalia to define sexuality (7,86,87). These operations (sex reassignment

surgeries) are performed on infants whom the medical literature calls intersex children (88,89). In general, these rationales for female genital surgeries are less prominent than those of the preceding century.

Cosmetic Genital Surgery

A different rationale for female genital surgeries has also begun to emerge. Triggered by standards of genital beauty established by the pornographic industry, fearing the aging of genitalia, and seeking the ultimate orgasm, women are both demanding and being tempted to undergo surgical alterations for cosmetic reasons (90,91). This practice seems to have escaped the scholarly literature, although the medical establishment has begun to enjoy its financial benefits (92). As documented in the popular press, genital plastic surgery appears to be a growth area within the field of cosmetic surgery (93). Procedures once aimed at therapeutic interventions to correct incontinence, congenital malformations, and injuries sustained during childbirth are now sold as elements in the architectural redesigning of the vulva (94). The old procedures now carry new names, such as elective vaginal enhancement, vaginal rejuvenation, female genital aesthetics, vaginoplasty (tightening of the vagina), hoodectomy (unhooding of the clitoris), labiaplasty (reduction of the labia minora or labia majora), reduction of the mons pubis, hymenaplasty (reconstruction of the hymen), and raising the aging pubis (95).

The internet has been a major contributor to the spread of vulvovaginal aesthetic surgery, and studies have abounded on the demographics and psychosexual dynamics of these requests for genital cosmetic surgeries, as well as surveys describing the level of satisfaction with such procedures (96,97).

CONCLUSION

This chapter has examined the different rationales that were offered to legitimize female genital surgeries or alterations. These procedures, which began in the early 19th century, were rooted in the great terror associated with masturbation. The sustained effort for more than 100 years to control the bodies of women and children gave rise to a vast array of devices and techniques to surgically alter their genitalia. In retrospect, the therapeutic rationales offered since the early 1800s are clearly specious. Given the World Health Organization's definition of female genital mutilation ("all procedures that involve partial or total removal of female external genitalia and/or injury to the female genital organs for cultural or any other nontherapeutic reasons"), then the conclusion that the Western history of female genital surgery should be considered genital mutilation is compelling. More troubling is the realization that the procedures now conducted in the name of elective genital enhancements in Western countries are no less a form of mutilation. Thus, genital mutilation is not a practice peculiar to faraway developing countries.

Furthermore, in light of the continuing prevalence of female genital alterations in many traditional countries and the development of thriving cosmetic vaginal surgery industry in the West, a compromise solution has been offered by two researchers to allow female genital nicks as a way of preserving cultural tradition in many developing countries (98). A storm of ethical concerns has recently been raised again about terminology and practices. The debate over such a controversial topic continues.

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Female genital cutting*

Cultural challenges and health complications

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Ritual female genital cutting (FGC) comprises all procedures that involve partial or total removal of the external female genitalia or injury to the female genital organs for cultural or nontherapeutic reasons (1). The World Health Organization (WHO) estimates that over 140 million women and girls worldwide have been subjected to this practice and that each year about 3 million more girls are at risk of some form of genital cutting. It occurs at high rates in 28 countries in Africa and to some degree in certain countries of the Middle East and Asia (Yemen, Oman, Saudi Arabia, United Arab Emirates, Bahrain, northern Iraq, Malaysia, Indonesia, Pakistan, India, and among minority groups in southern Israel). The WHO defines four main categories of FGC (Figure 33.1) (2):

- *Type I:* Excision of the prepuce with partial or total excision of the clitoris (clitoridectomy).
- *Type II:* Excision of the clitoris with partial or total excision of the labia (clitoridectomy and/or labial excision). (Types of FGC that involve cutting of the clitoris are known in some places as the *Sunna* form.)
- *Type III:* Excision of part or all of the external genitalia and narrowing and covering the vaginal opening by joining and fusing the raw edges of the labia with stitches or glue, leaving a small opening for the flow of urine and menses (infibulation, also known as the *Pharaonic* form.)
- *Type IV:* Includes other forms of non-therapeutic genital alteration such as pricking, piercing, incising the clitoris or labia; stretching the clitoris or labia; cauterizing the clitoris and surrounding tissue; scraping the vulvar vestibule; cutting the vagina; and introducing caustic substances, poultices, or herbs into the vagina to create a tightening or narrowing of the vaginal vault.

Because ritual cutting often involves rudimentary techniques, the WHO describes subsets of these categories in order to approximate the range of possible outcomes (Table 33.1) (2).

Growing numbers of immigrants from countries where this ritual practice is common have settled in North America, Western Europe, Australia, and New Zealand, bringing the practice with them. Global authoritative bodies, which have declared the procedure a violation of bodily integrity and human rights, use the term female genital mutilation. Because women from affected regions may not view themselves as having been mutilated, this review uses the neutral term, FGC. The authors have a particular interest in how FGC affects a woman's quotidian quality of life, from everyday menstrual health and hygiene, to sexual health, pregnancy, childbirth, and postmenopausal challenges. This review describes the cultural determinants of the practice, its impacts on health and well-being, and areas where further research is needed. The goal is to address the health and emotional concerns of these women with sensitivity so that we can improve their quality of life.

PREVALENCE

The practice of FGC has ancient sources, although no definitive evidence exists on how it began. It was part of ancient Egyptian culture and has been found in mummies (3). Some speculate that it may have originated with the ancient Greeks or in pre-Islamic Arabia. In the 19th century, clitoridectomy was advocated in England and North America for the treatment of hysteria and masturbation, a theory that was eventually debunked (4). Today, ritual cutting is most prevalent in 28 countries of Africa, with the highest rates in Egypt, Somalia, Sudan, Eritrea, Guinea, Sierra Leone, Mali, and Djibouti (Table 33.2) (5–22). The type of FGC varies depending on the country, the traditional practices of the region, religious beliefs, levels of education and economic development, and the ethnicity and tribe to which the woman belongs (Table 33.3) (6,8,10–14,16,17,22–24).

The practice continues among immigrants to the developed world. The European Parliament estimated that up to half a million women living in the European Union have been subjected to FGC, with 180,000 more at risk (25). In 2001, it was estimated that 174,528 women residing in England and Wales had been born in a country that practices FGC, a figure considered to be an underestimate (26). Based on the 2000 U.S. census, the Centers for Disease Control and Prevention and the African Women's Health Center in Boston estimated that over 200,000 girls and young women in the USA were at risk of undergoing FGC (27). Between 2000 and 2012, the population of African-born immigrants to the USA more than doubled, from 750,000 to 1,724,000 (28). Forty-eight percent are women and 68% are from countries in North Africa, Eastern Africa, and Western Africa where FGC is most prevalent (28). Although prevalence varies by ethnicity, region, and tribe, assuming that the prevalence of FGC among women in immigrant communities reflects that reported by the WHO for their country of birth overall, we estimate from 2012 figures that roughly 340,000 women in the USA may be affected or at risk of FGC (Table 33.4) (5,28).

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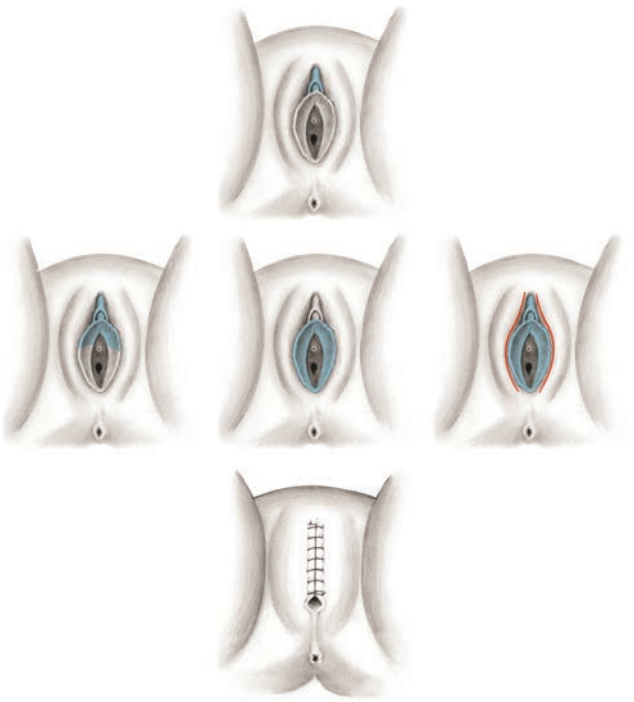

Figure 33.1 Anatomical perspective on some of the major forms of female genital cutting. Blue color represents the excised portion of the anatomy. Due to rudimentary cutting techniques, variants of lesser or greater severity may be observed (see Table 33.1). First row—type I: full clitoridectomy. Second row—major type II variants: removal of the clitoris and partial removal of the labia minora; removal of the labia minora only; total excision of the clitoris and labia minora (red lines indicate where cut edges of the labia majora may be created in the progression to type III). Third row—type III: infibulation achieved by excision of the external genitalia and apposition of the cut edges of the labia majora.

U.S. health care providers should be aware of this growing at-risk population. The states with the largest African-born populations are California, New York, Texas, Maryland, and Virginia (29). Sizeable numbers of immigrants from affected countries reside in the major metropolitan areas of Los Angeles–Riverside–Orange County–San Diego and San Francisco–Oakland–San Jose, CA; New York–Northern New Jersey–Long Island, NY–NJ–PA; Houston–Galveston–Brazoria and Dallas–Fort Worth, TX; and Washington–Arlington–Alexandria, DC–VA–MD–WV (27). In addition, sizeable enclaves of refugees from countries with civil unrest have formed in some mid-Western cities. Somalis, for example, represent the largest influx of African refugees to the USA in the last two decades; 50,000 or more have settled in Minnesota and represent one in five immigrants to that state (30). As of 2012, over 45,000 have settled in Columbus, Ohio, with 200 more arriving each month (31).

CULTURAL DETERMINANTS

FGC is traditionally performed on young girls as an obligatory social norm to ensure an honorable and worthy womanhood. The age and manner in which the ritual is performed varies. In some cultures, midwives and birth attendants perform the procedure on infants; in others, it is the purview of older female relatives or traditional circumcisers. In Egypt, traditional midwives or *dayas* were called upon historically, but today, medical personnel perform more than half of all procedures (6). In most countries, girls are typically cut between the ages of 4 and 18 years, although the procedure is most often accomplished before menarche. In Egypt, for example, 80% of girls are cut between the ages of 5 and 9 years (32); in The Gambia, between the ages of 4 and 7 years (33); in Mali, the median age is 6 years, with a range of 1–16 years (34); in Tanzania, the median age is 10 years (13); in Ethiopia, over 80% are cut by 11 years of age (12); among Somalis, at least half are cut by 8 years of age and 95% by 12 years of age (8).

In traditional societies, girls are held down with spread legs and the operation is performed without anesthesia using unsterilized knives, razorblades, scissors, cut glass, or sharp stones. In type I FGC, the most common form, the clitoris is

Table 33.1 World Health Organization Classification of Female Genital Mutilation/Cutting

Classification	Anatomical involvement[a]	Subcategories[b]
Type I	Clitoridectomy: partial or total removal of the clitoris and/or the clitoral hood (prepuce)	Type Ia: removal of the clitoral hood or prepuce only Type Ib: removal of the clitoris with the prepuce
Type II	Clitoridectomy and/or labial excision: partial or total removal of the clitoris and/or the labia minora, with or without the removal of the labia majora	Type IIa: removal of the labia minora only Type IIb: partial or total removal of the clitoris and the labia minora Type IIc: partial or total removal of the clitoris, the labia minora, and the labia majora
Type III	Infibulation: removal of the external female genitalia and sealing or narrowing of the vaginal opening by joining opposing cut parts of the labia, using stitches. The clitoris may or may not be removed. A small opening is left for urination and menstruation	Type IIIa: removal and apposition of the labia minora Type IIIb: removal and apposition of the labia majora
Type IV	All other harmful procedures to the female genitalia for non-medical purposes	These include, pricking, piercing, incising and stretching the clitoris or labia, burning the clitoris, scraping the vestibule, and cauterizing the vaginal vault with corrosive substances or herbs

Source: Adapted from World Health Organization (WHO). Classification of female genital mutilation. In: *Sexual and Reproductive Health. Topics. Female Genital Mutilation. Overview*. Geneva: World Health Organization, 2014. http://www.who.int/reproductivehealth/topics/fgm/overview/en/

[a] In some cultures, types I and II are referred to by the Arabic term *Sunna*, and type III by the term *Pharaonic*.

[b] The subcategories attempt to make finer distinctions for research purposes, but in practice, the cutting procedures are rudimentary and imprecise; considerable variability will exist.

Table 33.2 Prevalence of Female Genital Cutting in Traditional Societies of the Developing World

Country or region	WHO estimate of overall prevalence % (5)	Year (5)	Other published studies on demographic variability	Year	Source
North and East Africa					
Egypt	91	2008	94%–97% of married women 50.3% of schoolgirls	2000–3 2005	(6,7)
Somalia	98	2006	Among Somali refugees in Ethiopia, 52% circumcised by age 7–8 years 95% by ages 11–12 years	2004	(8)
Sudan, northern	90	2000	87%–100%	2001	(9)
Djibouti	93	2006 2012	Severity varies by ethnicity Types II and III most prevalent	2012	(10)
Eritrea	89	2002	n.a.		
Ethiopia	74	2005	92.3% in Kersa district (self-reported) Associated with Christianity, illiteracy,and ethnicity 82.2% in schoolgirls, Hadiya zone, Southern Ethiopia	2008 2011	(11) (12)
Kenya	27	2008/9	n.a.		
Tanzania	15	2004	17% among patients at a clinic in Kilimanjaro Prevalence higher among Muslims and illiterate patients and lower among Christians and the educated or Chagga ethnicity	1999	(13)
Uganda	0.8	2006	n.a.		
Western Africa					
Benin	13	2006	33% circumcised before age 11 years	2001	(6)
Burkina Faso	72	2006	74% Secular declines	2005–7	(14)
Cote d'Ivoire	36	2006	36.5%	2005–7	(14)
The Gambia	78	2005/6	79%	2005–7	(14)
Ghana	~4	2006	<6%	2005–7	(14)
Guinea	96	2005	n.a.		
Guinea-Bissau	50		45%	2005–7	(14)
Liberia	58	2007	n.a.		
Mali	85	2006	n.a.		
Mauritania	72	2007	72% 70% Secular declines	2005–7 2000–1	(14) (15)
Nigeria	30	2008	22% overall, ranging from 2% in Abuja to 58% in Kwara region 45.9% among a clinic population Varied by ethnicity and religion(29%–69%) 26% in survey of 10 countries Secular declines	2003 2005–7	(16) (17) (14)
Senegal	28	2005	A community-led approach (Tostan) has reduced the practice	n.r.	(18)
Sierra Leone	94	2006	94%	2005–7	(14)
Togo	~6	2006	<6%	2005–7	(14)
North Central Africa					
Chad	45	2004	n.k.		
Cameroon	1.4	2004	n.a.		
Central African Republic	26	2008	n.a.		
Niger	2.2	2006	<6%	2005–7	(14)
Western Asia and Middle East					
Yemen	38	2003	45% in 1997; 38% in 2003	1997, 2003	(19)
Saudi Arabia			Anecdotal evidence; figures are lacking		
Iraq	–	–	Among Kurds in Erbil City, self-reported prevalence, 70%; 59% by examination 43% overall in Iraqi Kurdistan	2007–9	(20,21)

Abbreviation: n.a.: not available; n.k.: not known—no detailed demographic breakouts found; n.r.: not reported.

Table 33.3 Types of Female Genital Cutting in African Countries

Country or region	Year	Types of female genital cutting (% of total)				Demographics of population studied	Source
		Nicked	Tissue removed (WHO types I or II)	Sewn closed (WHO type III)	Unknown or other		
North and East Africa							
Egypt	–	n.r.	Most common form	N/A	n.r.	38,826 schoolgirls	(6)
Sudan	1989–90	14.8	2.7	82.4	0.1	Figures are for adult women Among girls aged 4–9 years seen in a clinic, prevalence of type III was 66%	(22,23)
Somalia	2004	n.r.	63.9	36.1%	n.r.	Somali refugees in Ethiopia	(8)
Djibouti	2012	n.r.	n.r.	93% either type II or III	n.r.	Varies by ethnicity (types I and II among Afars, type III among Issas)	(10)
Eritrea	2002	46.0	4.1	38.6	11.3	n.r.	(22)
Ethiopia	2008	N/A	92	10.4	1.2	Kersa district	(11)
	2013	N/A	82	N/A		Hadiya zone	(12)
Kenya	2008	0.3	82.7	13.4	1.6	n.r.	(22)
Tanzania	2002	n.r.	97% type I 3% type II	n.r.	n.r.	Kilimanjaro (N = 63)	(13)
Western Africa							
Benin	2006	0.5	93.8	3.9	1.8	n.r.	(22)
Burkina Faso	2010	16.6	76.8	1.2	5.4	n.r.	(22)
Cote d'Ivoire	2012	4.7	71.1	8.7	15.6	n.r.	(22)
The Gambia	2010–11	n.r.	75.6% type I 24.4% type II	n.r.	n.r.	Clinic patients	(24)
Guinea	2005	1.7	86.5	9.3	2.58	Prevalence >90% in 5 of 6 ethnic groups	(22)
Mali	2006	3.0	75.8	10.2	11.1	Prevalence >90% in 5 of 6 ethnic groups	(22)
Mauritania	2000–01	5.5	75.3	n.r.	19.3	n.r.	
Nigeria	2008	3.0	45.4	5.3	46.4	Ethnicity, religion, and education level most significant predictors	(17,22)
Senegal	2010–11	9.9	52.7	13.8	23.6	n.r.	(22)
Sierra Leone	2008	3.2	82.0	2.6	12.2	n.r.	(22)
North Central Africa							
Chad	2004	19.6	76.0	2.3	2.1	n.r.	(22)
Niger	2006	0.8	77.8	13.3	8.2	n.r.	(22)

Abbreviation: N/A: not available; n.r.: not reported

held between the thumb and forefinger and amputated with a single stroke. Packing the wound with bandages under pressure stops the bleeding. Trained personnel may stitch the clitoral artery. In type II FGC, the clitoris and labia minora may be removed with the same stroke, and the extent of cutting varies. In type III FGC, the clitoris, labia minora, and inner surface of the labia majora are removed, and the cut surfaces of the labia majora are stitched together with thorns or glued with sticky substances to create fusion. The girl's legs will be bound for several weeks to accomplish healing, during which time female relatives attend to her. The procedure creates a hood that covers the urethra and most of the vagina, leaving a small opening for the passage of urine and menses. By contrast, in subgroups such as the Arab Bedouin tribes of southern Israel, the ritual remains culturally important but has been reduced to a clitoral nick with one or two stitches (35).

FGC is a deeply rooted societal norm and a number of cultural beliefs contribute to its significance (10,36,37). It is a tradition and social obligation that brings honor to the girl and her family. Cutting reduces sexual drive and ensures that the girl remains chaste, marriageable, and faithful. Although practiced by members of various religious traditions (17,35), in predominantly Muslim communities it is often believed to be a religious obligation, and the vernacular term *Sunna*, which also conveys the traditions of the Prophet, imbues some religious significance (10,37). However, in recent years, government bodies and religious leaders have campaigned against the practice, particularly in its most extreme forms. Hygiene and esthetic norms also play a role. In some societies, the external genitalia are considered unclean and unsightly; the clitoris is viewed as a male appendage that must be removed or an organ that must be bled for cleansing and purification (38). Lastly, FGC is a rite of passage that reinforces cultural identity and a sense of belonging.

In some societies, the ritual is secret and young girls are unaware of the event until they are taken aside by their mothers or female relatives to have the procedure done. In others, girls will be advised that a special event is about to transpire, although its details may not be fully understood. Still others are told they will be cut but reassured that although it is painful, they will recover. Cultural cues reinforce its social significance (38). Uncut girls may not be allowed to serve tea or prepare food because they are unclean, and may be teased or ostracized by their cut peers.

Table 33.4 Estimates of African-Born Immigrant Populations in the USA Potentially Affected or at Risk of Female Genital Cutting (FGC) Based on 2012 American Community Survey, U.S. Census Bureau

African country of birth	Estimated numbers in the USA from this African country, 2012	WHO estimate of FGC prevalence in country of origin (%) (5)	Estimate of African-born women residing in the USA affected or at risk of FGC[a]
North and East Africa			
Egypt	234,754	91	102,541
Somalia	124,431	98	58,532
Sudan	48,692	90	21,035
Djibouti	n.r.	93	n.a.
Eritrea	n.r.	89	n.a.
Ethiopia	239,670	74	85,131
Kenya	57,445	27	7445
Tanzania	n.r.	15	n.a.
Uganda	10,949	8	420
Western Africa			
Benin	n.r.	13	n.a.
Burkina Faso	n.r.	72	n.a.
Cote d'Ivoire	n.r.	36	n.a.
The Gambia	n.r.	78	n.a.
Ghana	96,654	4	1856
Guinea	n.r.	96	n.a.
Guinea-Bissau	n.r.	50	n.a.
Liberia	56,219	58	15,651
Mali	n.r.	85	n.a.
Mauritania	n.r.	72	n.a.
Nigeria	272,591	30	39,253
Senegal	13,993	28	1881
Sierra Leone	19,413	94	8759
Total	1,174,811		342,504

Source: Adapted from US Census Bureau. American Fact Finder. Selected population profile in the United States. 2012 American Community Survey 1-yr estimates. Country of birth. Table S0201. 2012. factfinder2.census.gov/faces/tableservices/jsf/pages/productview.xhtml?fpt=table. Community survey of African immigration to the USA, 2012 estimates.

[a] Assumes women represent 48% of African immigrants from any region (the proportion reported for all African born immigrants in the 2012 American Community Survey). Does not account for age or ethnic and regional differences in country of origin.

Abbreviation: n.r.: not reported; n.a.: not available.

Well-known derogatory terms reinforce the view that remaining uncut would be shameful. In some communities, FGC is a celebratory rite of passage. In Sierra Leone, for example, FGC takes place as part of a group initiation into the Bondo Society, a secret society of women (39). The event, run by a society leader who also performs the cutting, takes place in a private clearing in the bush, where the girls will spend days or weeks to be instructed in the norms of womanhood. Initiates are rewarded with celebrations, gifts, and public recognition. Whatever the context, the procedure is initially painful and traumatic, but girls are reassured that they have been brave and strong and are now pure, beautiful, and worthy (38). Through affirmation and inclusion, cut girls develop a sense of pride, cultural identity, and social acceptance. Mothers and grandmothers gain respect for having done their duty to foster an ideal young woman.

HEALTH CONSEQUENCES

Immediate Complications

When ritual cutting is performed in the traditional manner, the immediate complications can include: severe pain; hemorrhage from the internal pudental artery or the dorsal artery of the clitoris; damage to the urethra, vulvar vestibule, and vaginal walls; urinary retention during the period of healing from type III cutting (infibulation); bone fractures due to pressure applied to the struggling girl; tetanus from unsterilized instruments; septicemia; shock due to blood loss; and death (Table 33.5) (1,24,33,34,40–56).

