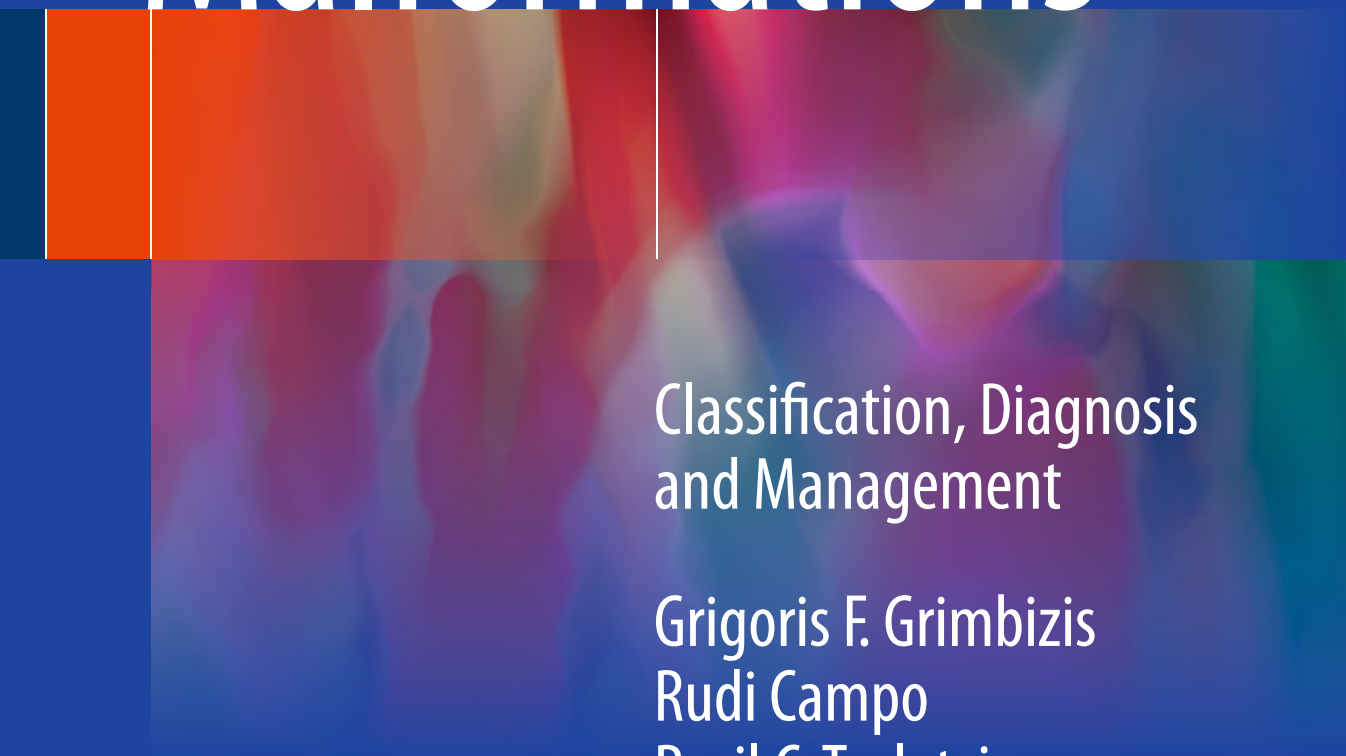
Female Genital Tract Congenital Malformations



Classification, Diagnosis and Management

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Editors

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Preface

Female genital tract malformations represent a common clinical challenge for the gynecologist. Although gynecology is the specialty most frequently involved in their diagnosis and treatment because of their close relationship with the reproductive potential of the woman, a lot of other specialties are faced with them. Pediatricians, adolescence gynecologists, and pediatric surgeons since some of the anomalies are presented with clinical problems during puberty and adolescence, radiologists because they are implicated in their diagnosis and, sometimes, general and plastic surgeons in cases of complex anomalies required sophisticated surgical treatment. Apart from them, basic scientists, embryologists, and geneticists contribute to their etiology and pathogenesis.

Their clinical importance is related to a variety of reasons. First, they are quite common; it is estimated that more than 5 % of women in the general population have a kind of deviation from normal anatomy, and more importantly, malformations are more frequent in selected populations and especially in patients with recurrent pregnancy losses. Secondly, dependent on the type and degree of anatomical abnormality, they are associated with severe health problems (e.g., obstructing anomalies), potentially dangerous complications (e.g., "ectopic" rudimentary horn pregnancy), and mainly an impaired reproductive potential either in the achievement or in the evolution of pregnancy.

During the last two decades, the better understanding of female genital malformation pathogenesis, the availability of new noninvasive techniques for their diagnosis, and the increased experience from their treatment have radically changed their management. The reader will have the opportunity to assess the latest information by invited experts, who will share their knowledge and experience going through the recent advances in their field.

Pathogenesis of female genital anomalies is a crucial issue for understanding the process of their origin; it is the result of defects in normal embryological development, and it is presented in the first chapter of this book. It is true that their etiology is not yet fully elucidated, despite research efforts in this field.

A presentation of all the available data is the topic of the second chapter. Impaired implantation in cases of uterine anomalies might explain the decreased reproductive potential of the patients, and all the available data from recent research on that subject are critically reviewed. Classification of

female genital anomalies is an extremely important issue for their management, and the new ESHRE (European Society of Human Reproduction and Embryology)/ESGE (European Society for Gynaecological Endoscopy) are presented together with a brief description of old proposals.