Long-Term Complications

Dermatological Changes

Tissue damage and improper healing occasioned by the rudimentary cutting techniques create several complications. Chronic vulvar pain may result from trapped or unprotected nerve endings. Keloid scars, which are particularly common in people of African descent, result from progressive overgrowth of dense fibrous tissue (collagen) after wound healing (24). Numerous cases of clitoral or vulvar epidermal inclusion cysts have been reported (40–43,57,58). Inclusion cysts arise from invagination of the keratinizing epidermis into the dermis, and the cyst is lined with a wall of true epidermis. They are slow growing, beginning as a painless swelling at the cut site and gradually increasing in size over several years to form a

Table 33.5 Health consequences of Female Genital Cutting (FGC)

Health consequences	References
Short-term complications	(1)
• Severe pain (no anesthesia) • Hemorrhage • Shock • Urinary retention • Infection, such as tetanus or sepsis • Bone fractures • Death	
Long-term complications	
Dermatological	
Chronic vulvar pain from trapped or unprotected nerve endings Excessive scar tissue (keloids) Epidermal inclusion cysts in the clitoris, labia, or infibulation scar Damage to vulvar lymphatic tissue Neuroma	(33,40–43)
Urological	
Slow or painful micturition Urinary retention Dribbling urinary incontinence Recurrent urinary tract infections	(44,45)
Menstrual health and hygiene	
Slow and painful menstruation (dysmenorrhea) Pelvic congestion and infection	(24,46)
Sexual health	
Dyspareunia (painful intercourse)	(47)
Labor and childbirth	
Prolonged or obstructed labor Perineal tears Genitourinary fistulas (necrosis of tissue between the urethra and vagina or vagina and rectum due to obstructed labor) Incontinence	(48–52)
Menopause	
Hypoestrogenism leads to vulvovaginal atrophy in postmenopausal women (studies are lacking in women with FGC)	
Infectious disease and cancer	
Higher prevalence of bacterial vaginosis and herpes simplex-2 infection Indirect association with HIV (group circumcision with unsterilized instruments, coital bleeding, and herpes simplex-2 infection as risk factors) Increased cervical cancer rate	(53,54) (34)
Psychological	
Post-traumatic stress disorders	(55,56)

large clitoral or vulvar mass (in one study, 40% were larger than 3.5 × 6.5 cm at an average age of 17 years) (59). Cysts are socially stigmatizing when they interfere with walking or sitting or are apparent to the spouse. Besides cysts and abnormal scars, two rare complications are neuroma of the clitoris, which also presents as a mass (24), and vulvar lymphangiectasias, which appear as itchy, wart-like papules resulting from damage to the lymphatic tissue (60). The papules may be superimposed on lichenified tissue due to chronic scratching.

Urological Effects

Damage to the urethra can result from any form of cutting. Slow, painful micturition, dribbling urinary incontinence, urinary retention, and recurrent urinary tract infections are common sequelae of infibulation (44,45).

Menstrual Health and Hygiene

Women who have undergone infibulation suffer high rates of dysmenorrhea due to congestion from obstructed menstrual flow (hematocolpos) (24,46). Often women do not understand the cause of their symptoms, unless they learn about the health complications of FGC through educational efforts or discover relief from symptoms after undergoing defibulation by a health care professional (37).

Limited research exists on menstrual hygiene in these populations. A prospective, examiner-blind clinical trial of disposable sanitary napkins was performed in Abuja, Nigeria, among 283 women aged 18–45 years, 20% of whom had undergone type I FGC (61). The study compared a locally produced disposable pad and an imported pad designed to trap and keep fluid away from the skin. Mean numbers of pad changes during the menstrual period ranged from 1.20 to 3.30 per day, depending on flow levels. The imported pad was preferred for lack of soreness or tenderness and for not feeling wet during wear. Neither product was associated with adverse effects.

A hospital-based case–control study of cervical cancer in Mali, which examined women who had undergone FGC (95.1% of cases and 92.8% of controls), found that lack of care in cleaning the genitalia was associated with a 5.6-fold increased risk of invasive cancer (34). Use of commercial sanitary napkins or tampons was virtually non-existent in the population. Reusing homemade sanitary napkins was almost exclusively restricted to cancer cases, resulting in a 46-fold increased odds ratio for cervical cancer associated with this practice when adjusted for age, availability of a toilet inside the home, parity, and human papilloma virus serostatus (34). Malian women often report repeated use of menstrual pads that were not always clean, possibly due to a lack of access to tap water. Poor menstrual hygiene and the rewashing of rags for menstrual protection have been linked to genital infections in other resource-poor countries (62). For example, poor genital hygiene was also associated with cervical cancer in rural China, while sanitary napkin use was protective (63).

Obstetric and Perinatal Complications

FGC is associated with adverse obstetric and perinatal outcomes and the excess risk depends on the severity of cutting. A large, prospective collaborative study sponsored by the WHO in 2006 examined 28,393 patients at 28 obstetric centers in Burkina Faso, Ghana, Kenya, Nigeria, Senegal, and Sudan (48). Cut women were at higher risk of cesarean section, postpartum hemorrhage, extended maternal hospital stay, infant resuscitation, stillbirth or early neonatal death, and low birthweight. The excess risk rose with the extent of cutting: women with type III FGC had a 69% higher risk of postpartum hemorrhage, a 98% higher risk of extended hospital stay, a 66% excess risk of requiring infant resuscitation, and a 55% excess risk of stillbirth or early neonatal death (48). Parity did not significantly affect these relative risks. FGC was estimated to lead to an extra one to two perinatal deaths per 100 deliveries.

Numerous studies have been performed in various locations and utilizing different approaches (case series, case–control studies, cross-sectional surveys, etc.). A recent meta-analysis of 28 comparative studies, involving almost 3 million

women, provides considerable supporting but not conclusive evidence that FGC is associated with obstetric complications (49). The analysis found that cut women were 3.3-times more likely to experience difficult or prolonged labor and twice as likely to experience obstetric hemorrhage. Vaginal stenosis and obstruction around the introitus associated with more invasive forms of FGC could contribute to prolonged labor; the inelasticity of vulvovaginal scar tissue could contribute to the increased risk of perineal tears and hemorrhage.

Rates of maternal morbidity and mortality are higher in countries that practice FGC compared to more developed regions, with hemorrhage being the leading cause of maternal mortality (64). Countries in which the majority of women undergo the most extensive forms of FGC, such as Somalia and Djibouti, have a higher maternal death rate (>700 per 100,000 live births) than countries with a much lower prevalence of FGC but similar midwifery practices, such a Kenya and Tanzania (<500 per 100,000 live births) (10).

Some excess risk may persist among immigrants to developed countries. Studies dating to the initial time period of Somali immigration to the USA and Europe suggested that immigrant women were at higher risk of perineal laceration and postpartum hemorrhage (65–67), perhaps due to challenges in communicating effectively with immigrant patients and their resistance to Western obstetrical interventions (31). However, other investigations of immigrant women with FGC receiving modern obstetric care in Saudi Arabia, Israel, and Western Europe have found no differences in rates of prolonged labor or perinatal complications (68–70).

Obstetric fistulas, a potential complication of FGC, result from necrosis of urogenital structures when compressed between the fetal head and the mother's pelvis during obstructed labor. Urinary incontinence results from sloughing of the posterior wall of the bladder or urethra and fecal incontinence from pressure necrosis of the posterior vaginal wall and neighboring rectum. These consequences are devastating to the woman, both physically and socially. Several case reports involve women who have undergone type III FGC or caustic narrowing of the vagina (50,51). However, a recent study in Ethiopia found that types I and II FGC were not independent causative factors in the development of vesicovaginal fistula from obstructed labor (52). The high rate of obstetric fistulas in countries where FGC is prevalent could also be related to risk factors such as early marriage when pelvic growth is incomplete coupled with a lack of emergency care.

Sexual Health

Studies of the sexual health of women who have undergone FGC vary in location, methodology, quality, and the types of cutting represented, making broad conclusions difficult. A systematic meta-analysis of 17 comparative surveys of cut and uncut women, comprising a total of 12,755 participants, concluded that the evidence base was insufficient to draw conclusions about the psychological and social consequences of FGC (47). The analysis suggested that cut women are more likely to experience pain during intercourse, reduced sexual satisfaction, and reduced sexual desire, but the quality of the evidence was judged too low to conclude a causal relationship with FGC.

Blood-Borne and Sexually Transmitted Infections

Wound infections and sepsis can develop due to the unsterile conditions employed when girls are cut, and group cutting with the same instrument may increase the risk of transmitting blood-borne diseases such as hepatitis B and HIV. Among pregnant women in Yemen, for example, being cut was significantly associated with seropositivity for the hepatitis B antigen (71). Cut women with type II FGC in rural Gambia had a 66% higher risk of bacterial vaginosis, which the investigators speculated might be related to removal of the labia minora (33). Cut women also had a 4.7-fold higher prevalence of herpes simplex-2 infection (33), an epidemiologic risk factor for HIV throughout Africa (53). Analysis of demographic variables among 3167 Kenyan women aged 15–49 years suggests that FGC is indirectly associated with HIV risk through associated practices in adulthood (54). Specifically, cut women are 1.72-times more likely than uncut women to have older partners (perhaps through arranged marriage) and women with older partners are 2.65-times more likely than women with younger partners to test positive for HIV; moreover, cut women have 1.94-times higher odds than uncut women of initiating sexual intercourse before they are 20 years of age, and women who experience their sexual debut before 20 years of age have 1.73-times higher odds of testing positive for HIV. However, a study of 379 clinic patients in Tanzania found no association of FGC with hepatitis B, HIV, or reproductive tract infections (13).

Psychological Impact

Human rights advocacy groups and women's health centers that serve immigrant women affected by FGC obtain poignant testimony of the psychological trauma they endure (37,72,73). Evidence of post-traumatic stress disorder has been observed in subsets of women in their home countries and among immigrants to the West (55,74). Not all women process their experience in the same way; it is colored by the meaning they create of this tradition and their own adaptive styles.

Postmenopausal Health

Vulvovaginal atrophy is a natural consequence of hypoestrogenism following the menopausal transition (reviewed by Farage et al. (75)). This is a growing women's health concern as the population of the industrialized world ages. In the intact woman, the labia atrophy and lose elasticity, the introitus narrows, and the clitoral hood may become phimotic. The vagina becomes shorter and narrower and loses the typical folds (rugae); the vaginal epithelium is more friable and prone to friction-induced bleeding. Vaginal pH rises above 4.5, increasing susceptibility to infection. Atrophic symptoms in the intact woman include vaginal dryness, itching or burning, painful intercourse, increased urinary frequency, dysuria, and nocturia.

However, in the less-developed countries of Africa, the risks of HIV infection, maternal mortality, and limited access to health care reduce life expectancies to some of the lowest levels globally. Life expectancy for women in Tanzania, for example, is 53 years, and FGC is a risk factor for early death (76). African immigrants to the USA are less likely to be over 65 years of age than the native or foreign-born population; two-thirds of African-born immigrants are under 45 years of age (28,30). No systematic studies are available on postmenopausal urogenital health in women who have undergone FGC, and their needs are unaddressed. Health professionals in the developed world who serve immigrant communities must examine the sequelae of aging in cut women, raise awareness, and address the impact of FGC on postmenopausal health and quality of life.

EFFORTS TO END FGC

Over the last three decades, the international community has mounted efforts to end the practice of FGC, spearheaded by organizations within the United Nations, the WHO, the legislatures of affected countries, and non-governmental organizations (NGOs). In numerous international and regional declarations, FGC is acknowledged to be a violation of human rights and bodily integrity, as the practice has no therapeutic benefits, is known to cause physical and psychological harm, and is often carried out on children too young to give informed consent (1). Although the practice remains deeply rooted, slow progress has been made. Prevalence remains high in Somalia, Djibouti, and Egypt (77), but change is underway. In Somalia, for example, the adverse consequences of type III cutting have become more broadly acknowledged; however, some religious leaders defend milder forms of the practice, leading to the erroneous perception that the *Sunna* form is benign and fulfills religious obligations (37,78). Prevalence has dropped most dramatically in Burkina Faso, Mauritania, and Senegal (14,77). In Burkina Faso and Mauritania, authorities employ a multi-pronged approach: they initiate educational programs to change perceptions, enlist prominent groups to champion eradication, gain support from practitioners such as midwives and traditional healers, promote alternative symbolic rites of passage, and enforce legislation (14). Tostan, a NGO working in rural areas of Djibouti, Guinea, Guinea-Bissau, Mali, Mauritania, Senegal, Somalia, and The Gambia, fosters respectful and inclusive community-led training for broad-scale development and social change (18). A 3-year community empowerment program with trained facilitators provides villagers with information on human rights as well as practical skills in the areas of hygiene, health, democracy, literacy, math, and project management. Community members then determine a collective vision for their future, consider which practices in their villages do not lead to well-being, and make celebratory public declarations committing to end harmful practices such as FGC.

Ending the practice among immigrant communities in the West brings its own set of challenges. FGC-affected communities encounter an alien culture: promoting traditional norms maintains social cohesion against intrusive foreign ideas. These communities are deeply threatened by the sexual liberalism in Western society. The emphasis on individual rights over group identity is seen as discriminatory and in conflict with religious beliefs. To protect their daughters, women themselves keep the practice alive. The illegality of FGC in host countries drives the practice underground; it persists by enlisting the help of traditional circumcisers within the immigrant community or by sending girls to relatives in the home country for vacation cutting.

Women from FGC-affected societies have a culture of silent endurance, are unaware of the prevalence of complications, and may attribute their personal suffering to shameful behavior or unclean spirits. Because Western notions of individual rights do not resonate, changes in perception require interventions that are respectful and sensitive to the culture. An example from Norway illustrates the challenges of cross-cultural intervention (72). When a foreign speaker addressed a group of Gambian immigrants about the health consequences of FGC, the information was rejected as not credible. However, when a female Gambian doctor presented slides of little Gambian girls with scars, cysts, and fistulas caused by FGC, the information, though shocking, was believable; as the doctor hummed the secret songs from the initiation ceremony, the audience was galvanized by the realization that she too had been cut. Such discoveries are psychologically painful, however, prompting a deep sense of loss (72). Time and emotional healing are needed to process this new understanding. Consequently, educational efforts require great sensitivity, the cooperation of families and influential leaders, and access to culturally competent support groups. The power of social norms cannot be overemphasized. Only when communities feel it is not detrimental to do so will they change.

CONCLUSION

Ritual FGC is a deeply rooted social norm among women from several countries in Africa, the Middle East, and Asia. Growing numbers of immigrants from FGC-affected societies now reside in North America, the European Union, Australia, and New Zealand. To provide optimal care, health care providers in developed nations need training in order to better understand both the cultural context of this practice and its complications. The African Women's Center located at the Brigham and Women's hospital in Boston is the first and only African health practice in the USA that focuses on issues related to FGC. Founded by Dr. Nawal Nour, a native of Sudan, its mission is to holistically improve the health of refugee and immigrant women affected by the tradition, and it is a source of culturally sensitive information for patients and health care providers (79). The WHO offers numerous resources, including a manual on the prevention and management of female genital mutilation for nursing and midwifery students (80).

FUTURE PERSPECTIVE

Formal training on FGC will be developed for health care providers, school personnel, and social service workers. Pediatric care providers will learn about the cultural norms and benefit from training on how to address the practice and its complications at a point of early intervention in a factual yet sensitive manner. Training for school counselors and nurses will cover the cultural context of FGC, the urinary and menstrual complications that affect these girls, and their potential need for information on adequate menstrual hygiene. Obstetricians, gynecologists, nurses, and midwives will be formally trained on how to care for these patients, how to provide information on obstetric interventions and gynecological complications, and how to interact with their spouses in a culturally competent way. Virtually nothing is known about the postmenopausal experience of these women. Prospective research must and will be initiated in immigrant communities as the emphasis shifts to aging populations and geriatric care. Psychological and sociological research will explore how affected girls, women, and families process the information that cutting is not universal and how this influences their integration into the host country at various life stages, from school to marriage and beyond. Community centers may be established to facilitate culturally competent collaboration between women's health advocates, health care providers, immigrant thought leaders, families, individuals, and social welfare organizations in an effort to build trust and encourage positive change over the long term.

EXECUTIVE SUMMARY

Definition and Types of FGC

- Ritual FGC comprises all procedures that involve the partial or total removal of the external female genitalia or injury to the female genital organs for cultural or non-therapeutic reasons.

- The WHO has defined four major categories of FGC. Type I is clitoridectomy; type II is clitoridectomy and/or partial or complete removal of the labia; type III, or infibulation, involves excision of part or all of the external genitalia and narrowing and covering of the vaginal opening by joining and fusing the raw edges of the labia, leaving a small opening for the flow of urine and menses; and type IV is any other form of altering the external female genitalia for non-therapeutic reasons.

Prevalence

- FGC is prevalent in 28 African countries and in various communities in the Middle East and Asia. Over 140 million women and girls worldwide have been subjected to this practice. Each year, about 3 million more girls are at risk of some form of genital cutting. Up to half a million women living in the European Union have been subjected to FGC, and 340,000 girls and young women in the USA may be affected or at risk of FGC.

Cultural Determinants

- FGC is performed on young girls as an obligatory social norm. Depending on the society, midwives, traditional circumcisers, respected elders in society, older female family members, or medical practitioners may perform ritual cutting.
- Reasons for the practice include ensuring chastity and marriageability, hygienic and esthetic reasons, to comply with perceived religious obligations, as an act of purity, as a coming-of-age ritual, and to preserve tradition and cultural identity.

Health Consequences

- Short-term complications include severe pain (no anesthesia), hemorrhage, shock, infections (including tetanus or sepsis), shock, and death.
- Dermatological complications include vulvar pain, keloid scars, clitoral or vulvar inclusion cysts, neuroma, and vulvar lymphangiectasias.
- Urological complications include slow and painful micturition, urinary retention, urinary incontinence, and recurrent urinary tract infections.
- Menstrual health complications include dysmenorrhea, pelvic congestion, and infection.
- Possible sexual consequences include painful intercourse, reduced sexual satisfaction, and reduced sexual desire.
- Women with FGC are 3.3-times more likely to experience difficult or prolonged labor and twice as likely to experience obstetric hemorrhage. The excess risks rise with the severity of cutting. There is also an increased risk of perinatal complications such as the need for infant resuscitation and neonatal death.
- Group cutting with the same instrument may increase the risk of transmitting blood-borne diseases such as hepatitis B and HIV. Cut women are at higher risk of bacterial vaginosis and herpes simplex-2 infection.
- The experience of FGC is traumatizing and subgroups of women show signs of post-traumatic stress disorder.
- Life expectancy is low in FGC-affected countries, immigrants to the West are relatively young, and little is known about postmenopausal urogenital health in women who have undergone FGC.

Eradication Efforts

- Although the practice remains deeply rooted in traditional societies, slow progress has been made. Two approaches have met with some success. One is a multi-pronged effort toward community change that includes educational programs to change perceptions, enlists prominent groups to champion eradication, gains support from practitioners such as midwives and traditional healers, promotes alternative symbolic rites of passage, and enforces legislation. Another approach is a village-by-village empowerment program by the NGO Tostan that combines knowledge of human rights, respectful sharing of information in a non-judgmental way, and teaching of practical skills for sustainable development. This allows communities to develop their own holistic vision for changing practices that affect their well-being, including FGC.
- Among immigrants to developed countries, the encounter with the libertine mores of an alien culture is threatening. Sustaining traditional norms maintains social cohesion and cultural identity. The practice is perpetuated by enlisting the help of traditional circumcisers within the immigrant community or by sending girls to relatives in the home country for vacation cutting. The discovery that cutting is not universal and may cause women to suffer can be psychologically painful. Consequently, educational efforts require great sensitivity, the cooperation of families, and access to culturally competent support groups and professionals.

Serving the Needs of Immigrants from FGC-Affected Societies

- More comprehensive training will assist health care providers to provide optimal and culturally sensitive care for patients and families affected by FGC.
- The long-term health issues of cut women must be examined in order to address the unmet needs of these women as they age.
- The medical communities have to confront an understudied concern of what happens as this population ages. This will be a challenge that will need to be addressed in order to provide optimal health care to women affected by FGC.
- Developing community centers that take a holistic approach to the needs of refugee and immigrant women may build trust and empowerment in underserved communities.

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Classification of the labia minora

Cindy Wu, Lynn A. Damitz, and Denniz A. Zolnoun

INTRODUCTION

According to the American Society for Aesthetic Plastic Surgeons' (ASAPS) 2014 statistics, there was a 49% increase in the number of vaginal rejuvenation procedures between 2013 and 2014 (1) and a 16.1% increase between 2014 and 2015 (2). Labia minora reduction (most commonly described as labiaplasty) has become an increasingly popular procedure, both for functional and cosmetic indications. The Franco classification (3–5) for labia minora hypertrophy was based on the length of the labia minora, but did not specify in which dimension. A more recent classification system by Chang et al. (6) is based on the labia minora protrusion in relation to the labia majora in the superior–inferior dimension. However, the uni-dimensional natures of these classifications do not account for the width or depth of the labia minora. We describe a new classification system of labia minora that factors in all three dimensions, which allows more detailed description of the deformity, thus facilitating more practical surgical application. We also describe labia minora anatomy as analogous to the lip, which as a conceptual framework also allows the plastic surgeon to more easily plan for reconstruction.

METHODS

Primary and secondary labiaplasties were performed with a plastic surgeon in conjunction with a gynecologist specializing in clinical neurophysiology and urogenital pain. Labiaplasty was contraindicated if patients had active gynecological disease (infection or malignancy). Prior to the procedure, a preoperative diagnostic test called sensory mapping (not published) was performed to ensure the proposed areas of resection did not correspond to critical sensation pathways. Markings were adjusted as needed after discussion with the patient. A central wedge resection (7–9) was performed. Since our collaboration began in 2010, we have found that the previously existing classification systems did not adequately describe the variety of labia minora anatomy that we encountered. A labia minora classification system was subsequently developed based on a Cartesian coordinate system of three-dimensional space in which the x-axis describes the horizontal plane, the y-axis describes the vertical plane, and the z-axis describes the depth of the plane. Each individual labia minora shape can be characterized with this system by describing the three dimensions: (i) labia minora length (along the vertical, y-axis); (ii) labia minora width (along the horizontal, x-axis); and (iii) labia minora height (representing depth, z-axis) (Figure 34.1). In addition, we adhered to the principles of lip reconstruction when performing labiaplasties, due to the analogous anatomy. Both the classification system and the translational anatomy of the lip have guided our surgical management of the labia minora.

RESULTS

The classification system and lip reconstruction principles were used on 35 primary and secondary labiaplasties. The main indication for surgery was dyspareunia (26/35, 74.3%), followed by discomfort in clothing (8/35, 22.9%) and unacceptable cosmetic appearance (1/35, 2.9%) (Table 34.1). After a mean follow-up of 221 days, the wound dehiscence rate was 2.9% (1/35), dyspareunia 14.3% (5/35), unacceptable cosmetic appearance 2.9% (1/35), and recurrence of presenting symptoms 20% (7/35) (Table 34.2 and Figures 34.2 and 34.3).

Labia Minora Classification

There are many variations in labia minora anatomy, and our classification scheme describes the labia in three dimensions: the width (medial/lateral dimension) or x-axis; the length (anterior/posterior dimension) or y-axis; and the height (superior/inferior dimension) or z-axis (Figure 34.1).

Labia Minora Width (x-Axis)

The x-axis represents the base width of the labia minora from the most medial to lateral extent. The labia minora width is individualized; however, the tissue types from medial to lateral can be generalized and are analogous to the lip.

Analogous Anatomy between the Labia Minora and the Lip

The labia minora, like the lip, are one of several places in the body that have a defined mucocutaneous junction (Figure 34.2). As in lip augmentation or reconstruction, these anatomical landmarks must be preserved. The labia minora are made up of a wet mucosa (analogous to the wet vermillion of the lip), a dry mucosa (analogous to the dry vermillion), and a keratinized, often pigmented epithelium (analogous to the skin bordering the dry vermillion, separated by the white roll). Each of these zones average 1 cm in length, but may vary. The wet mucosa in the posterior vestibule is typically 1.5-times wider than the anterior vestibule. Because of these anatomic similarities, lip vermillion reconstruction using a full-thickness labia minora graft has previously been reported (10).

Labia Minora Length (y-Axis)

The y-axis is the anterior–posterior length of the labia minora (Figure 34.1). The length of the labia minora varies greatly, but in general, three main types have been observed:

Class I: Clitoral hood with labia minora extension before the vaginal opening (midpoint).
Class II: Labia minora extend to the vaginal opening (midpoint).
Class III: Labia minora extend to the posterior fourchette.

The class I variant is the least common. In our experience, the class II variant tends to be subjectively perceived as the aesthetic "ideal." Class II anatomy may be difficult to achieve if a

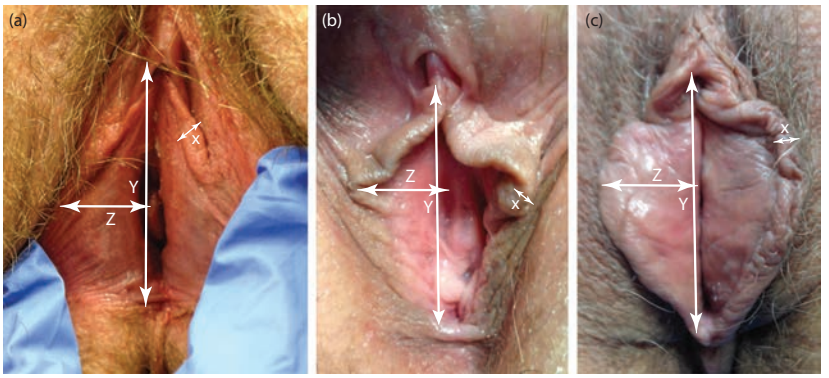

Figure 34.1 Three-dimensional labia minora classification. The classification system is applicable to all variations of labia minora anatomy: (a) Class I, (b) Class II, and (c) Class III. The vertical y-axis represents the labia minora length in the anterior–posterior plane. The horizontal x-axis represents the labia minora width in the medial–lateral plane. The z-axis represents the depth or height of the labia minora in the superior–inferior plane.

Table 34.1 Patient Characteristics

	Primary labiaplasty	Secondary labiaplasty
Total (N = 35)	16	19
Risk factors		
BMI	25.2	28.6
Diabetes	0	0
Hypertension	1	2
CAD	0	0
PVD	0	0
Prior MI	0	0
Current smoker	0	1
Former smoker (>1 year quit)	1	2
Indications		
Dyspareunia	11	15
Discomfort	4	4
Abnormal sensation	0	0
Unacceptable cosmetic appearance	1	0

Abbreviation: BMI = body mass index (kg/m^2); CAD = coronary artery disease; MI = myocardial infarction; PVD = peripheral vascular disease.

Table 34.2 Outcomes of Primary and Secondary Labiaplasties

	Primary labiaplasty	Secondary labiaplasty
Total (N = 35)	16	19
Wound dehiscence	1	0
Dyspareunia	2	3
Discomfort	0	0
Unacceptable cosmetic appearance	0	1
Average follow-up (days)	227	216

class III patient has sensory mapping that precludes resection of redundant labia minora.

Labia Minora Height (z-Axis)

The z-axis signifies the height (or prominence away from the body) of the labia on gentle stretch.

Class A: Labia minora are behind the labia majora.
Class B: Labia minora are at the level of the labia majora.
Class C: Labia minora protrude past the level of the labia majora.

When re-approximating tissue, care must be taken not to inadvertently over-stretch the labia in the z- or x-axes prior to resection, as this may result in eversion and subsequent exposure of the wet mucosa (Figure 34.3).

SURGICAL APPLICATIONS

Preoperative Considerations

In labiaplasty, the surgeon must take these anatomic variations into consideration when reconstructing the labia minora (Video 34.1).

If a patient has a class I labia minora variant, labiaplasty may result in tethering of the clitoral hood, causing discomfort and pain. The class II labia minora variant seems to be the aesthetic ideal. In the class III variant, in which the labia minora are circumferential, the surgeon must counsel the patient that obtaining a result similar to a class II type is more difficult given the redundant tissue. This is especially true if sensory mapping prohibits large resection areas. Patient education and expectation management is critical to patient satisfaction.

In performing a labiaplasty, resecting too much tissue in the anterior–posterior extent (y-axis) can cause tethering on the clitoral hood, thus affecting clitoral function. Excessive resection of the base width (x-axis) can splay the labia apart, creating an effacement of the labia minora fold. The resultant mucosal eversion can be painful, and the cosmetic outcome is suboptimal. The ideal candidate for labiaplasty is one with excessive length (y-axis) and height (z-axis) of the labia minora. Resection in the z-axis is safer than in the x- or y-axes for the above-mentioned reasons. The central wedge resection is safe because it removes tissue from the y- and z-axes. The clamp and sew method should be utilized with caution because, although it decreases the z-axis, it effaces the delicate mucocutaneous junction between the internal mucosa and external hair-bearing skin, thus risking mucosal eversion and irritation.

SENSORY MAPPING TECHNIQUE

Sensory mapping is a preoperative technique our group routinely uses prior to labiaplasty that localizes critical sensual areas prior to resection. Briefly, the surgeon performs the preoperative markings for the labiaplasty in the preoperative area. These areas are tested with the cotton end of a swab, and the

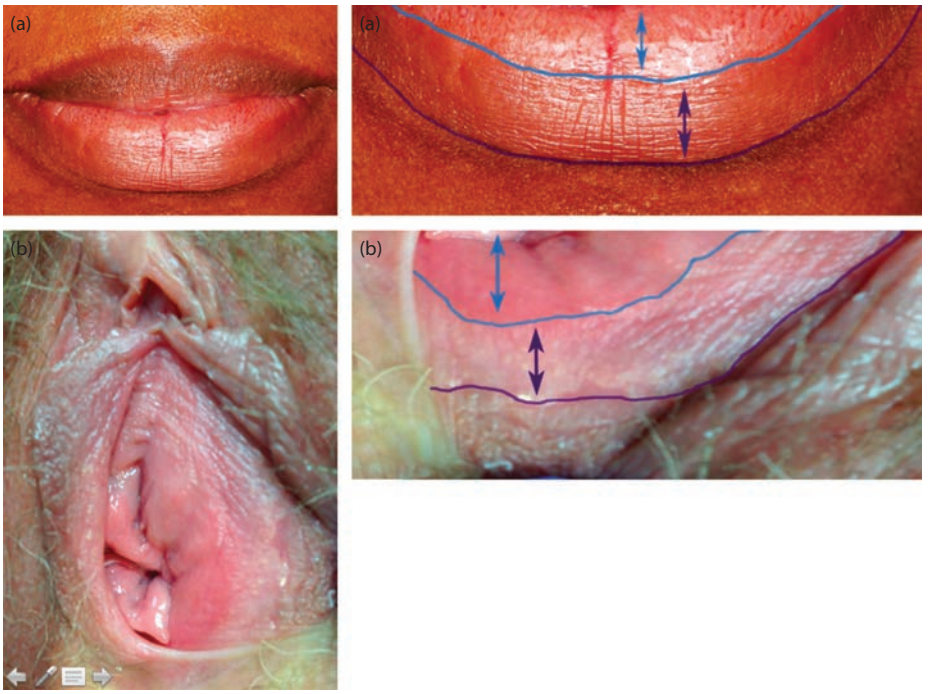

Figure 34.2 Analogous anatomy between the labia minora and the lip. (a) Upper and lower lip of a healthy 25-year-old female (global and close-up view of the lower lip). (b) Class III labia minora of a healthy 30-year-old female (global and close-up view of the left labia minora). The labia minora is made up of a wet mucosa (analogous to the wet vermillion of the lip; blue arrow), a dry mucosa (analogous to the dry vermillion; purple arrow), and a keratinized, often pigmented epithelium (analogous to the skin bordering the dry vermillion, separated by the white roll).

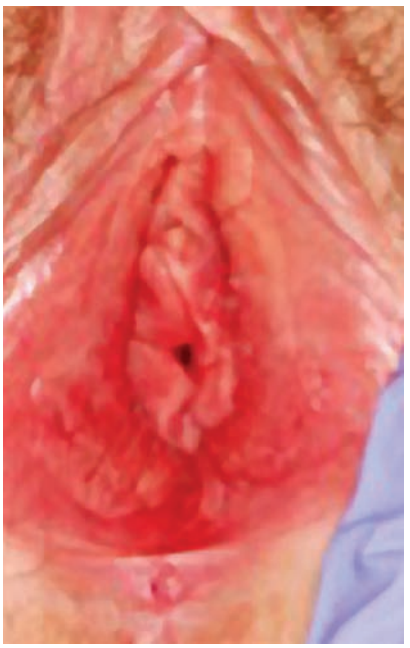

Figure 34.3 Mucosal eversion after primary labiaplasty. This 40-year-old female had a primary labiaplasty that resulted in over-resection in the horizontal x-axis, resulting in wet mucosal eversion, dryness, and irritation. Note the redness and injection of the wet mucosa posteriorly.

patient is asked whether these areas elicit a sensual or non-sensual feeling. If the proposed areas of resection lie within critical sensory pathways, the markings are adjusted if the patient wants to maintain these areas. The final markings are performed after discussion with the patient. Sensory mapping is our method of preserving innervation to the labia minora provided by the dorsal clitoral nerve.

LABIAPLASTY TECHNIQUE

The patient is then put under intravenous sedation or general anesthesia. The patient is then prepped with Betadine®. The labiaplasty incisions are reinforced with a pen. One-percent lidocaine with epinephrine 1:100,000 is used to anesthetize the labia minora. A wedge of mucosa and outer skin is removed while preserving as much subcutaneous tissue as possible for adequate closure (7–9). The dermis is closed with a buried 4–0 V Monocryl® suture and the epidermis with a running 4–0 Monocryl® subcuticular suture. The patient is dressed with bacitracin, gauze, and a mesh undergarment. No postoperative antibiotics are prescribed. Patients are allowed to shower the next day, but tub immersion is not permitted. The patients are instructed to keep the suture line clean and dry, and are seen a week later in the clinic. They are advised to refrain from any vaginal intercourse or heavy lifting for 4 weeks. During menstruation, patients are advised to use a pad instead of a tampon.

DISCUSSION

Prior attempts at labia minora classification have described the anatomy only in one dimension. Since the labia minora anatomy

is so individualized, we have developed a three-dimensional classification system that better captures the different anatomic variations of the labia minora. Three-dimensional anatomy is important in accurate resection and functional reconstruction; therefore, a three-dimensional classification system logically would facilitate these goals more easily. Our classification provides the conceptual framework within which this preoperative planning can occur.

In addition, the analogous anatomy of the labia to the lip lends itself to reconstruction according to the principles of lip reconstruction. One of the fundamental guidelines of lip reconstruction is to precisely identify the vermillion border in order to re-approximate the tissue without visible step-off deformity. Since the labia minora have analogous tissue layers, we adhere to these principles when re-approximating the labia after a central wedge resection. Specifically, the border between the dry mucosa (analogous to the dry vermillion on the lip) and the keratinized pigmented epithelium (analogous to the skin bordering the dry vermillion, separated by the white roll) needs to be preserved during suturing in order to prevent irregularities in this landmark ("scalloping"), much like when the vermillion border is misaligned on the lip. Failure to re-approximate these landmarks can cause labial eversion or notching, which is functionally and aesthetically suboptimal. In addition, the deflational changes that occur in the lip with age are also observed in the labia minora, and the surgeon must take into account the atrophic dermis when planning the method of closure. This surgical paradigm shift has allowed us to view the labia minora as a structure to reconstruct rather than an extraneous tissue to excise.

From this classification system, we have developed guidelines for primary and secondary labiaplasties that serves as a surgical planning aid:

1. Labiaplasty is safest when performed resecting in the y- and z-axes.
2. Avoid excessive resection in the y-axis, as this can cause tethering of the clitoral hood, affecting arousal.
3. Avoid excessive resection in the x-axis, which can cause labia eversion and splaying, resulting in irritation and exposure of the wet mucosa.
4. Maintain the mucocutaneous junction in labiaplasty, similar to lip reconstruction, which is important to prevent notching of the labia minora.
5. Meticulous closure of the skin edges is critical for proper wound healing and for preventing long-term complications of dermal atrophy.
6. Sensory mapping is an important preoperative diagnostic test that identifies critical sensory pathways in the labia minora.

Our patient population not only included primary labiaplasties, but secondary revisions as well. For these patients, surgical planning must include restoring form and function to the labia minora. The spectrum of complications from primary labiaplasties range from: labial eversion causing mucosal dryness (from excess resection in the x-axis); foreshortening of the labia minora causing clitoral head tethering (from overly aggressive resection in the y- and z-axes); new-onset or persistent dyspareunia and/or discomfort; and difficulty with arousal. None of these patients have had sensory mapping performed at the time of primary labiaplasty. Since scarring often distorts the labia minora anatomy, we find that sensory mapping is especially important in secondary labiaplasties to map the critical sensory pathways in order to locate entrapped nerves for scar release or to avoid remaining critical sensory areas with revisional surgery. Our surgical guidelines for secondary revisional labiaplasties are the same for the primary labiaplasties, but additional procedures for hydrodissection-assisted scar release, vaginal mucosal advancement flaps, and fat grafting may need to be incorporated into the surgical plan in order to correct unfavorable results. Further research on revisional labiaplasties is currently being performed.

One of the limitations of this study is the small sample size. However, since our recent collaborative experience began, our institution has started to accrue more labiaplasty patients, in particular revisional labiaplasties. Future studies should include comparison of primary and secondary labiaplasties outcomes and the use of sensory mapping in primary and secondary labiaplasties.

CONCLUSIONS

We describe a novel classification system of the labia minora anatomy that is three-dimensional, practical, and serves as a guide for preoperative planning of labiaplasty procedures. We have identified several key operative considerations that aid in surgical planning and avoid complications. Labiaplasty is not purely an aesthetic procedure, and plastic surgeons must consider the three-dimensional anatomy in order to preserve or restore sexual function. Aesthetic primary labiaplasties should be performed with this classification in mind in order to prevent unfavorable outcomes. In secondary revisional labiaplasties, this classification system, along with sensory mapping, can help restore form and function to the labia minora. Future considerations include investigating the influence of tissue elasticity as another classification attribute, and its influence on surgical correction.

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VIDEO

Video 34.1 Three-dimensional classification of the labia minora. https://youtu.be/HZctuWPsvNU

Danger zones in labiaplasty

Cindy Wu, Lynn A. Damitz, and Denniz A. Zolnoun

INTRODUCTION

According to the American Society for Aesthetic Plastic Surgeons' (ASAPS) 2014 statistics, there was an increase of 49% in the number of vaginal rejuvenation procedures between 2013 and 2014 (1) and a 16.1% increase between 2014 and 2015 (2). Labia minora reduction (most commonly described as labiaplasty) has become an increasingly popular procedure (3,4), both for functional and cosmetic indications. Many have published studies on the surgical techniques for labia minora reduction, labia majora reduction and augmentation, clitoral hood reduction, and vaginoplasty (5–17). To date, there are no papers describing the neuroanatomical correlates of surgical planning for labiaplasty. From our sensory mapping experience, we have elucidated danger zones in the labia minora that have helped us develop a topographical guideline for labiaplasty.

METHODS

A retrospective review of all labiaplasties performed since 2011 was performed. Patient demographics and postoperative complications were recorded. At the initial consultation, the chief complaint was noted as well as the area of greatest aesthetic concern. Our plastic surgeons collaborate with a gynecologist specializing in clinical neurophysiology and urogenital pain for the sensory mapping portion of the procedure. The results from the sensory mapping were used to create a neuroanatomical diagram of safe and danger zones for resection.

Sensory Nerve Mapping Technique

On the day of surgery, sensory mapping is performed by the surgeon in the presence of a female nurse (Video 35.1). The patient is informed that the cotton end of a swab will be used to touch areas of the labia minora, and she will be asked to say if that area elicits a sensual or non-sensual feeling. To establish a "sensual" feeling, the clitoris (innervated by the dorsal nerve of the clitoris) is touched, and the patient is asked to establish this sensation as a "positive control" from which to compare the other areas subsequently tested on the labia minora. To establish a "non-sensual" feeling, the anterior thigh (innervated by the anterior cutaneous branch of the femoral nerve) is touched, and the patient is asked to establish this sensation as a "negative control." Sensory mapping proceeds with the patient in lithotomy, and the surgeon marks the border between sensual and non-sensual areas with a pen. If the intended resection area falls in a sensual region, a discussion between the surgeon and patient ensues about her desires for resection in this region.

Labiaplasty Technique

The patient then undergoes intravenous sedation or general anesthesia and is placed in the lithotomy position (Figure 35.1a–d). The labiaplasty incisions are marked, then the perineum prepped with Betadine®. A wedge of mucosa and outer skin is removed while preserving as much subcutaneous tissue as possible for adequate closure (5–7). The dermis is closed with a buried 5–0 Monocryl® suture and the epidermis with a running 5–0 Monocryl® subcuticular suture. The wound is cleansed and dressed with bacitracin. No postoperative antibiotics are prescribed. The patient is asked to refrain from vaginal intercourse, tampons, or douching for 4 weeks, and showering but no tub immersion is permitted.

RESULTS

Sixteen primary labiaplasties were performed. Patients presented with dyspareunia (N = 11), discomfort in clothing (N = 4), and unacceptable cosmetic appearance (N = 1). The average body mass index was 25.2 kg/m², one patient had hypertension, and one patient was a former smoker (quit >1 year ago). Sensory mapping was performed in 8/15 (50%) labiaplasties. Of those patients who had sensory mapping, four had the chief complaint of dyspareunia, three had discomfort, and one had unacceptable cosmetic appearance. At an average of 226 days after labiaplasty, these eight patients did not have recurrence of dyspareunia, discomfort, or unacceptable cosmetic appearance, giving a success rate of 100%. The only patient that was noncompliant with postoperative activity restrictions developed a wound dehiscence that resolved with local wound care (Table 35.1). Sensory mapping from these patients revealed erogenous zones that should not be resected (danger zones). Safe zones for resection include the pigmented labia minora caudal to the urethra, while the mucocutaneous regions tend to be sensual and should be avoided (Figure 35.2).

Case Report

This is a 36-year-old parous female who desired cosmetic and functional labiaplasty. She disliked the prominence of her labia minora and complained of dyspareunia and irritation in clothing. Sensory mapping was performed prior to labiaplasty. At 3 months, she had no change in her arousal, no dyspareunia, and no discomfort in tight clothing (Figures 35.3a–c to 35.4a–c).

DISCUSSION

Applied and translational anatomy is important in the field of plastic surgery. The ability to innovate based on general concepts and to restore form and function by applying these themes in a new situation is the cornerstone of our field. This is particularly noteworthy since many of the best practices for inguinal hernia repair in men are readily applicable to labiaplasty in women.

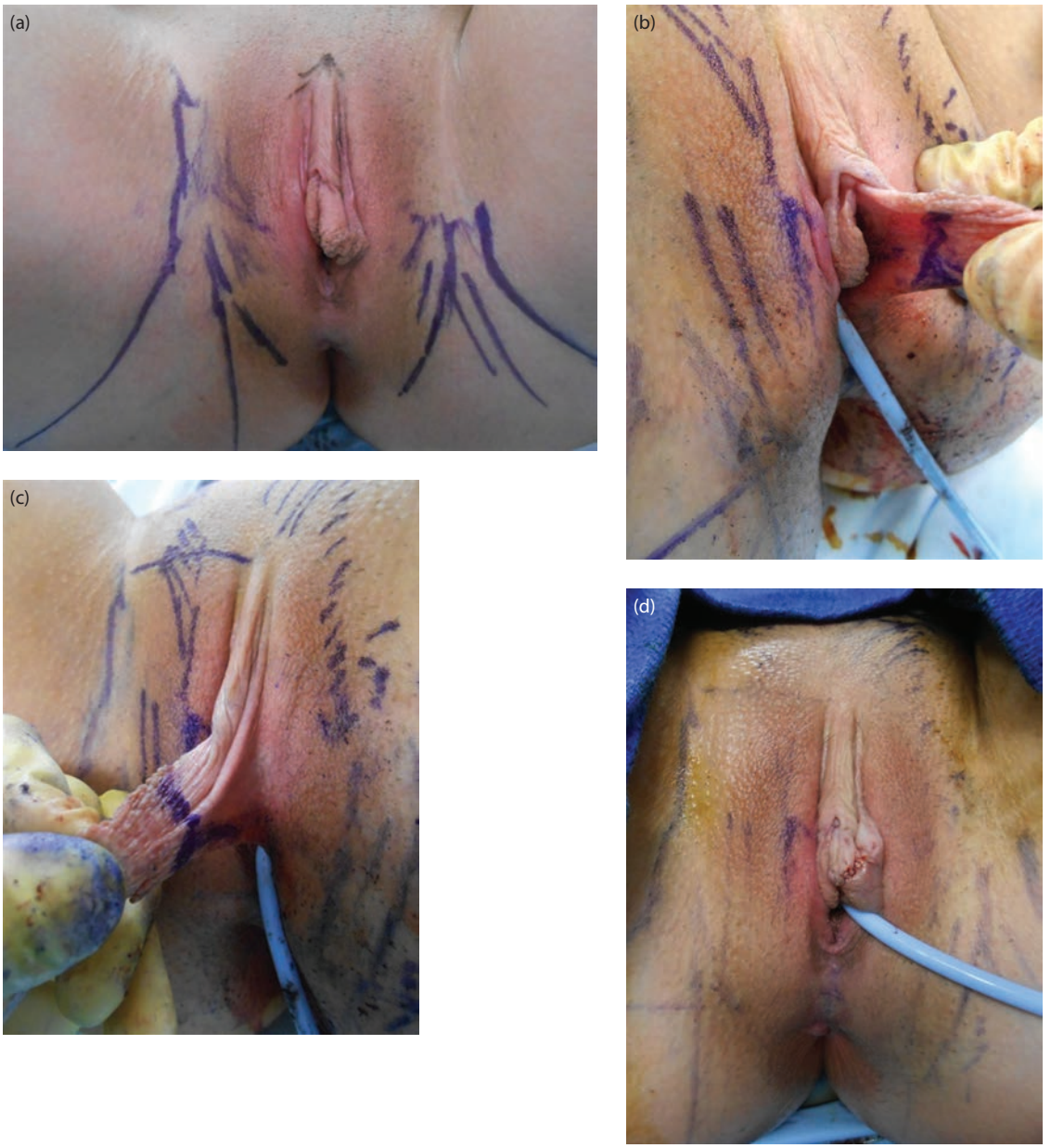

Figure 35.1 (a–d) Labiaplasty technique. This is a patient who was bothered by her prominent left labium minus. Seen marked are the branches of the pudendal nerve, which were drawn for reference. The wedge marked out was not sensual. We use Alter's central wedge technique, whereby the excess wedge of tissue is marked, excised, then sutured with a dermal 5–0 Monocryl® suture and a running subcuticular Monocryl® suture. This patient was early in our experience. We have since stopped using Foley catheters during labiaplasty. The patient is asked to refrain from vaginal intercourse, tampons, or douching for 4 weeks, and showering but no tub immersion is permitted.

For example, the anterior and posterior scrotum is innervated by the ilioinguinal and pudendal nerves. While the anatomical landmarks for the anterior and posterior scrotum are well delineated in men, in women, the analogous anatomical regions are not well characterized. The same applies to important nerves involved in female sexual function. The concept of genitofemoral nerve preservation during herniorrhaphy in men is an established one. This nerve follows the same path in women and ultimately innervates homologous structures. However, the nerve topography in women is more tightly packed than in men (millimeters versus centimeters), and the anatomical borders are not as distinct. In an anatomical study of 16 male and female cadavers, the genital branch of the genitofemoral nerve was reliably found on the ventral side of the spermatic cord; however, without a cremaster muscle to innervate, this motor branch was not found in some women (43.7%). In some female cadavers (28.1%), it was found to be incorporated with the ilioinguinal nerve (18).

This higher-density innervation in female external genitalia has been shown on an immunohistochemical level as well.

Table 35.1 Patient Demographics and Results

				CC				Comp				Reop			
Pt	BMI	HTN	Prior smoker	Dy	Di	Cos	SM	WD	Dy	Di	Cos	GETA	Local	FU	Compliant
1	24.3	N	N	N	Y	N	Y	N	N	N	N	N	N	72	Y
2	22.9	N	N	Y	N	N	N	N	N	N	N	N	Y	432	Y
3	30	N	N	Y	N	N	Y	N	N	N	N	Y	Y	212	Y
4	21.5	N	N	Y	N	N	N	N	Y	N	N	Y	N	477	Y
5	21.9	N	N	Y	N	N	N	N	N	N	N	N	N	634	Y
6	22.6	N	N	Y	N	N	Y	N	N	N	N	N	N	75	Y
7	44.3	N	N	Y	N	N	Y	N	N	N	N	N	N	32	Y
8	24.2	N	N	N	N	Y	Y	Y	N	N	N	Y	N	151	N
9	28	Y	N	Y	N	N	N	N	N	N	N	N	N	345	Y
10	19.6	N	N	Y	N	N	Y	N	N	N	N	Y	N	284	Y
11	25.2	N	N	N	Y	N	Y	N	N	N	N	N	N	220	Y
12	21.3	N	N	Y	N	N	N	N	N	N	N	N	N	238	Y
13	19	N	N	N	Y	N	Y	N	N	N	N	N	N	10	Y
14	22	N	N	Y	N	N	N	N	N	N	N	N	N	66	Y
15	23.5	N	Y	Y	N	N	N	N	Y	N	N	N	Y	312	Y
16	32.8	N	N	N	Y	N	N	N	N	N	N	N	N	67	Y

Abbreviation: Pt: patient; BMI: body mass index (kg/m²); HTN: hypertension; Prior smoker: >1 year of quitting; CC: chief complaint; Dy: dyspareunia; Di: discomfort; Cos: unacceptable cosmetic appearance; SM: sensory mapping; Comp: complications; WD: wound dehiscence; Reop: reoperation; GETA: general endotracheal anesthesia; FU: length of follow-up (days from surgery date to last clinic visit); Complaint: compliant with postoperative activity restrictions; Y: yes; N: no.

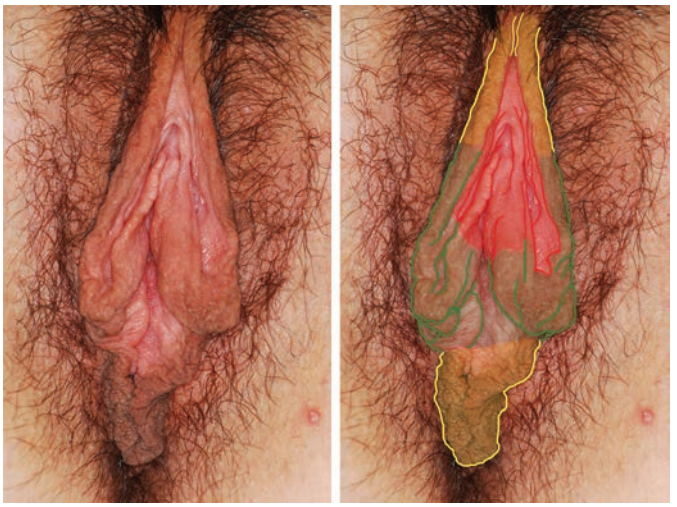

Figure 35.2 Danger and safe zones for labiaplasty. This is a diagram of the general safe and danger zones for labiaplasty, based on our sensory mapping. These zones are variable and surgeons should map out each individual patient's region prior to labiaplasty, and use the above diagram as a guideline only. Shown in red are the areas associated with definite arousal that should not be resected. Shown in yellow are the areas associated with mild arousal that should be spared if possible. Shown in green are the areas not associated with arousal that can be resected.

Shih et al. showed that not only is there a differential innervation between the introital and external labia minora, but also that receptor density is much more condensed in the glans clitoris compared to the glans penis (19). It therefore makes sense to preserve important sensory areas during labiaplasty. For these reasons, sensory mapping prior to labiaplasty is particularly important in order to preserve quality of life.

Furthermore, the topography of the labia minora is different in every woman, and individualized sensory mapping prior to labiaplasty is important in order to preserve these areas. Our collaboration with a gynecologist with ongoing research and clinical expertise in sensory neurophysiology has increased our understanding of preserving these sensual areas during labiaplasty. This topic, while researched extensively in the pain literature, has only recently begun to translate into the fields of gynecology (20,21) and plastic surgery. As a result, we feel that as plastic surgeons performing perineal surgery, it is important that we fully understand the individual neuroanatomy of patients undergoing such sensitive surgery. The concept of nerve preservation is not new to our field, as upper and lower extremity nerve decompression (22), neurotized flaps, and nerve conduits are all within the scope of our practice.

We acknowledge that there is a small sample size in our labiaplasty cohort. We have many more revisional labiaplasty patients referred to us, but we chose to focus on primary labiaplasties because their neuroanatomy has not been previously altered by surgery. In the future, we plan on accruing more patients into the primary sensory mapping cohort, to compare this cohort to a control group who have not undergone sensory mapping, and to administer pre- and post-operative patient questionnaires.

CONCLUSIONS

We describe a novel concept of preoperative sensory nerve mapping that reveals safe and danger zones for resection. This individual neuroanatomical map serves as a guide for the preoperative planning of labiaplasty procedures. From our experience, we have found that as a rule of thumb, safe zones for resection include the pigmented labia minora caudal to the urethra, while the mucocutaneous regions tend to be sensual and should be avoided.

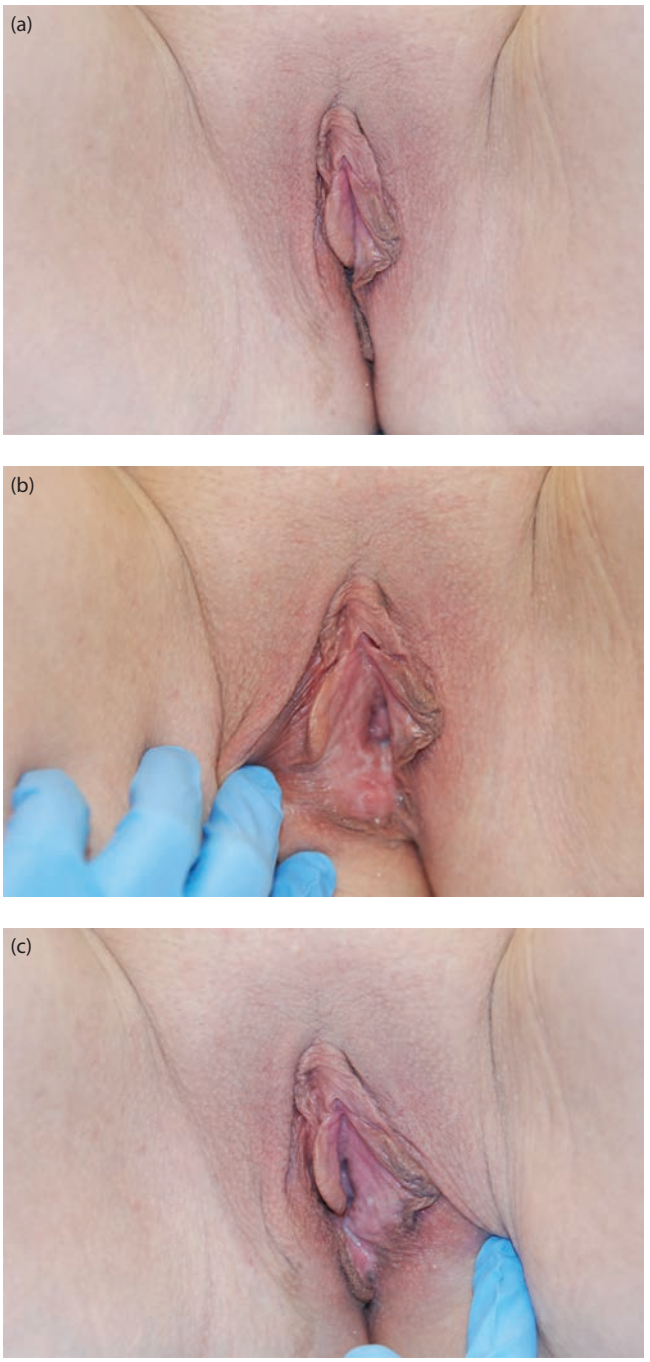

Figure 35.3 (a–c) Preoperative views.

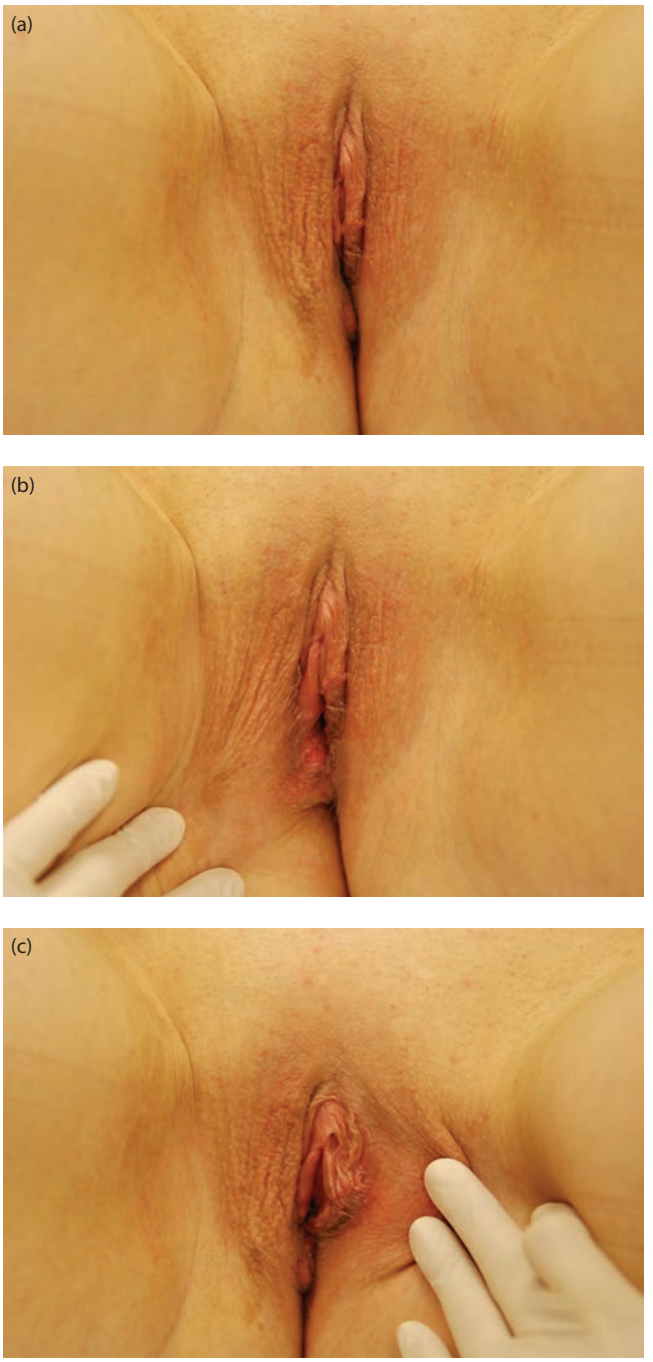

Figure 35.4 (a–c) Three-month postoperative views.

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VIDEO

Video 35.1 Sensory mapping technique. Sensory mapping is performed in the preoperative holding room with the surgeon and a nurse. The patient is awake and in the lithotomy position. The surgeon tells the patient that the labia minora will be touched with a cotton tip, and the patient will be asked to report if the area touched elicits a sensual or non-sensual feeling. Prior to starting the sensory mapping, the clitoris (innervated by the dorsal nerve of the clitoris, a branch of the perineal nerve) is used as a positive control and the anterior thigh (innervated by the anterior cutaneous branches of the femoral nerve) as a negative control. The borders between sensual and non-sensual areas are marked. Careful prepping and draping is then performed so as to preserve these marks. https://youtu.be/Wl9n1AQw9uM

PART 4

Vulvar Care

Genital hygiene
Culture, practices, and health impact

Miranda A. Farage and Mario Bramante

INTRODUCTION

Hygiene practices are affected by personal preferences, cultural norms, and other societal influences. This chapter describes female genital hygiene issues from infancy to old age, with reference to regional and cultural differences in hygiene practices and to the potential implications for gynecological health.

GENITAL HYGIENE OF INFANTS

Vulvar Anatomy and Vaginal Discharge

The vulva of the newborn exhibits the effects of residual maternal estrogen. Immediately after birth, the labia appear swollen and a white, mucoid discharge is present for the first few weeks of infancy. The discharge is normal and can be cleansed by wiping gently from front to back with a damp washcloth, moistened cotton wool, or wipe. As the influence of residual maternal hormones declines, slight blood spotting may occur due to endometrial estrogen-withdrawal bleeding. These effects cease within 3–4 weeks of birth once the influence of residual maternal hormones dissipates fully.

Labial adhesions sometimes occur in late infancy and in the toddler years, most often between the ages of 2 months and 2 years. This condition, related to estrogen deficiency, creates a flat vulvar appearance that may elicit parental anxiety. Labial adhesions are usually asymptomatic and outgrown without the need for treatment. Occasionally, urinary tract or vulvovaginitis symptoms result if there is blockage of the free flow of urine. In this event, topical estrogen is used to promote separation of the labia.

Diaper Dermatitis

Managing incontinence is the principal urogenital hygiene challenge in infants. Global diapering practices vary: disposable paper diapers are used widely in Western industrialized countries; typically, cloth is used in the developing world.

Prolonged genital skin contact with urine and feces can cause irritant dermatitis on the vulva, perineum, and buttocks of diapered skin (diaper rash). The etiology is multifactorial (Figure 36.1) (1–5). In brief, prolonged contact with urine increases skin wetness and skin pH, making the skin vulnerable to damage by friction and local irritants. Wet, occluded skin has a higher coefficient of friction and is more vulnerable to damage from abrasion (1). Urinary ammonia, however, is not a primary irritant, as once thought (6). Ammonia produced by bacterial action on urea increases the local pH; this, in turn, disturbs the normal acid mantle of the skin, impairs skin barrier function (1,7), elevates the activity of fecal enzymes that compromise skin integrity (1,7), and reduces the acid inhibition of microbial pathogens that cause secondary infections on compromised skin. Accelerated gastrointestinal transit also raises fecal enzyme activity, resulting in a higher frequency of diaper dermatitis after bouts of diarrhea (1,8,9).

The etiology of irritant diaper dermatitis provides a scientific basis for recommending the use of barrier preparations and superabsorbent diapers to maintain drier skin and limit the effects of urine and feces (1,2,10–13). These recommendations are supported by clinical evidence of efficacy in reducing rash (1,14–18). Figure 36.2 illustrates representative results for diapers. However, such products are not always available or affordable in many regions of the world. To limit skin contact with urine and feces, frequent diaper changes and good perineal hygiene are recommended as a general practice, regardless of the mode of diapering.

GENITAL HYGIENE AMONG PREMENARCHAL GIRLS

General Hygiene

Poor vulvar hygiene may lead to the accumulation of smegma, a pasty agglomeration of epithelial cells and sebum that collects in moist areas of the genitalia such as the clitoral folds. Smegma hardens over time, causing itch or pain often exacerbated by scratching. Routine gentle washing of the vulva prevents this condition.

Toilet Habits

Maintaining proper toilet habits and perineal hygiene in young girls can be a challenge when parental supervision is first withdrawn (19). To avoid vulvar contamination with fecal material, young girls should be taught to consistently wipe from front to back after toileting.

Common sense dictates that establishing good hygiene habits is desirable and healthful, but research on the contribution of hygiene to premenarchal vulvovaginitis has produced mixed results. A case study of 54 patients, drawn from a North American population of low socioeconomic background, concluded that most noninfectious cases of vulvitis in young girls were caused by improper perineal hygiene (20). Only cases with visible inflammation and discharge were confirmed to be of infectious origin. Complaints of vulvitis with no infectious cause were judged to be hygiene related based either on clinical observation of stool or smegma or on the resolution of symptoms with improved hygiene and toilet practices.

Conversely, an Australian case–control study of pediatric vulvovaginitis (50 per group) found no difference in personal hygiene habits, consistent with these researchers' empirical

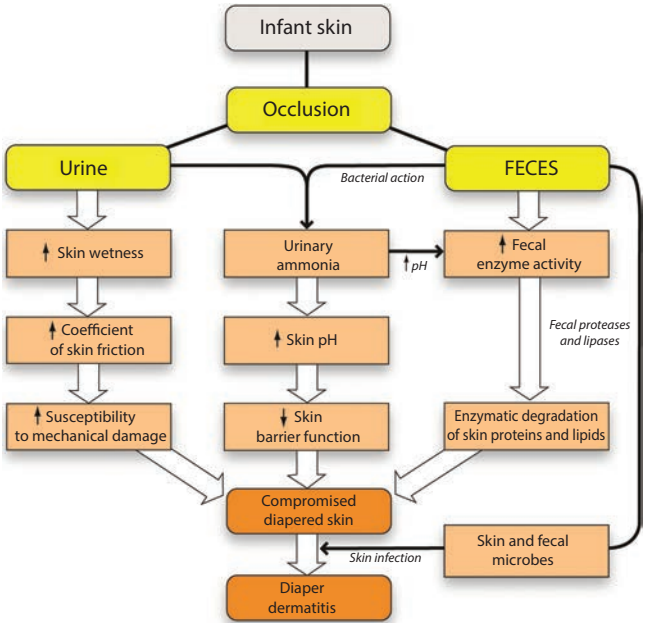

Figure 36.1 The etiology of diaper dermatitis (diaper rash) in infants. Based on the research of (1–5,10,189).

experience that most premenarchal girls with vulvovaginitis exhibit good hygiene (21). Because most cases of pediatric vulvitis in this study were neither infectious nor attributable to improper hygiene, the investigators postulated that vulvitis of nonspecific etiology may be common in early childhood.

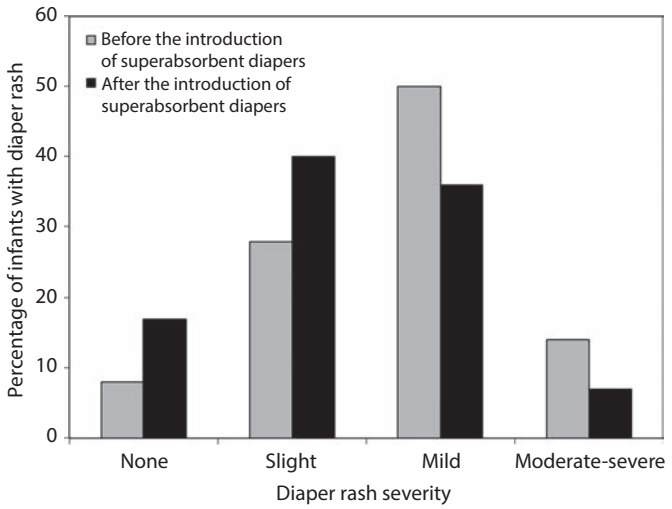

Figure 36.2 Changes in diaper rash severity before and after the introduction of superabsorbent disposable diapers. Data represent the aggregate rash frequency and severity from six clinical studies conducted between 1984 and 1988 involving 1850 infants (prior to the introduction of superabsorbents) and six clinical studies conducted between 1988 and 1995 involving 1975 children (after the introduction of superabsorbents). (Adapted from Odio M, Friedlander SF. *Curr Opin Pediatr* 2000; 12: 342–6. With permission.)

An alternative hypothesis was proposed by a different group of Australian investigators, who examined 130 young girls with vulvar complaints and determined that the majority had a dermatologic condition of the vulva (irritant or atopic dermatitis, psoriasis, or lichen sclerosus) (22). Poor hygiene was infrequently causative. These researchers proposed that most pediatric vulvar complaints of "nonspecific" etiology may be the result of undiagnosed dermatological conditions (23).

These disparate conclusions probably reflect demographic differences in the populations from which the study participants were drawn. Inadequate hygiene may contribute to pediatric vulvovaginitis in some groups of patients, whereas when hygiene practices are adequate, other factors may predominate among those with vulvar complaints.

Fecal contamination of the vulva and perineum in young children is not always due to improper hygiene, but can result from fecal overflow around rectal blockage caused by constipation. This often unrecognized cause of fecal soiling is a precipitating or perpetuating factor in recurrent urinary tract infections (UTIs) in young girls. Because the anus and urethra are closer in premenarchal girls than in mature women, poor hygiene and toilet practices are often emphasized as primary contributing factors. However, vulvar hygiene does not play a singular role. The most important risk factors for recurrent UTIs unrelated to physical abnormalities are a combination of:

1. Infrequent voiding
2. Inadequate fluid intake
3. Stool retention due to constipation

Inadequate hygiene and toilet habits usually coexist with these variables (24).

Vaginal foreign bodies, a relatively uncommon result of improper toilet practices by young girls, cause a foul-smelling, occasionally brown or blood-tinged discharge (19,25,26). Bits of cloth or toilet paper, deposited when the child wipes herself after urinating, are the most common culprits (27). These can be removed with cotton swabs or by vaginal irrigation.

Pinworm Infestation

Inadequate hygiene plays a role in rectal infestation of pinworm (*Enterobius vermicularis*), a common worldwide nuisance in children. The condition causes an intense vulvovaginitis (27–29) with discharge in up to 20% of afflicted girls (30). Among the risk factors identified in urban and rural regions worldwide are overcrowded schools, daycare settings or dwellings, improper sanitation, lack of handwashing after toileting and before meals, and inadequate water supplies (31–35). Rectal itching that worsens at night (when the female emerges to lay eggs) is the primary symptom. Scratching spreads the eggs to other parts of the child's environment. To eradicate the infection effectively, the entire family must be treated at the same time, with scrupulous attention to cleaning bedding, clothes, bathrooms, and surfaces in the home. Similar action should also be undertaken at the site of acquisition.

Genital Autoinoculation with Pathogens

Secondary infections of the genitalia resulting in vulvovaginitis can occur when a child inoculates herself with organisms

from an upper respiratory tract, pharyngeal, or skin infection (25). The most common organism is the group A β-hemolytic streptococcus (23,29,36). Vaginal discharge should be cultured in order to determine whether a specific organism is involved. The discovery of sexually transmitted organisms points to sexual abuse (21,29).

Aberrant Hygiene Practices

Rare cases of aberrant genital hygiene practices in young girls have been reported in the North American medical literature (37,38). They involve three classes of behavior. The first is a ritualistic focus by the parent on invasive and sometimes painful inspection and washing of the child's genitalia. This may be related to parental suspicion of sexual abuse. The second is a form of Munchausen syndrome by proxy, whereby the parent repeatedly solicits medical intervention for perceived or fabricated genital problems in the child. The third is an overt form of abuse, usually by a male, involving the application of creams or ointments to the child's genitalia for the purpose of the perpetrator's sexual gratification. All three classes are forms of abuse requiring intervention, which may include referral of the child and the caregiver for treatment and, when appropriate, reporting to child protective services.

GENITAL HYGIENE AMONG WOMEN OF REPRODUCTIVE AGE

Menstrual Hygiene

In many cultures, menstruation is a taboo subject considered the private province of women (39–44). Theories abound regarding the historical and cultural underpinnings of this pervasive attitude. Perhaps the link to reproduction and birth imbues the menstrual cycle with a certain mystique. Bleeding is usually a sign of injury: our ancestors may have viewed cyclical bleeding—without dying—as a supernatural event. The notion that blood flow carries a basic life principle, with both beneficial and harmful consequences, is powerful in some parts of the world (45,46). From 1st century Rome to 19th century England, menstruation was thought to render women periodically dangerous (47). In the 1920s, scientists reported isolating a lethal toxin from menses (48), a finding discredited in the 1950s as an artifact of bacterial contamination (49). As recently as 1985, a quarter of young Australian women believed that menstrual flow rids the body of wastes (50). This view is held by many cultures worldwide. Some orthodox religious traditions consider the menstruating woman to be spiritually unclean (50). Not surprisingly, therefore, social, cultural, and religious norms influence menstrual hygiene practices profoundly.

Menstrual Hygiene in the Industrialized World

Habits and Practices

The use of disposable sanitary pads, panty liners, and tampons is ubiquitous in Western industrialized countries. The cultural acceptance of disposable external and internal protection in industrialized nations evolved over time. Although invented in 1896, disposable sanitary pads were not successfully introduced to the North American market until 1921. Perhaps for cultural and economic reasons, for two more decades some women still employed cloth rags to absorb menstrual flow, boiling them for reuse after each menstrual period (51).

In 1936, commercial tampons were introduced in the USA as "a civilized solution to the problem of sanitary protection" (52). In reality, tampons have been used in many cultures since ancient times (51,53). As early as the 15th century BCE, Egyptian women used soft papyrus. Ancient Japanese women made tampons from paper and Roman women employed wool. Some nomadic Africans use absorbent material from indigenous mosses and plant seedpods, and traditional Hawaiian women employ the furry portions of native ferns. Prior to the commercial introduction of tampons, the more avant-garde women in American culture used natural sea sponges cut to size or made their own tampons from tightly rolled surgical cotton (54).

In Western societies, tampons were initially controversial. The medical and popular literature between 1936 and 1966 cites concerns about the presence of a foreign body in the vagina, the potential for sepsis, and the impact on virginity and sexuality (51). Beginning with women's entry into the workforce during World War II and through the Women's Liberation Movement of the 1970s, tampons became more widely accepted for their convenience and for the increased freedom they provide in order to participate fully in the workplace, sports, and social activities.

Although product sales figures are available, surprisingly little published information exists on present-day menstrual hygiene practices in developed countries. The available data indicate that a sizeable proportion of women use tampons or tampons and pads in combination. A 1996 survey of 193 women from urban southeast Texas (mean age, 23 years) found that 48% of respondents used tampons exclusively, 19% used sanitary pads, 18% used pads and tampons in combination, and 10% used panty liners (Table 36.1) (55). Tampons were used intermenstrually by 13% of respondents. Tampons and pads were changed at least every 6 hours by a majority of women. About 95% reported washing their hands after doing so at least some or most of the time.

A 1999 survey of middle-class Californian women ranging in age from 18 to 96 years indicated that tampon use

Table 36.1 Menstrual Protection Practices among 193 Texan Women Aged 18 Years or Older (1996)

	Percentage prevalence					
Products and practices	Never	Sometimes	Half of the time	Most of the time	Always	Not reported
Tampons	11	15.5	11	12	48	2.6
Sanitary pads	24	30	11	12	19	2.6
Tampon/pad combinations	40	24	7	5	18	6
Panty liners	22	44	9	11	10	3.6
Tampons/pads/liners between periods	82	9	1	0.5	2	5
Washing hands after use	2	4	3.6	14	74	2.6
Limiting bathing during menstruation	70	9	4	2	10	9

Source: Data from Czerwinski BS. *Appl Nurs Res* 1996; 9: 123–9.

Table 36.2 Menstrual Protection Practices by Age among 180 Middle-Class Californian Women (1999)

Products and practices	Percentage frequency		
	<41 years old (N = 180)	41–47 years (N = 171)	48–57 years (N = 83)
Natural sea sponges	2	2	1
Reusable cotton pads	0	1	1
Tampons	81	63	72
Sanitary pads	71	61	73
Tampon/pad combinations	54	47	51
Panty liners	75	60	78
Tampons/pads/liners between periods	14	12	24
Wash hands after using	94	75	94
Limit bathing during menses	11	3	4

Source: From Czerwinski BS. *J Obstet Gynecol Neonatal Nurs* 2000; 29: 625–33.

declined from 80% among women younger than 41 years to 72% among menstruating women between the ages of 48 and 57 years (Table 36.2) (56). The frequencies of pad and panty liner use were similar in those younger than 41 years (71% and 75%, respectively) and those over 48 years of age (73% and 78%, respectively). For unexplained reasons, the prevalence of use of all product types was lowest in the age group of 41–47 years. In the Texas study, 43% of respondents limited bathing during their menstrual period; in the California study, the proportion of women who reported limiting bathing during menstruation declined from 11% in the under 41 years of age group to 4% among women aged 48–57 years. About half reported handwashing before using sanitary pads and 70% reported doing so after changing them.

About a quarter of American women begin using sanitary protection before their period starts and about a third continue use for several days after flow ends. Panty liners are the most common product choice for intermenstrual use, although all three forms of protection are reportedly employed before and after the menstrual period. Tampon use is prevalent among American adolescents and young women. Surveys conducted in the 1990s indicate that 70% of adolescents and 81% of college students used tampons alone or in combination with pads (57,58). Mothers and friends were the most influential in determining teenagers' choice of tampon use (58,59). Clinicians report that American girls are expressing an interest in tampons at an earlier age, and athletes are particularly eager to use tampons (60).

A Texas-based survey conducted in the late 1980s among Caucasian, African–American, and Mexican–American women indicated that significantly more Caucasian women used tampons alone (26%) or with pads (36%) than African–American women (61). Proportionately more African–American women used tampons alone (16%) or with pads (27%) as compared to Mexican–Americans, 11% of whom used tampons alone and 21% used tampons with pads. In this study population, tampon use started in the teenage years, but the highest frequency of tampon usage, either alone (26%) or with pads (33%), occurred in the group aged 20–29 years.

Published information on the number of menstrual products used annually is scarce. A toxicological risk assessment published by the Danish National Institute for Public Health and the Environment (RIVM) reported average yearly consumption rates per user group in the population to be 325 menstrual sanitary pads, 598 panty lines, and 50 postpartum sanitary pads (62).

Health Implications

The principal health concern related to tampon use is its association with menstrual toxic shock syndrome (TSS). TSS is a rare but recognizable and treatable disease (see Table 36.3 for signs and symptoms) (63). Women aged 15–24 years are the highest-risk group for menstrual TSS, with adolescents making up a significant proportion of cases (64,65). The reported incidence of menstrual TSS peaked in the early 1980s and has since declined significantly (65). All tampons are associated with a low risk of menstrual TSS; the risk is independent of chemical composition per se, but increases with tampon absorbency (66). Other hygiene practices, such as bathing frequency, douching, and use of feminine deodorants, are not associated with menstrual TSS risk (67).

Although a full understanding of the pathogenesis of menstrual TSS is still being sought, one of the most important individual risk factors is whether a woman has serum antibodies to TSS toxin (68). Most women have substantial levels of antibody and are at low risk of the disease (65,69).

Today, millions of women use tampons safely. Physicians consider them a reasonable choice for girls and women who express a preference and are able to use them appropriately (54,60). Because young girls may be less aware of the risk factors for menstrual TSS, adolescent education is important. In the USA, statements on package inserts suggest that women use the lowest tampon absorbency required to absorb their level of flow; they may substitute tampons of lower absorbency or sanitary pads as their menstrual flow tapers. Beginning users must remember to remove that last tampon: the forgotten tampon is the most common vaginal foreign body complaint in adolescents (70).

Tampons are regulated as medical devices by the U.S. Food and Drug Administration (FDA). The FDA promulgated revised nomenclature for tampon standardized absorbency labeling (Table 36.4) (71–73). The FDA recommends that tampons not be worn 24 hours a day, 7 days a week, but be alternated with pad use (74). Although supporting scientific evidence is lacking, women are advised to change tampons often (every 4–8 hours). Package inserts suggest that tampons can be used overnight for up to 8 hours.

In the European Union, where disposable tampons are regulated as "articles," the European Disposables and

Table 36.3 Signs and Symptoms of Toxic Shock Syndrome[a]

A sudden high fever (usually 102°F or higher)
Vomiting
Diarrhea
A rash that looks like sunburn
Dizziness
Muscle aches
Fainting or near fainting when standing up

Source: From Reingold AL et al. *Ann Intern Med* 1982; 96: 875–80.

[a] Five clinical criteria include fever, hypotension, rash, desquamation, and abnormalities in three or more organ systems. Desquamation may not be apparent with early treatment and discharge.

Table 36.4 Tampon Absorbency Ratings (U.S. Food and Drug Administration)

Absorbency range in grams[a]	Descriptive term for absorbency
Less than 6	Light
6–9	Regular
9–12	Super
12–15	Super plus
15–18	Ultra-absorbency
Above 18	None

Source: From Medical devices; labeling for menstrual tampon for the "ultra" absorbency, U.S. Food and Drug Administration, HHS. *Fed Regist* 2000; 65: 62282, and Medical devices; labeling for menstrual tampons; ranges of absorbency, change from "junior" to "light." U.S. Food and Drug Administration, HHS, Final rule. *Fed Regist* 2004; 69: 52170.

[a] These ranges are defined, respectively, as follows: less than or equal to 6 g; greater than 6 g up to and including 9 g; greater than 9 g up to and including 12 g; greater than 12 g up to and including 15 g; greater than 15 g up to and including 18 g; and greater than 18 g.

Nonwoven Association (EDANA) implemented a voluntary Code of Practice in 2001 that provides for a harmonized system of categorizing tampon absorbency throughout Europe and for package inserts on TSS symptoms and safe tampon usage. The EDANA code of practice has been adopted by all major European tampon manufacturers.

Between 1977 and 1989, reports on vaginal ulcers associated with tampon use appeared in the medical literature (75–82). Most often associated with the prolonged use of superabsorbent tampons, these microlesions were typically asymptomatic and healed spontaneously. Another case involving prolonged use presented as intermenstrual bleeding (83). Ulceration can be avoided by choosing tampons with an appropriate absorbency and using the products as recommended (54).

In recent years, research on the health effects of sanitary pads has appeared in the medical literature. External sanitary protection is not generally associated with significant health concerns. An industry-sponsored series of prospective trials of pads and panty liners conducted in North America and Europe between 1984 and 2003 found no evidence that modern products cause adverse gynecological effects, adverse dermatological effects on the vulva or perineum, or clinically meaningful changes in the isolation frequencies or cell densities of vaginal and vulvar microflora (84). The 12 separate trials included a cumulative total of 1600 adult and adolescent participants.

Anecdotal reports of contact dermatitis to pads exist (85,86). Such problems are usually transient, secondary to another condition such as a vulvar dermatosis or infection, or due to a pre-existing sensitivity to perfume raw materials or adhesives (85,86). A woman who has a prior sensitivity to such materials may be unable to tolerate exposure from other sources; she should try an alternative version from the same product line or another brand.

Manufacturers avoid materials that induce contact sensitization by controlling the composition and quality of raw materials used in these products and by conducting toxicological risk assessments of the raw materials (87,88). Confirmatory repeat insult patch testing prior to market introduction (89) and the use diagnostic patch tests both prior to marketing and in post-market surveillance systems are important complements to the safety assurance process (84,90,91).

It has been suggested that pads may increase the risk of UTIs by transferring intestinal flora such as *Escherichia coli* to the vulva (54). No meaningful evidence exists for this hypothesis. Because enteric microbes often reside on the perineum and external labia majora in the absence of introital or urethral colonization, their mere presence is not a risk factor for infection (91,92). The most important risk factor for recurrent UTI in women of reproductive age is sexual intercourse (93,94), which promotes colonization of the introitus and urethra with uropathogenic *E. coli* in susceptible women (95,96). Host factors play a major role in determining individual susceptibility to this disease (97–99). Clinical trials in women wearing pads under a variety of conditions have failed to show a clinically significant change in genital microbial populations associated with their use (84).

It is also postulated that external sanitary pads and liners, nylon underwear, pantyhose, and tight clothing may trap heat and moisture in the genital region, creating an environment in which yeast can multiply. Several epidemiological studies assessed a possible link to vulvovaginal candidiasis (VVC), but the weight of the evidence fails to support this theory (100). For example, two retrospective case–control studies involving university students (one with 157 and the other with 1300 participants) found no association of VVC with tight-fitting clothing, synthetic fabric underwear, pantyhose, type of menstrual protection, or pad use between periods (101,102). A prospective study of 163 sex workers found no link between recurrent VVC and tight clothing or synthetic underwear (103), and a survey of perianal colonization with *Candida* species—a potential reservoir for urogenital re-colonization—found no correlation between recurrent VVC and use of tight-fitting trousers or synthetic fabric underwear (104).

A recent study linked patient-reported and non-laboratory-confirmed cases of recurrent VVC in women on maintenance antifungal therapy with wearing panty liners in the same week or in the week before an episode (105). Statistical associations suggesting a temporal link to panty liner use are fraught with confounding factors. For example, patient-reported diagnoses are unreliable, and diagnoses based solely on signs and symptoms can be inaccurate 50%–70% of the time (106,107). Moreover, panty liner use may be temporally (though not causally) linked to urogenital infections because absorption of vaginal discharge is a common reason for using these products. Moreover, panty liners are worn in anticipation of the onset of menses; because patients often report an exacerbation of VVC symptoms just prior to menstruation, this temporal coincidence could contribute to a spurious statistical association. Panty liner use to absorb post-coital discharge may also result in a non-causal association with VVC because monthly intercourse frequency, intercourse frequency in the weeks preceding infection, and oral intercourse frequency in the month prior to infection have been associated with both episodic and recurrent cases (102,108,109).

Prospective, examiner-blind clinical trials in the general population failed to show a connection between panty liner use and an increased risk of vulvovaginal infection. A 6-month, prospective clinical trial involving 204 women comparing daily panty liner users to non-users found no increase in the prevalence of vaginal or vulvar colonization with *Candida* species and no evidence of symptomatic infection based on culture results (110). A trial comparing the microbiological effects of the daily use of thick and ultrathin menstrual pads for 2 months led to the same conclusion (111).

Menstrual Hygiene in the Developing World

In the developing world, cloth and household absorbent materials (e.g., cotton wool, tissue, and gauze) are often used for menstrual protection, particularly in rural areas and among economically disadvantaged groups. Economic factors favor the use of reusable cloth. Moreover, in many cultures, girls are committed to the traditions and practices learned from their mothers and other female relatives (39).

Traditional beliefs also discourage the use of tampons. For example, the notion that unimpeded blood flow is related to good health permeates many indigenous cultures worldwide (45,46,112,113). Such traditions hold that the menstrual flow is necessary to rid the body of toxins and to dispel unclean substances introduced by intercourse.

Finally, pervasive taboos exist against revealing that one is menstruating. This can discourage the use of disposable pads or tampons, as well as participation in household and social activities. Some traditional religious cultures segregate women during the menstrual period and women undergo ritual cleansing after flow ceases.

Habits and Practices

In Latin America, rural women typically use cloth for menstrual protection. Because the woman washes the cloth herself, she believes that she maintains good hygiene and gains control against revealing odor and infection. Cloth is both economical and reusable, an advantage for those with limited disposable income. Moreover, cultural taboos exist against disposing of blood-soaked materials, hence discreet washing and reusing of cloth is the most acceptable practice. Less traditional women who choose disposable protection may choose cotton wool, tissue, or gauze instead of cloth, because they consider these materials more economical than commercial products and because they are readily available in the home.

Among schoolgirls in India, mothers, female relatives, textbooks, and magazines are principal sources of menstrual information (114–116). Schools are a source of information less frequently than in the USA (117,118). Rural Indian girls' understanding of menstrual physiology is quite rudimentary (115,116,118,119). The use of cloth as a menstrual absorbent predominates among urban and rural schoolgirls; urban girls cite lack of confidence as the main reason for not choosing commercial pads. Menstrual absorbents are typically washed or disposed of in the *Dhoby* (a pond or river bank used for public laundry) or in a canal. Girls take special baths to promote hygiene and may consume certain foods to promote menstrual flow and, therefore, good health.

It is impossible to generalize about African practices because traditional customs and attitudes vary among sub-Saharan communities (45). For example, traditional Nigerian culture does not encourage family discussions of sexuality. A study involving 352 schoolgirls found that a large proportion were inadequately informed about menstruation, although girls whose parents had at least secondary school education had received instruction on menstruation and hygiene from their parents (120). Half the girls used tissue paper as an absorbent; 22% used sanitary pads, 12% used cloth, and 3% used tampons.

In traditional Zimbabwean society, menstruation is associated with desires of the flesh and is considered spiritually unhygienic (113). At menarche, a girl first informs her grandmother of the event, who then informs the mother. Cloth or cotton wool is used commonly to absorb menses, and it is the grandmother who teaches the girl how to prepare her pads and pleat them so they will not show. Women with higher levels of education understand menstrual cycle physiology; less educated women view menstruation as an occurrence that signals the ability to bear children, cleanses the system, and helps maintain a trim abdomen. Menstruating women refrain from intercourse.

In China, menstrual practices are influenced by the concept of Yin and Yang (121). Yin, the negative female force, represents darkness, coldness, and emptiness. Yang, the positive male force, promotes light, warmth, and fullness. These opposing forces must be balanced for health and harmony to prevail. The most symbolic blending of Yin and Yang is the union of wife and husband.

Because sexuality is a taboo subject in traditional Chinese culture, menstrual information is not discussed proactively. However, strict behavioral norms are imparted once girls reach menarche: "hot" Yang foods are eaten to strengthen the body and "cold" Yin foods are avoided. Similarly, hair should not be washed, as it induces cold.

Urban Chinese women typically use commercial sanitary pads for menstrual protection. Tampons are commercially available; however, some Chinese clinicians express a concern that tampons may promote cervical ectopy. In the Chinese medical paradigm, cervical ectopy is traditionally viewed as "chronic cervicitis," an ulceration or erosion of the ectocervix thought to predispose women to infection. Western culture considers cervical ectopy a physiologically normal, hormonally regulated phenomenon that regresses with age (122–124).

Cloth is used in rural parts of China (125). Women wash the cloth and reuse it repeatedly, but, for traditional reasons, never dry the cloth in the sun. In poorer districts, women may resort to paper and unwashed cloth to meet their needs.

Health Implications

Because data from the developing world are lacking, definitive statements cannot be made about the impact of indigenous menstrual hygiene practices on gynecological health. Inadequate menstrual hygiene has been implicated as a risk factor for genital tract infection, particularly when cloth rags are used and washed in contaminated water (126). A study in rural China (where cloth is typically used as a menstrual absorbent) found a strong statistical link between menstrual hygiene, genital hygiene, and cervical cancer risk; the use of commercial sanitary pads was a protective factor (125).

Most statistics on gynecological morbidity in developing countries are derived from antenatal and family planning clinic patients or from studies on populations at risk of sexually transmitted diseases (STDs) (114,126–129). Population-based studies are rare, and limited resources make the conduct of large, systematic studies difficult. Moreover, cultural barriers may inhibit women from discussing intimate problems or revealing symptoms that may be stigmatizing (130).

Menstrual Practices in Orthodox Judaism and Traditional Islamic Societies

In Orthodox Jewish society, ritual law regarding menstruation is defined in Leviticus (one of the five books of the Hebrew Torah) and further interpreted in the Mishnah (44,131). A menstruating woman becomes "*niddah*" and is considered spiritually unclean (*tame'ah*) just prior to the beginning of flow, during menstruation, and for 7 days afterward (132). Standards for ritual practice vary among Orthodox sects. In the most conservative interpretations, the menstruating woman is segregated from her husband and

forbidden contact with the synagogue and sacred objects. Some traditions uphold the custom that a menstruating woman may not prepare food or wine. After checking for the absence of flow for 7 days after the menstrual period, the woman undergoes a ritual bath or immersion (*Mikvah*) to reinstate spiritual and marital cleanliness. Orthodox Jewish girls get menstrual information from mothers and girlfriends (131). In Israeli Orthodox schools, the wife of a rabbi may present lectures on sexual development, marriage, and motherhood.

In Islamic societies, menstrual practices depend on the degree of cultural and religious conservatism, which differs among countries and between urban and rural regions. In conservative cultures, menarche signals that the girl is becoming a young woman and must observe the tradition of modest dress (*hijab*) and separation of the sexes (133). The Quran dictates certain restrictions be placed on the menstruating woman (44,134). Sexual intercourse is prohibited during the menstrual period. The menstruating woman is considered spiritually unclean with regard to religious duties until she completes a ritual washing; therefore, while menstruating, she is exempt from entering a mosque, from ritual prayer and fasting, and from making the pilgrimage to Mecca (*Hajj*).

A Muslim girl learns about menstruation from her mother, her sisters, and religious books (133). In conservative societies, menstruation is strictly a woman's issue, never to be discussed in the presence of men. The mother informs the father privately of the girl's menarche. Sanitary napkins are the most commonly used menstrual protection product; a virgin woman, for fear of losing her virginity, does not use a tampon. Some girls refrain from exercise and many ordinary activities due to fear of pain or increased blood loss (135). Some believe they should not bathe until the end of the menstrual period. In one study, Saudi girls reported refraining from changing their sanitary protection at school or work for up to 8 hours, for fear of increasing blood loss or, paradoxically, of trapping menstrual flow within the body (133,135). A ritual wash is performed at the end of the menstrual period. Traditional beliefs hold that hot drinks, including indigenous herbs, will relieve pain and prevent blood clotting within the body, but that cold foods should be avoided.

Other Genital Hygiene Practices

Routine Perineal Cleansing

Perineal hygiene is part of routine bodily cleansing. In America, showers and baths are the norm, with showers being more common. Hand-held showerheads are popular in Western Europe but are less popular in America: in a California study, they were used by a quarter to a third of women (56). Sponge baths and the use of hand-held showerheads become more prevalent with increasing age as expected, when reduced mobility becomes a factor. The bidet, common in Europe, is used rarely in America (56).

Ethnic differences in genital hygiene may be related to cultural beliefs. For example, studies in the UK found that immigrants of Afro-Caribbean descent were more likely than Caucasian women to wash the vulva with bubble bath or antiseptic (136). This appears consistent with the traditional belief system that rigorous bodily cleanliness is essential to health and well-being (112). However, cleansing with harsh soaps, chemicals, and antiseptics may cause vulvar contact dermatitis (137,138). For example, such practices were reported by 68% of patients with persistent vulvar symptoms (139).

In some parts of the developing world, practices are adapted to the lack of running water. In rural China, for example, mothers teach their daughters to cleanse the genitalia using water from a basin. This is done every day from an early age, in the evening before going to bed, or before sexual intercourse (125). Washing from a basin, sponge baths, and bathing in rivers and streams are practiced in other regions of the world lacking running water.

Wet Wipes

Wet wipes are gaining popularity in North America and Western Europe. In the California study cited previously, usage rose with age from 26% among women younger than 41 years of age to 40% among women older than 48 years of age (56). Such products are often used more than once a day. Baby wipes, premoistened toilet wipes, and feminine wipes are all common choices (Procter & Gamble, unpublished data). In the late 1980s, reports appeared of allergic contact dermatitis to preservatives in some European wipes (140). The preservative in question (methylchloroisothiazolinone) is now highly regulated. Moreover, quantitative sensitization risk assessments have progressed over the last 20 years such that it is now possible to safely formulate consumer products containing such preservatives at levels that are so low that they pose no significant risk of inducing contact sensitization.

Feminine Hygiene Sprays

Scented feminine hygiene sprays were popular in the USA in the 1970s. They fell out of favor as anecdotal reports of inflammatory reactions ensued (141). Clinicians consider deodorant sprays unnecessary and generally recommend against their use (54). However, the sprays continue to appeal to women who have deep-rooted beliefs about the need to avoid odor.

Douching

Vaginal douching is the insertion of a device into the vagina for flushing liquid into the vaginal vault. A preponderance of evidence links the practice to serious adverse health effects, with limited evidence of benefits. Nevertheless, douching is a strongly held cultural norm and a difficult habit to change among those who practice it (39).

Douche Preparations

Several types of douche preparations are used. Substances found in the home reportedly used as douches include vinegar and water, household bleach, Lysol® (Reckitt & Coleman, Wayne, NJ), baking soda, yogurt, and water (142). Commercial preparations include solutions of vinegar or other acidifying agents (e.g., sodium citrate, sodium lactate, and diazolidinyl urea), antiseptics, antibacterial preparations, alcohol, surfactant solutions, and antimicrobials (povidone-iodine).

Pre-filled disposable bottles, refillable hanging bags, or refillable expandable bags are employed to irrigate the vagina. Bag-type applicators deliver a significantly greater volume and an eight-fold higher exposure duration than do disposable bottles (143).

Prevalence

Twenty-seven percent of American women douche regularly (Table 36.5). Among ethnic groups, African–American and Latino women are more likely to douche than Caucasians (144), and Afro-Caribbean immigrants to the UK are more likely to douche than Caucasian British women (136). Douching is also

Table 36.5 Percentage of North American Women who Douche Regularly by Age and Ethnicity (U.S. National Survey of Family Growth, 1995)

Age range (years)	Total	Non-Hispanic black	Non-Hispanic white	Hispanic
15–44	26.9	55.3	20.8	33.4
15–19	15.5	36.8	10.8	16.4
20–24	27.8	60.4	20.4	32.5
25–29	30.0	58.7	23.9	38.0
30–34	30.6	60.4	24.5	35.1
35–39	28.9	62.5	21.9	41.2
40–44	26.9	53.1	21.1	38.5

Source: From Abma JC et al. *Vital Health Stat* 1997; 23: 1–114.

commonly practiced in Africa: 29% of South African women (145) and 97% of pregnant women in Cote d'Ivoire (146) reported douching. Douching with a variety of substances (soap and water, shampoos, toothpaste, and commercial antiseptics) is a routine practice among sex workers in developing countries (147,148).

In the USA, douching is more prevalent among women who are less educated, living in poverty, or who have a higher risk of sexually transmitted infections (143,144,149). One survey found douching to be least frequent among adolescents aged 15–19 years (16%) and most common among women aged 20–24 years (28%) (144). A California survey among middle-class white women found a higher prevalence of douching by those older than 41 years of age (27%–30%) compared to those younger than 41 years of age (19%) (56). The frequency of douching among U.S. women ranges from daily to monthly.

Motivating Factors

Women who douche do so primarily to feel clean and they consider douching to be a sound advice of the mother, family, or friends; Caucasian American women are more influenced by the media (150). The majority of practitioners begin douching at menarche (39).

The importance of feminine cleanliness is paramount among women who douche. It is a principal motivating factor among African–Americans who favor this practice (150,151). This may be due to traditional belief systems, which maintain that cleanliness contributes to health and that the body should be kept clean inside and out (112). Women also douche to avoid odor and to become clean after menstruation and sexual activity; hence, in both Europe and North America, early onset of douching is more prevalent among those who initiate sexual activity at an earlier age (152,153).

Strongly held cultural beliefs and the perceived lack of suitable alternatives make it difficult for women to give up douching (150). Warnings that douching may be harmful are not highly persuasive; women reason that commercial douche preparations would not be widely available if they were unsafe. Among African–American women who douche, health care providers are not viewed as credible sources of information when their advice conflicts with trusted sources such as family members (112,150). Caucasian women who douche are somewhat more likely to consider douching as unhealthy and may be more readily influenced by health care providers to give up the practice (154).

Health Implications

Epidemiologically, douching is associated with an increased risk of bacterial vaginosis (BV), pelvic inflammatory disease (PID), ectopic pregnancy, preterm births, STDs, and cervical cancer (142). Potential confounding factors cloud the epidemiologic assessment of the health risks, making it difficult to assess whether douching is a causative factor or simply a more common behavior among the demographic groups that are at risk of such health conditions (Table 36.6). The strength of the association varies widely among case–control studies; few prospective studies are available.

In laboratory studies, douching preparations were antimicrobial to vaginal organisms (155). Depending on their composition and antimicrobial properties, these preparations caused either a transient washout effect in the vagina or a decrease in the density of vaginal microbes beyond the washout effect (156). Microbial counts eventually recovered (157).

Table 36.6 Health Conditions Epidemiologically Associated with Douching

Health condition	Hypotheses supporting a causative role for douching	Potential confounding factors
BV	Douching temporarily alters the microbial ecology of the vagina, which may facilitate disease acquisition	Women may douche in response to BV symptoms Women who douche share risk factors with women at risk of BV and STDs
STDs	Douching temporarily alters the microbial ecology of the vagina, which may facilitate disease acquisition Douching with irritating substances may make the vaginal mucosa and cervix more susceptible to colonization by invading pathogens	Women douche to feel clean after sexual intercourse Douching is more prevalent among sexually active women Women who douche share demographic characteristics with women at risk of STDs Women may douche in response to symptoms of infection
PID	The physical pressure of douching may facilitate uterine colonization by ascending pathogens The risk of PID is linked to douching frequency	Early sexual debut, having multiple sex partners, exposure to STDs, and other demographic risk factors for PID are also common to women who douche
Ectopic pregnancy	Douching may promote upper and lower genital tract infections that increase the risk of ectopic pregnancy	Ectopic pregnancy is more common in women with a history of PID. Such women share common risk factors with women who douche
Preterm births	Douching may play a role in infection-related preterm births	Preterm birth and douching are more prevalent among certain demographic groups
Cervical cancer	Sexually transmitted infection with human papilloma virus is a risk factor for cervical cancer Cancer risk rises with douching frequency	Risk factors for STDs are shared by women who douche

Abbreviation: BV: bacterial vaginosis; PID: pelvic inflammatory disease; STD: sexually transmitted disease.

BV is associated with an anaerobic shift in the vaginal microbial ecology that causes a fishy, malodorous discharge. Several studies have demonstrated an increased risk of BV among women who douche. For example, African–American and Afro-Caribbean women—groups that douche more often than Caucasians—also have a higher risk of BV (136,158). It is unclear whether the statistical link to douching reflects the fact that women with malodorous discharge are more likely to douche or whether alterations in the vaginal flora caused by douching predispose women to acquiring BV. Douching is more common during menstruation and after intercourse, a time of instability in some vaginal microbial populations (159,160). In one study, douching after menstruation was the strongest predictor of BV (159). Others found that douching with commercial antiseptics was strongly associated with BV risk (136) and that the acquisition of BV was linked to having a new sexual partner and douching for hygiene (161). Such findings support the theory that douching may alter the protective balance of the vaginal flora and contribute to the acquisition of BV.

PID is a polymicrobial infection of the upper urogenital tract initiated by ascending pathogens. BV, non-Caucasian race, low socioeconomic status, multiple sexual partners, and exposure to sexually transmitted organisms, which are the major risk factors for PID, are also common in women who douche. A meta-analysis of research published between 1965 and 1995 concluded that douching increases the risk of PID by 73% and the risk of ectopic pregnancy by 76% (136). Although women who douche and women at risk of PID share many of the same characteristics, douching serves as a pressurized vehicle for ascending microbes, which may facilitate the acquisition of PID. PID is also a risk factor for ectopic pregnancy, which may explain the statistical link of the latter to douching.

Douching is more prevalent among women at risk of STDs and HIV (162,163). In a study of racial and ethnic differences in vaginal flora, douching more than once a month was associated with vaginal colonization by sexually transmitted microbes, although the latter was associated more consistently with race than with behavioral factors (158). Most studies indicate a statistical association of douching with STDs and HIV infection; however, a few studies in developing countries among women at high risk of STDs suggest that the practice lowers the risk of HIV infection (164) and human papilloma virus regression (165) in such populations.

Based on the weight of the evidence, the consensus remains that douching is unnecessary for genital hygiene and may have serious adverse consequences on reproductive health. Nevertheless, few professional organizations have explicit policies on the health consequences of douching. This may be due to the difficulty in drawing firm conclusions about causation from cross-sectional epidemiologic studies. A randomized controlled trial of douching intervention (B-WELL) will evaluate the efficacy of intervention in changing adolescent douching behavior (166). Successful intervention strategies may ultimately provide a tool for prospectively assessing the risks and benefits of vaginal douching.

Perineal Powders

In the USA, some women customarily apply talc powders to the perineum on a daily basis. Such women are more likely to be overweight and to douche, smoke, and drink alcohol (167). The average duration of exposure can exceed 20 years (168).

Since 1979, numerous retrospective epidemiological studies have linked perineal talc exposure to ovarian cancer. The increased risk is highest for invasive forms of the disease. Some studies among women who use perineal powders suggested that tubal ligation was protective (168,169).

The statistical link between perineal talc application and ovarian cancer is highly controversial because of weak odds ratios, the absence of a clear dose–response relationship, and the lack of a robust mechanistic hypothesis to explain how talc exposure may cause or promote ovarian cancer.

A 2003 meta-analysis of 16 studies with an aggregate of 11,933 subjects found a 33% increased risk of ovarian cancer in perineal talc users, but no clear dose–response relationship (170). Conversely, analysis of a subset of hospital studies showed no relationship to talc use, suggesting that a spurious statistical association may account for population-based data.

These studies were all retrospective. By contrast, a long-term prospective study of 121,700 nurses found no overall association between perineal talc powder and ovarian cancer (171). There was a moderately increased association for invasive forms of the disease. The risk of epithelial ovarian cancer among talc users was no higher among women who had not had a tubal ligation.

Hence, the weight of the evidence among retrospective case–control studies, coupled with the results of the large, prospective study involving nurses, suggests that the statistical association between perineal talc exposure and ovarian cancer risk may be the result of selection bias or other confounding factors. Body mass index may be one such factor, since overweight women are more likely to use perineal powders and are at higher risk of ovarian cancer (172). Uncontrolled socioeconomic variables may also play a role in the observed association.

Hair Removal

In the West, pubic hair removal is practiced for aesthetic reasons. Common methods include shaving, the use of chemical depilatories, wax epilation, electrolysis, and laser hair removal. All methods tend to cause occasional mild folliculitis. Rare instances of severe cases progressing to keloid scars have been reported on the legs (173). In the late 1990s, an epidemic of allergic contact dermatitis to colophonium in epilating wax occurred in Europe (174). Occupational allergy to colophonium was also reported in a beautician who handled epilating waxes (175).

Pubic hair removal is performed in some Islamic cultures. In response to a survey of 635 Turkish women, 98% reported pubic hair removal on a regular basis (once a week, every few weeks, or once a month) (Farage MA, unpublished data). Hair removal is performed before or after the menstrual period, either with a lemon–sugar paste or by shaving. Those who shaved reported a higher frequency of skin irritation than those who used a lemon–sugar paste.

Genital Hygiene among Older Women

Hygiene Challenges Posed by Light Urinary Incontinence

Stress and urge urinary incontinence become more common with age. Stress incontinence is characterized by accidental spurts of urine following abdominal pressure (coughing, laughing, sneezing, or lifting). Urge incontinence is characterized by an urge to urinate and the rapid loss of urine (sometimes in significant amounts) prior to controlled micturition. Sufferers may have a combination of stress and urge incontinence. Some women begin experiencing light incontinence after having delivered children; for others, the onset is postmenopausal.

In Western Europe, the reported prevalence of stress incontinence ranges from 40% to 60%, urge incontinence ranges from 7% to 20%, and mixed stress and urge incontinence ranges from 20% to 50% (176–178). In North America and Western Europe, women cope with light incontinence in various ways. In a Swedish study of postmenopausal women, 4% of respondents (18% of stress incontinence sufferers) had urine loss sufficient to necessitate either the wearing of a sanitary napkin or changes in underwear several times a day (179). In general, to address this challenge, women use panty liners, menstrual pads, or pads designed for incontinence protection; some resort to frequent changes in underwear. Thirty percent reported some degree of vulvar irritation associated with their condition. Pelvic muscle exercises or Kegel exercises are conservative approaches to treating mild stress incontinence.

Hygiene Challenges Posed by Irregular Uterine Bleeding

The perimenopause is a transitional time between the reproductive years and menopause. Ovarian steroid hormone production decreases in stages, beginning with a drop in progesterone, reduced levels of both estrogen and progesterone, and, finally, a depletion of both hormones to postmenopausal levels. Irregular uterine bleeding and spotting can occur during this transition, necessitating anticipatory or daily use of sanitary pads or panty liners.

Approximately 30% of women over 40 years of age experience menorrhagia (i.e., abnormally heavy or prolonged menstrual bleeding). Benign uterine fibroid tumors are a common cause of this condition. Use of tampons and pads in combination, coupled with frequent changes, is often necessary to cope with excessive menstrual bleeding. The condition can be quite disruptive to everyday life and may pose particular problems for women in Orthodox religious traditions that consider a bleeding woman to be ritually unclean. Continuous use of oral contraceptives (omitting the placebo pills of the fourth week) is sometimes used to remedy the situation by eliminating menstrual cycling (133). Even in such cases, special dispensation may be needed from the Rabbi or Muslim cleric so that occasional breakthrough bleeding does not render the woman ritually unclean.

Perineal Hygiene among Older Women

Genital hygiene is of particular importance to the health and well-being of older women. The consequences of inadequate hygiene vary. Mild skin irritation and fungal or bacterial skin infections become more common in older people who have a diminished capacity to care for themselves. Atrophic vulvovaginitis is prevalent after menopause. Moreover, the risk of pressure ulcers and incontinence dermatitis can be significant when older women suffer impaired mobility and urinary or fecal incontinence. The health conditions linked to genital hygiene in older women are described in the following sections.

Intertrigo and Vulvar Folliculitis

Intertrigo is an inflammation of the genitocrural folds, labia, and perineum sometimes seen in older or morbidly obese women (180). It manifests with erythema and excessive moisture. Vulvar folliculitis presents as red, tender papules surrounding the hair follicles, and may be associated with staphylococcal and streptococcal infection. Both conditions result from an impaired ability to maintain adequate hygiene. Hygienic interventions and maintaining skin dryness are indicated treatments.

Tinea

Tinea is a fungal infection of the feet, nails, and vulvar skin folds. Though a rare condition, its prevalence rises in older women due to diminished cellular immune responses (181). The most characteristic presentation is a ring-shaped eruption with an actively advancing border and scaly, healing center. However, any pruritic, scaly eruption of the vulva is suspect: it should be scraped for microscopic examination and treated with antifungal therapy, if appropriate. Maintaining dry skin helps prevent this condition.

Incontinence Dermatitis

Preventing and managing incontinence dermatitis is the principal hygiene challenge in people with severe incontinence. Incontinence dermatitis is sometimes referred to as perineal dermatitis and is a broad term that encompasses inflammation and tissue damage to the vulva, perineum, perianal region, and buttocks. The condition creates much pain and discomfort in elderly sufferers (182).

Prevalence of Incontinence In North America and Europe, urinary incontinence is prevalent among people over the age of 65 years (183). A community-based survey of 1584 Caucasian and African–American women in the USA aged 70–79 years found a prevalence of 21% (184). Of these, 40% reported stress incontinence and 42% reported urge incontinence. The frequency of urinary incontinence was higher among Caucasian women (27%) than among African–American women (14%). Fifteen percent of Mexican–American women aged 65 years or older reported having urinary incontinence (185). A community-based survey of Italian women aged 65 years or older found a 26% prevalence rate (186).

Pathogenesis of Incontinence Dermatitis The etiology of incontinence dermatitis in elders (Figure 36.3) is inferred from research on pediatric diaper dermatitis. Elevated skin wetness, elevated pH, and the presence of fecal enzymes set the stage for skin damage. Hydrated skin is more susceptible to mechanical forces, while the elevated pH induced by urinary ammonia alters skin barrier function and activates fecal enzymes that compromise skin integrity. Moreover, several additional factors increase the risk of skin injury in older people (187,188). Skin atrophy makes the tissue inherently more fragile. Skin hydration following occlusion is significantly greater and is dissipated more slowly in aged skin (189). Immobility increases the impact of mechanical forces; moving an immobile person across a chair or bed not only produces superficial friction, but also generates shear forces in the underlying tissue due to pressure from the sacral bone (190). In those with impaired immune function, overgrowth of cutaneous pathogens or invasion of fecal bacteria is more likely to be a complication. Poor nutritional status can impede tissue recovery. Finally, impaired cognition can limit the person's ability to alert caregivers to incontinent episodes.

Incontinence dermatitis in older people begins with mild erythema of the skin, then progresses to an intense red appearance, often accompanied by blistering, erosion, and serous exudates. In darker skin, the initial inflammation reaction may be more difficult to detect. With urinary incontinence, dermatitis begins between the labial folds; dermatitis associated with fecal incontinence originates in the perianal area and progresses to the posterior aspect of the upper thighs. Secondary infection with *Candida albicans* causes erythematous, punctate vesicles

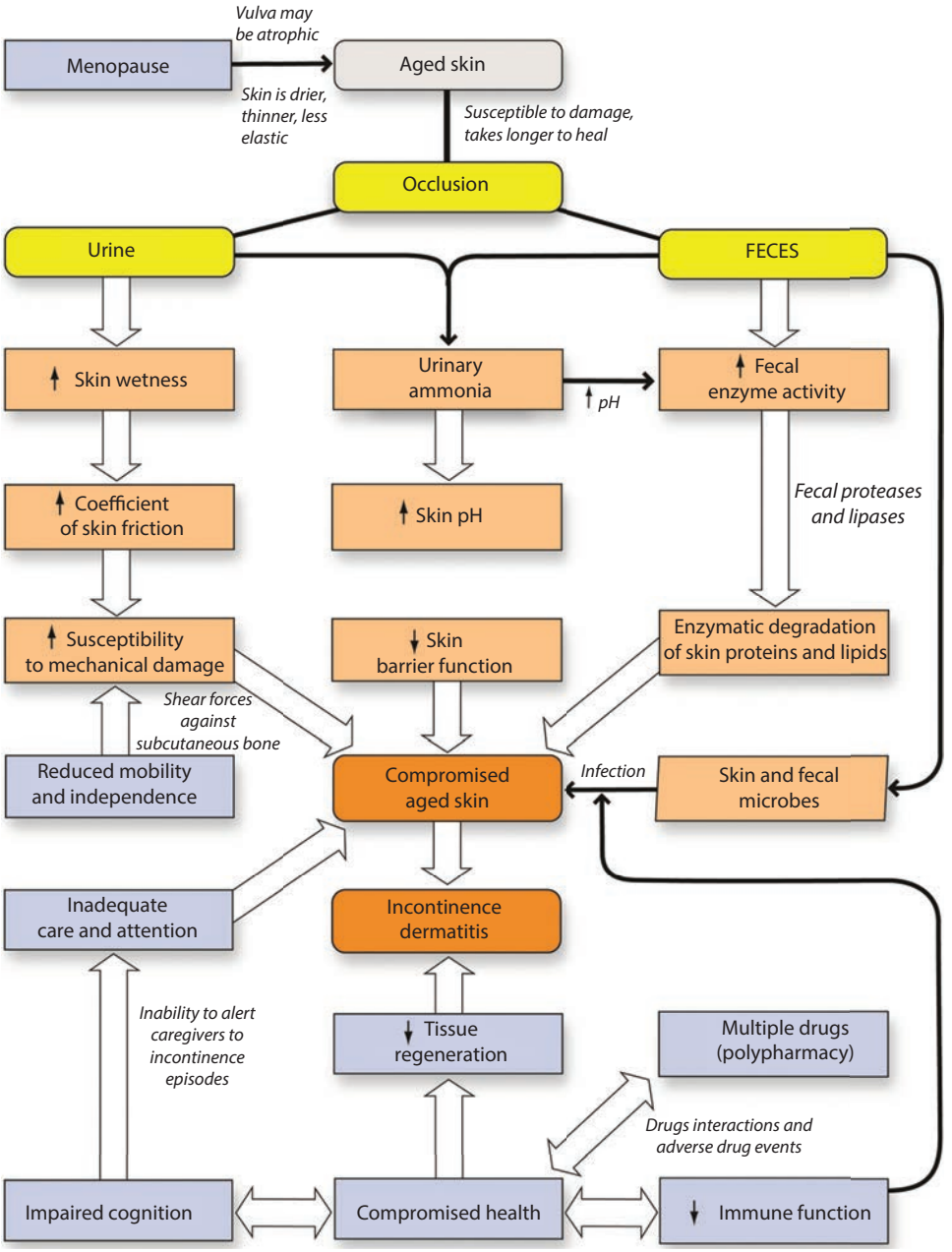

Figure 36.3 Factors that contribute to the morbidity of incontinence dermatitis in older people. Based on the concepts of (3,181–183).

that form a central confluence; satellite lesions may be visible on the border of the infection. Because of friction, vesicles may assume a macular appearance. The infected skin takes on a dark red color.

Hygiene Measures Examination and care of the genitalia should include gentle separation of the labia and exposure of the skin folds between the mons pubis and the inner aspect of the upper thigh. The buttocks should be separated and examined, as well as the crease between the buttocks and the posterior upper thigh. In women who are obese, skin folds of the lower abdomen must also be exposed and examined, particularly in women who are diabetic or immunocompromised (190).

Although no systematic trials exist on the impact of perineal hygiene on skin health, general guidelines have been developed for preventive care (190–192). The focus is on keeping the skin dry, maintaining a healthy skin pH, avoiding mechanical forces, and minimizing contact with urine and feces. The use of specially formulated perineal skin cleansers or disposable wipes is preferred over bar soap and a washcloth (193). The former avoid the high pH of most soap bars and the friction forces created by rubbing a washcloth against the skin (187). Powders are used to absorb excess moisture; cornstarch-based powders are sometimes favored due to the controversy regarding perineal talc. Moisture barrier preparations are also employed. Superabsorbent incontinence pads or garments are

used to absorb wetness and keep it away from the skin. Wet or soiled garments should be changed promptly.

Treatment of Incontinence Dermatitis Prospective clinical trials are needed in order to study the effectiveness of preventive hygiene measures, as well as the efficacy of therapeutic interventions (194,195). In 2015, a by-invitation-only study enrolled participants to compare wash wipes and standard care in the prevention of incontinence-associated dermatitis in the elderly (196). In 2014, a Phase III study was completed assessing the treatment of incontinence-associated dermatitis in older children and adults with two topical zinc oxide products, but as yet, the results are unpublished (197). To our knowledge, the only published prospective study of preventive care was a preliminary trial of structured nursing interventions in 15 institutionalized patients with dementia (198). An equal number developed dermatitis (two in the structured care intervention group and three in the unstructured care group) regardless of whether cleansers, moisturizers, or moisture barrier preparations were used. Dermatitis developed only in those with urofecal incontinence and followed more than four incontinent episodes in 24 hours. None of the patients was capable of informing caregivers of incontinent episodes. The small number of subjects and their poor mental health limit the conclusions that can be drawn from this study.

Case reports provide evidence for the effectiveness of barrier creams and hydrogel dressings in treating incontinence dermatitis (199,200). In one case report, applying a commercial barrier cream three times per day prevented dermatitis from postsurgical diarrhea (10–20 stools a day) during a 1-month follow-up period (199). In another, a 68-year-old woman who presented with candidiasis secondary to urofecal incontinence and diarrhea was treated with a regimen of skin cleansing followed by the application of an antifungal powder and then a layer of barrier cream. Her dermatitis cleared within 3 days (199).

Case reports also support the efficacy of hydrogel dressings for treating excoriation (200). The first case involved a disabled woman with incontinence who suffered perianal excoriation that was unresponsive to a titanium-based barrier cream and paraffin wax. Resolution was achieved in 3 days by applying hydrogel every 2 hours and after every incontinent episode. Another case involved a man who was incontinent of urine and who had perianal dermatitis and a sacral pressure ulcer. Application of hydrogel cream resulted in improvement after 5 days of treatment.

CONCLUSION

A woman's genital hygiene needs change dramatically over her lifetime. Menstrual hygiene practices vary by age, culture, and religious tradition. General hygiene practices may be constrained by family economics or the available infrastructure in different regions of the world. Some hygiene practices carry the potential for adverse health effects. Education is key to reducing these risks; however, resource limitations, cultural constraints, and the intimate nature of the subject matter can present barriers to effective intervention and the institution of more healthful hygiene practices.

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Products used on the vulva

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INTRODUCTION

Products for vulvar hygiene are becoming increasingly available and popular. In fact, more than $2 billion is spent annually in the USA on feminine hygiene products (1). Women use a wide variety of products on or around the vulvar area, including products for cleanliness and odor control, such as soaps and body washes, pre-moistened wipes and towelettes, douches, deodorant sprays, suppositories, body splashes, powders, and other fragrances. Moisturizers, lubricants, and hair removal products are also important to a woman's overall hygiene and beauty regimen. In addition, some subgroups of women may have special needs for products to control incontinence or for over-the-counter medications. Also, it is impossible to discuss vulvar hygiene without including menstrual products, such as tampons, pads, and panty liners. This chapter discusses the products women use in the vulvar area, the perceived and real benefits, and the potential health effects of these products.

PRODUCTS FOR CLEANLINESS

Soaps, Body Washes, and Bubble Bath

Soaps are water-soluble sodium or potassium salts of fatty acids produced by saponification or basic hydrolysis of a fat or oil with a strong alkali (2). An example of such a reaction is shown in Figure 37.1a (3). Evidence exists that several ancient civilizations knew of soap making and used the resulting material as hair-styling aids, to treat skin diseases, and for washing (2). However, it is likely that soap was not used routinely for personal cleansing until about the 2nd century CE. During the time of the Roman Empire, bathing was extremely popular, but its popularity declined with the fall of Rome in 467 CE. During the Middle Ages, bathing fell out of fashion in Europe until the 17th century. However, there were regions of the medieval world where personal cleanliness remained important throughout the Middle Ages. Daily bathing was a common custom in Japan during the time, and in Iceland, pools warmed with water from hot springs were popular gathering places on Saturday evenings.

In the late 18th century, methods were developed for making soda ash, or sodium carbonate, out of common table salt. However, soap making remained largely a household chore until the mid-19th century when higher-yield methods were developed, thereby improving the quality of soap products and lowering their cost. These discoveries, along with the development of power to operate factories, made soap making one of America's fastest-growing industries by 1850, and changed soap from a luxury item into an everyday necessity.

Investigation into the use of synthetic detergents began in the early 1900s and, with the end of World War II, synthetics starting replacing soaps for some cleaning chores, such as laundry and household cleaning (2). As surfactant chemistry became more and more sophisticated, these synthetic detergents began to replace soap in many of the bars and liquids used for personal cleansing. Examples of some common surfactants are shown in Figure 37.1b.

Synthetic detergents are "synthesized" or put together chemically from a variety of raw materials. They have a major advantage over soaps in that they do not combine as readily with mineral salts to form a soap curd film or bathtub ring (2). In addition, detergents offer excellent performance throughout a wide range of temperatures and water hardness levels, and are milder on the skin.

Whether it is a fatty acid soap or a synthetic detergent, the function of "soaps" is to reduce the surface tension of water and to solubilize materials such as grease and oils that cannot be removed easily by water alone. Materials used for personal cleansing, such as bar soaps, body washes, bubble bath, and feminine washes, all consist of mixtures of surfactants. Many of these products incorporate additional ingredients in order to provide added consumer benefits, such as fragrances, deodorant protection, antibacterial components, and skin moisturizers or softeners (4,5).

Most large manufacturers of personal cleansing products have rigorous approaches to evaluating the products and ingredients for adverse skin effects (6–10). A number of test methods have been developed. Many test protocols include exaggerated-use testing, or patch testing, on sensitive body sites. Extended-use testing by volunteer participants using the products at home is sometimes part of the safety assessment.

Many in the general public assume that soaps and other personal cleansing agents can contribute to vulvitis (11). However, given the broad use of these products, there are relatively few specific case reports of adverse reactions of the vulva as a result of using personal cleansing products. It is likely that consumers who experience mild irritant reactions that they perceive to be related to use of a specific product simply switch products.

Douches

Douching has a long and ancient history, reaching as far back as 1500 BCE, when an Egyptian papyrus recommended a garlic and wine douche for the treatment of menstrual disorders (12). In the days of Hippocrates, vaginal rinsing was thought to be the only method of curing vaginal infections. Different ethnic groups have used douching off and on throughout history, but in America, douching had its heyday beginning in the early 1920s and carried on through the 1950s, when women's magazines regularly featured advertisements for douche brands such as Lysol® (Lehn and Fink Products Company, Montvale, NJ), Sterizol® (Sterizol Company, Ossining, NY), and Zonite®

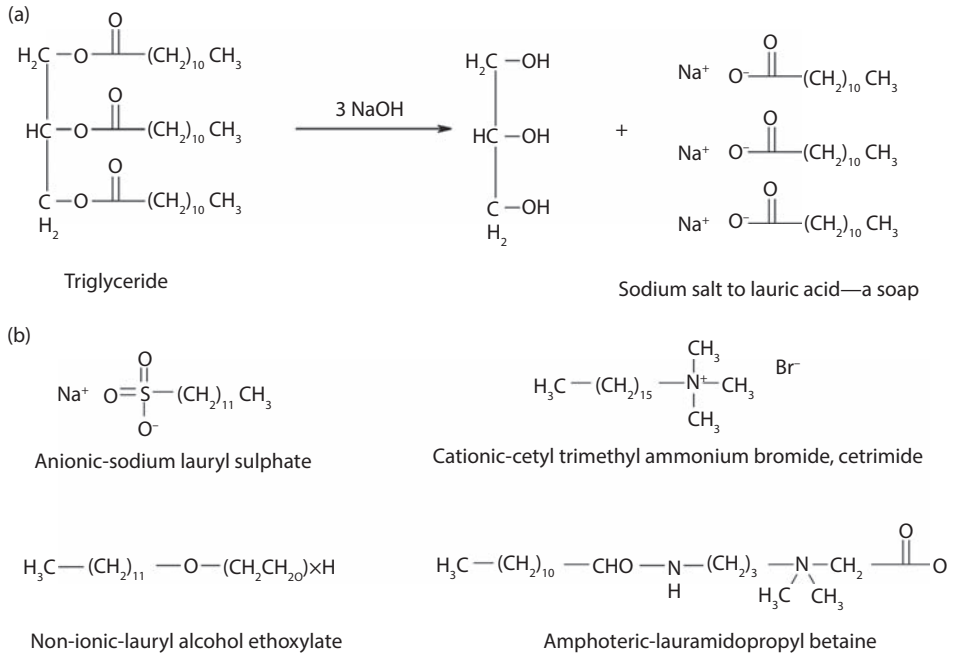

Figure 37.1 (a) Basic hydrolysis of a fat or oil with a strong alkali to form soap. (b) Structures of common surfactants: anionic, cationic, non-ionic, and amphoteric. ([a] Reproduced from Farage MA, Lennon L. Products for vulvar hygiene. In: Farage MA, Maibach HI, eds. *The Vulva: Anatomy, Physiology and Pathology*. 1st edn. New York, NY: Informa Healthcare, 2006, 217–33.)

(Lee Pharmaceuticals, El Mote, CA). As recently as the early 20th century, the medical community recommended douching for the treatment of specific gynecological conditions (12).

Selected reports on the prevalence of douching are summarized in Table 37.1 (13–25). Results of a 2002 survey indicated 32% of women in the USA practice douching, making it a common practice in the USA (13). Differences in the estimated occurrence of this practice in the USA are related to ethnicity, education, geographic location, and socioeconomic status. Overall, the highest reported prevalence was among non-Hispanic black women (59%), followed by Hispanic women (36%) and white women (27%) (14). Among college graduates, the prevalence of women who engage in the practice is lower; 52% of black women, 30% of Hispanic women, and 12% of white women (14). There are noted geographic differences, with the highest overall percentage in the south (48%), followed by the Midwest (32%), northeast (31%), and east (28%) (15). Income levels and age at first intercourse were inversely related to douching (14,15). Sixty-nine percent of adolescent females attending a family planning clinic in a small southern town reported douching (16).

There is some evidence that the practice may be declining slightly in the USA. In two summaries of the National Survey of Family Growth, the data from 1988 reported a prevalence of 36.7% (15), while the 2002 survey indicated a prevalence of 32% (14). Nevertheless, this remains a common practice.

Compared to the USA, vaginal douching is less common in the UK. In a study conducted in the UK among women attending a sexually transmitted disease (STD) clinic in London, only 7% reported using any cleaning agent as a douche; however, 30% reported applying these preparations through the vaginal introitus with a finger or wash cloth (20).

Studies in African nations indicate that the percentage of women who engage in this practice is extremely high (Table 37.1). Recent studies conducted in Egypt and Nigeria found the overall prevalence rates of vaginal douching to be 73% and 79.35%, respectively (24,25).

Most women who douche begin the practice around the time they become sexually active (13). Gazmararian and colleagues reported that family, friends, and the media reinforce the practice (17). In a prospective longitudinal study of 3620 women in 12 Alabama clinics, Brotman and colleagues (26) documented the most common reasons why women douched as: to feel fresh and clean (80%); to remove menstrual blood (34%); to remove vaginal odors (13%); or to remove discharge (5.9%). Some women also indicated they douched to please a partner and smell good, to prevent infection, or to clean before going to the doctor or nurse (26). Some women have the perception that douching kills germs, prevents pregnancy (27), prevents STD (28), and helps ameliorate vaginal itching and discharge (18). Women report douching after menstruation and/or intercourse for cleanliness and odor control (29).

In some cultures, there are additional perceived benefits to douching. In sub-Saharan Africa, it is perceived that the astringent properties of vaginal douches enhance sexual pleasure (23). Douching is considered a religious duty in order to purify the body in some cultures. Shaaban and colleagues (24) reported a 72% prevalence rate of the practice in Egypt, and the most commonly cited cause was religious duty (88.9% of those who douche), followed by personal cleaning (80.6%).

The composition of douches can range from homemade solutions of salt, vinegar, and water, or water alone, to purchased douches marketed expressly for the purpose. In a 2010 report (13), 42% of women who douche reported using a

Table 37.1 Summary of Selected Reports on the Prevalence of Douching

Type of study	Findings	Reference
USA		
Summarized from the 1988 National Survey of Family Growth	36.7% of women overall engage in this practice (66.5% of African–American women and 32% of Caucasian women)	(15)
Summarized from the 1995 National Survey of Family Growth	55% of African–American women, 33% of Hispanic women, and 21% of Caucasian women douche	(17)
Telephone survey of 535 adult women in the southeastern USA. conducted in 1997	59% of African–American women and 36.5% of Caucasian women responded that they engaged in this practice at the time of the survey	(18)
Survey of 169 adolescents attending a family planning clinic in a small southern town conducted in 1999	69% (75% of African–American women and 64% of Caucasian women) reported a history of douching	(16)
Summarized from the 2002 National Survey of Family Growth	32% of women overall engage in this practice (59% of African–American women, 30% of Hispanic women, and 12% of Caucasian women)	(13,14)
Survey of 114 postmenopausal women conducted in 2011 in northeastern USA	8% reported douching within the last 3 months	(19)
Other geographies		
Case–control study of women attending a sexually transmitted diseases clinic in London in 1994–1995 (100 women with bacterial vaginosis and 100 women without)	7% reported using any cleaning agent as a douche	(20)
Indonesian study among 599 pregnant women	91% had douched at least once in the month prior to the survey	(21)
Survey of 552 women in an antenatal clinic in the Ivory Coast	98% reported vaginal douching as a common practice	(22)
Survey of 543 female sex workers in Nairobi	72% douche regularly	(23)
Questionnaire survey of 620 Egyptian women with vaginal infections in 2011–2012	73% reported douching. Vaginal douching increased the incidence of preterm labor and pelvic inflammatory disease	(24)
Survey of 1535 female Nigerian college students in 2011–2012	Overall douche prevalence was 79.35%. Significant differences were found between tribal ethnicities and associations were found between the number of sexual partners and a higher likelihood of engaging in the practice	(25)

commercially prepared product, and only 2% reported using a homemade product. In a study conducted in the USA by Oh and colleagues (27), a majority of adolescent women surveyed used commercially marketed products. However, baking soda, Betadine® (Purdue Frederick Company, Norwalk CT), Pine-Sol® (The Clorox Company, Oakland, CA), and Lysol® were also used.

Not surprisingly, studies in non-western geographies reported homemade solutions as being more commonly used. In a recent study in Nigeria (30), 66.1% reported using a soap-and-water solution, 13% reported using water alone, and 17% reported using a commercial preparation. In a Nairobi study, Fonck and colleagues (23) found that water with soap was used most commonly (81%), followed by salty water (18%), water alone (9%), and a commercial antiseptic (5%). In Indonesia, soap and water (63%), water (19%), betel leaf (8%), and a commercial agent (2%) were used (21). Betel leaf is a traditional plant used for medicine. It contains antiseptic and irritant properties and is often used for cleaning the vagina in the postpartum period.

It is now recognized that douching is associated with a host of negative consequences. Douching kills beneficial bacteria that live in the vagina (lactobacilli). Stripped of lactobacilli, the pH balance of the vagina is altered, creating a risk of infection and a variety of adverse health effects. The adverse effects that have been associated with douching are outlined in Table 37.2 (12,13,19,23–25,30–36) and have been reviewed in additional publications (13,37). Effects include adverse reproductive effects, an increase in the occurrence of STDs and pelvic inflammatory disease, and an increase in risk of HIV and cervical cancer. Rajamanoharan and colleagues (20) found that any douching agent (proprietary products, vinegar and water, soaps, bubble bath, or antiseptics) was associated strongly with bacterial vaginitis. Baird and colleagues (12) showed that regular douching with water only, water and vinegar, or commercial solutions was associated with reductions in fertility.

Table 37.2 Negative Health Consequences Associated with Douching

Consequence	Reference
Impaired fertility	(12,30)
Preterm birth	(13,24,25,32)
Low birth weight	(25,33)
Ectopic pregnancy	(13,19,30,34)
Bacterial vaginosis	(13,23,25)
Pelvic inflammatory disease	(13,19,24,30,35)
Upper genital tract infection	–
Endometritis	(35)
Vulvovaginal candidiasis	–
Sexually transmitted diseases	(13,19,29,30)
Cervical cancer	(13,19,30,36)
HIV infection	(13,25,37)
Recurrent upper urinary tract infections	(25)
Chlamydial infection	(25)
Increased risk for endometritis	(13)
Menstrual irregularities	(30)

Pre-Moistened Wipes and Towelettes

Baby wipes were the first pre-moistened wipes to penetrate the market significantly. Today, this range of products includes

flushable personal cleansing cloths for cleaning after toileting and products targeted specifically for women in order to freshen the genital area. The formulations of these products vary, but consist mainly of water with a mild surfactant, preservatives, antimicrobials, and fragrance. Some brands include skin treatment agents such as lotions with vitamin E or aloe. It is estimated that 10%–15% of women use feminine wipes (1). Major manufacturers have developed means for testing pre-moistened wipes for potential skin irritant effects. These include long-term use testing (38), as well as exaggerated exposure methods designed specifically for these products, such as the modified forearm-controlled application test (39). Pre-moistened wipes and towelettes are more convenient and portable than soap-and-water washing and provide an effective and gentle means of perineal cleaning.

PRODUCTS FOR ODOR CONTROL

There is general agreement in the medical community that good general hygiene is more important for feminine odor control than other methods. Use of odor control products also carries the risk of masking symptoms that may be indicative of a more serious underlying medical condition. Nevertheless, many women use additional products to control what they perceive to be offensive odors.

Dusting Powder

Some women apply powder either directly to the vulva or indirectly through the application to menstrual pads, diaphragms, or condoms for odor control. It has been suggested that application of powder to the genital area may be associated with an increased risk of ovarian cancer (40). A confounding factor in many of the studies looking at a possible link is that, prior to 1973, most dusting powders were based on talc, and low levels of asbestos were sometimes present. All powder products marketed after 1973 have been required by law to be free of asbestos, and many dusting powders are now based on cornstarch or other non-talc materials.

More recent studies have failed to clarify a potential association between use of powder in the perineal area and increased cancer risk. A recent study (from 2014) followed a cohort of 61,576 postmenopausal women for 12.4 years (41). Among this group, 52.6% reported using perineal powder. There was no association between ovarian cancer risk and the use of powder applied directly to the perineal area, to sanitary napkins, or to diaphragms.

A 2013 study evaluated the association between genital powder use and ovarian cancer risk. The study compared powder usage among 8525 women with ovarian, fallopian tube, or peritoneal cancer to 9859 women in a control group (42). These investigators concluded that use of genital powder was associated with a modest increase in risk of ovarian cancer relative to women who reported no powder use.

Karageorgi and colleagues (43) evaluated any correlation between the genital use of talcum powder and the risk of developing endometrial cancer and noted a modest positive association among postmenopausal women. However, a subsequent investigation by another group found no such correlation (44).

Although the association between perineal powder use and ovarian or endometrial cancer is still unresolved, the position of the American Cancer Society is that, for any individual woman, if there is an increased risk, the overall increase is likely to very be small (40).

Feminine Deodorant Sprays

Feminine deodorant sprays first entered the market in 1962 in Europe and in 1966 in the USA. Typically, these products are packaged in an aerosol or pump spray for external use, primarily to be applied on or adjacent to the female genitalia to absorb moisture and deodorize, neutralize, or otherwise control odor. These products may contain antimicrobial agents, astringents, and perfumes. In their early days, some of these products contained talcum powder to absorb moisture, but the modern products replaced talcum with cornstarch or baking soda. The aerosol products also contain propellants. It is estimated that 4%–39% of women use feminine sprays (1). There are few reports in the scientific literature of adverse reactions to modern feminine deodorant sprays. A careful choice of ingredients and safety testing prior to marketing minimizes any risks of irritation or sensitization.

Feminine Suppositories

Recently, feminine suppositories for odor control have been becoming more common, with a number of different manufacturers entering the market. Such products may contain antimicrobials or odor-neutralizing materials and fragrances. Some may contain specialty ingredients such as tea tree oil. There is no indication that the materials used in these products are unsafe. However, as with many so-called feminine odor control products, routine use may carry the risk of masking symptoms of an underlying medical condition if done for a prolonged time.

Other Products for Odor Control

Body splashes or colognes are used by some women and can sometimes be applied to the genital area. Fragrances are ubiquitous in most consumer products. Most fragrances consist of a mixture of fragrance oils; the precise composition is usually a proprietary formulation. The fragrance industry has established strict standards for use levels and applications that allow fragrance materials to be used safely in the marketplace (21). However, typical body splashes and colognes may not be formulated for use in the genital area, where the properties of absorption through the transitional and mucous membranes may be different from those of the stratified squamous cell epithelium.

PRODUCTS INTENDED FOR COMFORT OR AESTHETICS

Some products are used on the vulva for greater comfort during intercourse or for aesthetic purposes. These products include lubricants and moisturizers, products for hair removal, and products to dye pubic hair.

Lubricants and Moisturizers

Vaginal dryness can occur as estrogen levels fluctuate. This condition is common with aging. In a recent report, 46% of sexually active postmenopausal women reported using a product for lubrication during sexual activity (19). In some younger women, vaginal dryness can occur during pregnancy, while

nursing, or at certain times in the menstrual cycle. In addition, some disease states can cause vaginal dryness, such as Sjögren's syndrome, an autoimmune disease that affects the body's moisture-producing glands.

A number of commercial lubricant products are available to counteract vaginal dryness. Typically, these are water-soluble, glycerin-based materials. Some women also use massage oils and vegetable and olive oils, although these tend to be messy. Petroleum-based lubricants, such as petroleum jelly, can harbor bacteria and cause damage to latex condoms, rendering them ineffective against unplanned pregnancy and STDs.

Lubricants are also available as vaginal suppositories or inserts. In addition to moisturizers and lubricants, some of these products contain vitamin E.

Hair Removal Products

Hair removal methods include trimming with scissors or a hair clipper, shaving, depilation, waxing, electrolysis, and laser hair removal. Trimming and clipping have few adverse effects, as long as they are done carefully to avoid cutting the delicate skin of the vulva. Shaving is easy to do at home, but can sometimes leave bumps on the skin. A number of depilatories are formulated specifically for use on the "bikini line." Use on areas outside the bikini line, such as the vulva, can lead to irritation.

The results of waxing last longer, since this practice actually plucks the hair from the root. Commercially available home products contain combinations of waxes and a resin that makes the wax adhere to skin. At-home products are formulated for use on the bikini line and not for other areas of the genitalia. Redness and bumps can sometimes occur with waxing methods.

A current popular trend for hair removal is sugaring or sugar-waxing. A number of commercially available sugar wax preparations are on the market. In addition, do-it-yourself recipes and directions are readily available online (e.g., (45)). The materials used in these preparations are primarily sugar, water, and lemon juice. The solution is heated, and then cooled to a paste. The paste is applied to the area and covered with a porous cloth that is quickly stripped off. Some commercial sugar-waxing products are available that do not require heating for use, but the homemade preparations must be heated. The materials used in this process are generally considered safe; however, heated sugar wax has the tendency to easily burn the sensitive skin of the genital area.

In laser hair removal, the laser is moved over the skin and the light passes through and is absorbed by the melanin (pigment) in the hair follicles (46). It is believed that the heat generated by the laser breaks apart the follicle and the hair falls out over a period of approximately 2 months. The treatment is best suited for fair-skinned people with dark hair. In darker-skinned people, the skin pigment can absorb the laser before it reaches the hair follicle, making the treatment less effective. Light-colored hair may not contain enough melanin. Multiple treatments are required to achieve a meaningful reduction in the amount of hair on the area. Adverse effects of laser hair removal include extreme sensitivity of the treated skin. Rarely, peeling, blistering, and burning of the skin may occur, as well as brown spots or a slight loss of pigment in areas where the laser has been used.

Electrolysis uses an electric current to destroy the hair root. Each hair is treated individually with either a needle epilator or a tweezers epilator. Home electrolysis devices are available, but it may be difficult to apply the device accurately to an area that cannot be seen very easily. Therefore, professional electrolysis is preferable. Adverse effects of electrolysis can include pain during treatment and swelling and inflammation after treatment. Electrolysis can cause scarring and changes in skin color in some people (46).

Dyes

Since pubic hair tends to be darker than hair color and grays with age, some women resort to dyeing. Home hair-coloring products are not formulated for use on the vulva and would likely cause irritation if used for that purpose. Pubic hair dyes are now commercially available for home use in a variety of colors, including bright colors such as hot pink and aqua blue (Figure 37.2). Some of these come with special applicators in order to minimize potential accidents. It should be noted that medical professionals never recommend do-it-yourself pubic hair coloring. An experienced professional colorist is preferred.

Vajazzling

Vajazzling is the practice of gluing or sticking crystals on or near the genital area (Figure 37.2). Specific kits are sold for this purpose. In most of these, the crystals come with adhesive already applied to the back. Do-it-yourself instructions available on the internet recommend the use of eyelash glues or other adhesives used on other body sites, such as bindi glue or spirit gum.

MEDICATIONS

Products to Address Itching

Genital itch can be a symptom of a number of more serious underlying conditions, such as yeast infection, bacterial infection, certain STDs, or lichen sclerosus. In these cases, the underlying cause should be identified and treated.

Minor irritations and perspiration can also lead to occasional itching with no concomitant, serious disease. In addition,

Figure 37.2 Examples of some products intended for aesthetics or beautification.

vulvar and vaginal atrophy (VVA) is a chronic condition resulting from a decline in estrogen in the urogenital tissues that affects up to 45% of postmenopausal women (47). Vaginal itching is a common symptom of VVA (47,48). In a 2010 report on a questionnaire-based study of over 1000 postmenopausal women, Huang and colleagues (49) found that about a third claimed to experience problems with vaginal itching.

Medicated or anti-itch creams are marketed for relief of external feminine itching. These products can include anesthetics (benzocaine), external analgesics (resorcinol), and antipruritics (hydrocortisone) (50). In a 2014 publication by Nicole (1), it was reported that 23% of women use anti-itch creams. Vaginal suppositories to treat itch are also available. The main risk associated with the use of these products is that they treat the symptoms without identifying and treating the underlying cause.

Antifungal Preparations

In the early 1990s, manufacturers began to make drugs for the treatment of candidal vaginitis available without prescription (i.e., over the counter [OTC]). A number of antifungal medications are now available as creams or suppositories without a prescription, including clotrimazole, miconazole nitrate, and tioconazole. Nonprescription antifungals are among the top 10 best-selling OTC drugs in the USA, with annual sales of approximately $250 million (50).

The primary advantages of OTC status to the consumer are patient autonomy, convenience, more rapid relief of symptoms, and cost savings by reducing the number of physician visits and the costs of the drug. The potential disadvantages are misdiagnosis, with resulting overuse of the antifungal drugs and the potential for developing drug resistance, as well as possible delays in the diagnosis and treatment of the actual underlying medical condition causing the symptoms (51). If the underlying condition is serious, such as a STD, the patient runs the risks of increased morbidity and/or inadvertently transmitting the disease to a partner.

MENSTRUAL PROTECTION PRODUCTS

Many products are used for menstrual protection, although disposable pads, tampons, and panty liners are the most common (Figure 37.3). However, some women use alternative protection such as menstrual cups, internally worn sponges, and washable pads made from fabric (Figure 37.4).

Tampons

The forerunners of the modern tampon were homemade from various materials such as papyrus (ancient Egypt), wool (ancient Rome), paper (ancient Japan), plant materials (Hawaii, Asia, and Africa), linen vinegar-dipped cloth (18th century

Figure 37.3 Examples of common menstrual protection products.

Figure 37.4 Examples of alternative menstrual protection (such as Diva Cup, sea sponges, and Padette interlabial pads).

France), cotton, wool, or linen with a string attached. Modern tampons began with cotton tampons from the Tampax® brand (Procter & Gamble Company, Cincinnati, OH) in 1936 (52). Today's mainstream market offers a large selection of tampon products of varying absorbencies made of cotton, rayon, or a combination of these two materials. They are typically about 2 inches in length and with a diameter of about half an inch, and a cotton string attached securely to one end for removal after use. Tampons are available with or without applicators (the applicators can be made of cardboard or plastic) and with or without perfumes (i.e., scented or unscented).

Modern tampons have been used safely for many years as convenient products for menstrual protection. The Food and Drug Administration (FDA) classifies tampons as class 2 medical devices, and they are therefore subject to testing requirements by the FDA (53). In addition, major manufacturers have developed detailed testing plans in order to ensure the safety of tampons prior to marketing and to confirm that the products cause no shifts in the vaginal microflora (54,55). Menstrual tampons require specific labeling in order to clearly identify the degree of absorbency of the tampon (Table 37.3) (56).

Superabsorbent tampons marketed in the late 1970s to the early 1980s were associated with toxic shock syndrome (TSS), a rare but treatable disease that can be life threatening in some individuals (57,58). However, changes in absorbency characteristics and composite materials saw a marked reduction in the incidence of TSS. Today, more than half of TSS cases cannot be linked to tampon use (59). There are no safety issues if modern tampons are used according to instructions.

A misperception by some is that tampons contain dioxin. Dioxin is a general term that describes a group of about 30 chemicals that are highly persistent in the environment and have been associated with cancer. They can be produced by a wide variety of processes, including combustion (as a result of cooking or internal combustion engines) and chlorine bleaching of paper pulp. The U.S. Environmental Protection Agency (EPA) has estimated that most dioxin exposure (>95%) occurs through the diet (60). The misperception about tampons is that their materials are subjected to chlorine bleaching and therefore contain dioxin. In fact, modern bleaching methods for absorbent products do not involve chlorine bleaching and are dioxin free (61). State-of-the-art testing of tampons and tampon materials has shown that dioxin levels are at or below the detectable limit of 0.1–1 parts per trillion (61).

Table 37.3 Standardized Tampon Absorbencies

Absorbency range (g)	Terminology of absorbency (56)
<6	Junior
6–9	Regular
9–12	Super
12–15	Super plus
15–18	Ultra
>18	No term

Disposable Pads and Panty Liners

For many years, women used rags to contain menstrual flow. These were not very reliable and had to be soaked and laundered after use. The first disposable sanitary pad was created in 1896 by Johnson & Johnson (New Brunswick, NJ; Lister's Towels), but failed to catch on. In World War I, nurses found bandages to be an excellent absorbing material for menstrual flow. Soon thereafter, Kimberly-Clark (Neenah, Wisconsin) introduced Kotex® in 1921, and Johnson & Johnson introduced Modess®, the first successful disposable pads. Disposable pads were definitely more effective and convenient than rags. However, they were a long way from current products. They had to be held in place with pins or special belts worn around the waist, and a range of protective gear was available to compensate for when the pads failed, such as special panties or "sanitary aprons" (made of cloth-coated rubber and worn backwards over the buttocks) (52,62).

The first major improvement in disposable pads came about 50 years after their initial introduction, when adhesive backing was introduced, enabling use of the pads without pins or special belts. The quality and effectiveness of pads has continued to improve in the last few decades. Performance improved substantially with the development of superabsorbent materials (i.e., polymeric gelling compounds developed to lock the moisture in the core of the pad and not release it under pressure). Procter & Gamble introduced ultrathin pads based on superabsorbent materials, which were seven-times thinner than the early pads, making them more comfortable and less noticeable in tighter-fitting fashions. In addition, many modern pads incorporate a top sheet designed to wick moisture into the core and away from the skin for a drier feeling.

Modern pads offer women a wide variety of products designed specifically to meet their needs. Procter & Gamble introduced "wings" or flexible side extensions of the pad that wrap over the edge of the panty to prevent panty soiling and to hold the pad securely in place. Pads are available in a number of sizes and lengths, ranging from small, thin panty liners for managing discharges between periods or to use in combination with tampons, to larger, longer pads that offer maximum protection overnight. Most brands come in scented or unscented varieties. Some are packaged with wrappers for discrete disposal. Emollients have also been introduced into the manufacturing of feminine hygiene pads to provide lubrication, moisturization, and a soothing feeling to the skin (63). After thorough pre-market testing, pads with emollients have been shown to be safe, effective, and dermatologically beneficial to the genital area.

Major manufacturers of pads and panty liners have developed and published methods of evaluating the safety of

these products. In-use clinical assessments of irritation and the impact of product use on the microflora of the vulva are important parts of this evaluation (9,64,65). New protocols have been developed that are designed specifically to evaluate the contribution of both the chemical composition of these products and the potential for mechanical irritation through friction (66–68). There have been some concerns that panty liners trap heat and moisture, thereby contributing to vulvovaginal candidiasis (VVC) or urinary tract infections. However, studies of the effects of panty liners on skin temperature and moisture levels showed no negative effects of these products in relation to VVC and the promotion of urethral colonization leading to urinary tract infections (69).

Alternative Menstrual Products

Several alternative forms of reusable menstrual protection products are available from specialty shops or the internet. Some women see these as a more environmentally friendly alternative to disposable products. Examples are shown in Figure 37.4. Menstrual cups are flexible, nonabsorbent containers made of natural gum rubber or medical silicon inserted into the vagina that can collect about 1 oz of menstrual fluid. They can then be emptied, washed, and reused. Sea sponges are also sold for menstrual protection, as are interlabial pads sewn from fabric or made from absorbent yarn (i.e., knitted or crocheted). Disposable interlabial pads are composed of materials similar to modern tampons. These are worn externally and held in place by the labia. They are most suited for light menstrual flow. For any reusable device, care must be taken to thoroughly clean and sanitize the product between uses.

PRODUCTS FOR INCONTINENCE CONTROL

Urinary incontinence or the accidental release of urine is a fairly common problem among women, with a prevalence of 10%–40% among women aged 15–64 years (70). The most common type is stress incontinence, which occurs when pressure is put on the bladder by coughing, laughing, sneezing, or physical activity. Urge incontinence—also called overactive bladder—is an urgent sensation to urinate even when the bladder may not be full. Some women suffer from a combination of stress and urge incontinence. The estimated prevalence of fecal or anal incontinence varies widely, from 2.2% to 25%, depending on the definition (71). Fecal incontinence can affect individuals at any age, but the prevalence increases with aging (72,73). Also, it is seen more commonly among women (73,74). Incontinence can have a profound negative effect on both physical and psychological well-being (75).

Contact with urine and feces in the perineal area can have adverse dermatologic effects on the skin (76). Modern products for incontinence utilize superabsorbent materials to minimize contact with urine and feces. These products are available in a wide variety of styles, including adjustable briefs (a diaper-style garment), pull-up briefs or undergarments, pads, panty liners, and pessaries. Barrier creams can provide a physical barrier on the skin surface that protects from irritant materials in excreta and prevents excessive moisture loss (76). Lipids in the barrier creams penetrate the skin surface to replace lipids that may be lost from the stratum corneum, and partially restore function. No-rinse, pH-balanced skin cleansers and wipes have been demonstrated to be an effective, gentle, and consistent means of perineal cleaning in the case of incontinent dermatitis (77,78).

CONCLUSION

The number and variety of products used by women in the genital area have increased dramatically in recent decades. They go well beyond absorbent products for menstrual control and soap and water for cleanliness. Products for the female genital area comprise a wide range, being used for cleanliness and odor control, to treat conditions such as dryness, itching, or even yeast infections, for use as personal lubricants and moisturizers to increase the comfort of daily life and activities, and for purely aesthetic or beautification purposes, such as hair removal products, pubic hair dyes, and crystal adhesions. When produced by a reputable manufacturer with careful safety testing programs, most of these products have minimal or no adverse effects. Some products designed to treat uncomfortable symptoms, such as fishy odors or severe itch, may sometimes mask serious, underlying health issues. In addition, practices such as douching can have detrimental health consequences. Women need to weigh the potential risks and benefits of using several varieties of products for the genital area.

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Consumer research and in-market comments

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INTRODUCTION

Feminine hygiene product development requires real innovation in order to connect "what is needed" and "what is possible"; that is, connecting a superior understanding of consumer habits and attitudes with leading-edge technology. That is why research and development, together with marketing and market research, observe consumers using their products at home, look for ways to improve the products, and find ways to simplify the overall in-use experience. With an opportunity identified, the product development team creates prototypes in the laboratories, working with technologies in product, process, and packaging design. These prototypes are tested with consumers in order to determine whether the product design works. The cycle of learning is iterative: a design is made in the laboratory, tested with consumers, and changed based on what is learned from consumers, and the modified product is retested until it is right, as judged by the consumer. This chapter describes the process of consumer research conducted on feminine hygiene products before the products are marketed and available for women to use.

WHAT DO WOMEN WANT FROM A FEMININE HYGIENE PAD?

First and most importantly, women seek protection: the avoidance of soiling of the underwear and/or outer garments during menstruation (Figure 38.1). Why is protection so important for consumers? Today, approximately 50% of all women experience at least one episode of staining of their undergarments during their menstrual period and approximately 10% of all women experience at least one blood stain on outer garments.

In addition to effective protection, women want to be reassured that wearing the pad will help reduce the malodor that may develop in the vulva area during the menstrual flow. Although the level of odor might not be very high, especially when the woman practices good vulvar hygiene, there is a psychological effect driving women to seek proper odor control from the pad. It is also important to women that the pad remains comfortable when it is worn over several hours. When both the basic protection performance and the comfort elements are satisfied, women claim that it is important that the pad provides the needed discretion. Women want to continue their regular activities as much as possible during the menstrual period and do not want the pad to limit activity or be noticeable through clothing.

CONSUMER RESEARCH PROCESS FOR FEMININE HYGIENE PRODUCTS

This section describes the process of developing a feminine hygiene product from the early phase of understanding women's habits and practices, the early generation of a novel idea, making prototypes leading to readiness for market, and ensuring that the product is widely available to all women.

Understanding Consumer Habits and Practices

First, a questionnaire is sent to a large number of women asking about their current habits and practices concerning their feminine hygiene routine. Women are asked to clearly list what products they use, how satisfied they are with their current products, and what their additional hygiene practices are, along with the use of these feminine hygiene products.

Laboratory Prototyping with Associated Laboratory Testing

Following an in-depth learning process regarding these habits and practices and an assessment of the need gaps, the developer begins by creating prototypes of potential products that can better meet the consumers' needs. First, simple laboratory tests are conducted on product parts (e.g., tests of core absorbent properties and product integrity tests) or on the total prototype product (e.g., speed of menstrual liquid absorption) in order to assess its likely performance in use. As the prototype approaches the final product design, more complex tests are conducted that involve the actual wearing of the product (e.g., leakage protection tests and stay-in-place studies).

Controlled Panel Tests

Once the prototype approaches its final design, the first test production runs are initiated in order to ensure the prototype can be converted into production. During this process of experimental production in the plant, the products are first made for further quality testing with women. At this stage, diary and technical perception testing may be conducted, during which women are supplied with the products and asked to wear them as they normally do. While wearing them, women are asked to keep a diary about their wearing experience, commenting on how well the product met their protection expectations and how comfortable the product was during actual use.

Another type of controlled panel test is the clinical test, which is conducted in order to assess the safety of using the product. The safety assurance program to support major innovations for feminine hygiene products often requires the performance of prospective, randomized, controlled clinical trials under practical conditions of use. The studies often share several common features, and standard protocols are developed with the input of respected academic and medical experts. The protocols employ objective, numerical scales for assessing tissue irritation and skin condition of the external and internal genitalia. All clinical studies must be approved by an independent institutional review board and/or by an ethics committee and should be examiner-blinded,

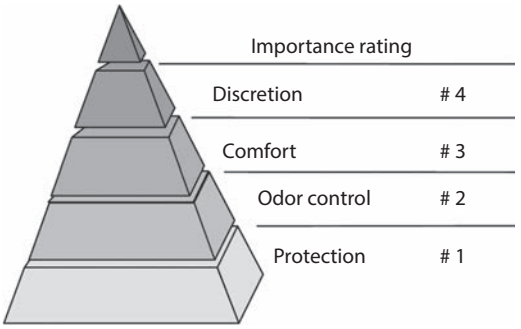

Figure 38.1 Factors of importance women seek from a feminine hygiene pad. (Courtesy of Research International Agency.)

utilizing independent academic physicians in obstetrics, gynecology, or dermatology as investigators. Subjects can be recruited from the population at large and must sign an informed consent form before participating (Internal Procter & Gamble Procedures on Product Development, unpublished information).

In-Market Consumer Tests

Different types of in-market consumer tests are undertaken in order to maximize the success of the new product design and to minimize the risk of consumer dissatisfaction when the product is finally made available to the marketplace.

Product Test

Within this large-scale quantitative test, women are exposed to the product design. They are asked to use the product under regular usage conditions over a menstrual cycle. At the end of the wearing test, women receive a questionnaire about the product, allowing them to rate the different product performance parameters and also to compare the new product with the one they ordinarily use.

Concept and Use Test

This is a pre-test market large-scale quantitative technique. In addition to evaluating the pure product performance, product manufacturers test the concept of how to clearly present it to consumers, as well as its "fit" with the overall brand under which it is envisioned to be sold in the market.

Test Market

Prior to a wide market rollout, a new product or product design might be launched first in a test market, allowing the product manufacturer to gain more in-market experience. Typically, for this test, a city with a representative population distribution is selected. Most companies developing feminine hygiene products follow extensive testing programs, as not only do they want to be sure that the new product design fully meets the consumers' needs, they also gather useful information about the safety of using the product.

QUALITY ASSURANCE FOR PRODUCTION OF FEMININE HYGIENE PRODUCTS

While the novel feminine hygiene product is being assessed for safety and effectiveness, the production process is being developed. A good-quality production process must ensure that the product and its manufacturing meet several requirements.

This applies to clinical studies, normal consumer studies, and market shipment alike.

1. First and foremost, consumers expect a good and functional product that delivers the desired performance. Production should follow good manufacturing practices. This means that high hygiene standards (in building, equipment, and operation) and high manufacturing quality must be provided.
2. On feminine hygiene products, there are numerous regulations worldwide that must be met. Governmental agencies, such as the U.S. Food and Drug Administration (FDA), reserve the right to audit manufacturers for compliance. A good-quality system reflects all necessary requirements in written procedures and ensures that regulations are met. These are properly included and documented in the relevant work processes.
3. A growing number of trade customers require a quality certification from the manufacturer. The ISO 9001:2000 certificate is the most common global system. This is the trade's safeguard ensuring that manufacturers follow a quality system that has been certified by a third party.
4. In many countries, liability laws have changed, and manufacturers have to provide evidence of their standards in court. Operations must be transparent and the work traceable. Production is allowed only according to approved standards, procedures, and good documentation. Production equipment and processes must be validated for their purpose, and only quality materials can be used. The product is released into the marketplace only when it meets all specifications.
5. A consumer response system is needed in order to provide the consumer with the means to ask questions or to provide testimonials or comments/complaints. Such a system not only helps to satisfy consumers, but also is a great analysis tool for learning of market successes and failures and improving internal systems in the manufacture of a product that will provide consumers with the desired experience.

CONSUMER COMMENTS FROM MARKET USE

The process described in this section is based on the experiences of the Procter & Gamble Company with their pads, tampons, and panty liners, but similar processes on handling post-launch consumer comments are available at other large companies producing feminine hygiene products. Products are launched in the market typically with the means to contact the producing company included in the package artwork (mostly located on the side or back panel), providing consumers with an easy way to express their experience with the product or marketing. When the consumer contacts the producing company, the consumer comments handling process is activated within the company.

Consumers contact the producing company for three different reasons:

1. *Testimonial*. Consumers may provide positive feedback to the producing company. For example, if they are very satisfied with the improved protection that the newly launched feminine hygiene product offers, they often claim that they would also recommend the product to their friends or family.

2. *Inquiry*. Consumers may ask questions or make requests and/or suggestions. For example, women might like to better understand the differences between the many feminine hygiene products a company sells or they may suggest a design/package improvement.
3. *Complaints*. Women may express dissatisfaction, complaining of a problem or an adverse event. For example, they may be unable to locate the product they want to buy or find that the product does not perform to their expectations. A more in-depth analysis of consumers' comments allows the company to define follow-up actions properly.

CONCLUSION

Innovation and understanding of consumer needs are the keys to developing effective feminine hygiene products upon which consumers can rely. Learning what women want in a feminine hygiene product is the result of thorough and thoughtful consumer research. The process of consumer research, which culminates in the introduction of the product to the marketplace, involves many phases, each guided subsequently by consumer feedback. Throughout the process, manufacturers follow the guidelines of governmental agencies such as the FDA and of third-party trade associations in order to obtain certification and assure consumers of product safety and manufacturing quality.

This development process—from initial understanding of consumer needs through development of products and safety testing up to final introduction of the new product to market—may take several years, and these development investments are performed in order to ensure that only quality products reach the market.

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