Diagnosis of female genital anomalies is clinically a prerequisite for their management. Nowadays, a lot of noninvasive methods are available, radically changing the field of diagnostic investigation of women. Hysterosalpingography is still in use, although historically it was the first method for the estimation of the anatomical status of the uterine cavity, giving additional information for the tubal patency; a very nice description of its expected findings in different types of anomalies, together with comments on its usefulness, is presented. Ultrasound seems to be the most currently applied tool for estimating female genital tract anatomy. Two-dimensional ultrasound is available in every gynecological setting, it is cheap, and gynecologists are familiar with its use. The information gained with its application seems to be reliable; 2D US findings in cases of female genital anomalies and the role of sonohysterography as an additional tool to increase the diagnostic accuracy are presented very nicely in a separate chapter of this book.

The introduction of three-dimensional (3D) technology has enormously increased the diagnostic capabilities of ultrasound. The findings with the use of this new technique, the new perspectives in the estimation of female genital anatomy, and the new horizons in differential diagnosis between the various types are excellently described. Magnetic resonance imaging (MRI) is a new diagnostic, noninvasive tool in our armamentarium for the diagnosis of female genital anomalies. Although still expensive, it could offer additional useful information for female genital anatomy; the use of this imaging technique is also presented. Despite all these advances in the noninvasive approach of female genital tract anatomy, endoscopy seems to have a role still remaining for many years the "gold standard" in the diagnosis of anomalies; a very attractive review of this topic is presented. In view of all these available options, an overall evaluation of their distinct role in our diagnostic strategy seems to be necessary; this difficult task is discussed in a chapter of this book.

Since anomalies are benign deviations from normal anatomy, their clinical consequences are the important parameter in estimating the need for treatment. The prevalence of anomalies in the general and selected populations is excellently reviewed, offering an indirect evidence for their role in the achievement and evolution of pregnancy. Obstructive and complex anomalies are associated with health problems seeking solutions; an overview of those problems is nicely presented. An interesting discussion within the literature is the impact of uterine anomalies on a woman's fertility; an effort to answer this crucial question based on the best available evidence is made. It is generally accepted that uterine anomalies have an impact on pregnancy outcome; this issue is meritoriously reviewed, giving the gynecologists all the necessary information for patients' counseling. Cervical weakness could be an occult clinical entity affecting pregnancy outcome in women with uterine anomalies; this clinical option is also presented and discussed in an excellent way, closing the field of the clinical importance of anomalies.

Vaginal aplasia, usually associated with uterine aplasia in the so-called MRKH syndrome, represents a difficult clinical entity seeking treatment since it is associated with inability to establish normal sexual activity. Due to the difficulty of surgical reconstruction, a lot of very sophisticated options are available. The simpler one is the expansion of the existing vaginal vault with the use of dilators, which is the nonsurgical alternative, and it is presented in the beginning of this part of the book. Vulvoperineoplasty is another proposal; this treatment modality, which is quite simple surgically, is nicely presented. Traction techniques are also based on the expansion of the vaginal vault; this very attractive minimally invasive surgical option and its results are presented together with the devices developed for this reason. One of the more sophisticated options in the surgical treatment of vaginal aplasia that is described in the next chapter is neovagina formation between the bladder and the rectum with the use of the peritoneum; although not recent, substitution of laparotomy as part of the procedure with laparoscopy has made this technique more attractive. The use of the bowel for neovagina formation is another surgical alternative, quite invasive and difficult to be applied; its description is also given. In view of all these alternatives, the decision is quite difficult; an overview of the comparative invasiveness, advantages, and disadvantages of each one is presented, trying to find out a treatment algorithm for patients with vaginal aplasia.

Obstructive anomalies are clinically important, seeking urgent surgical treatment. Certain types of vaginal anomalies, including imperforate hymen, are associated with obstruction, and their treatment is not always easy; their management is reviewed, and their surgical alternatives are given in an excellent way. Various types of cervical aplastic anomalies in the presence of a functional uterine cavity represent severe forms of obstructive malformations; their treatment is always difficult, especially if they are associated with vaginal aplasia too, a topic that is presented very nicely in the subsequent chapter of the book. Rudimentary horns are variants expressing clinically significant subclasses in cases of hemiuterus and vaginal aplasia; once they are associated with obstructive phenomena, surgical treatment is necessary, and different available options are described in detail.

Uterine anomalies are the most common types of female genital malformations and those that are associated with the impaired reproductive potential of women. Their treatment is quite simple, using the modern endoscopic techniques. T-shaped uterus is a variant that was thought to be associated with diethylstilbestrol (DES) administration. However, it is still present, and it seems to be associated with compromised fertility; its treatment is described in detail, focusing also on post-treatment results. Septate uterus is the anomaly associated with poor reproductive outcome, and hysteroscopic septum resection is the treatment of choice; the various surgical alternatives and their advantages and disadvantages are given, together with a review of postresection reproductive results. Bicorporeal uterus and its variants are fusion uterine defects, sometimes together with a septate element whereas in others presented as full division of the uterine corpus and the cervix (formerly didelphys uterus); treatment options are presented and discussed very nicely for the reader of this book.

Disorders of sex development are not actually congenital malformations. However, they are expressed as deviations from a female's normal genital anatomy. This is why they are included as the last chapter, having in this way the opportunity to present all the recent advances in classification and management.

We would like to cordially thank all the authors of this book for their contribution. All of them are experts with long-standing experience in the management of female genital anomalies. We hope that with this effort, all the recent advances are presented and that we will gain the interest of scientists interested in this clinical field.

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Part I

Basics

Normal Embryological Development of the Female Genital Tract

1

Maribel Acién and Pedro Acién

Introduction

Once the anomalies in sexual determination (by alteration of the sexual chromosomes, in the HY antigen and/or TDF gene [Testis-determining factor gene] or in the gonada) and in sexual differentiation (by abnormal esteroidogenesis, pseudo-hemafroditisms) are excluded, those affecting the development and morphology of the Fallopian tubes, uterus, vagina and of the vulvar introitus, with or without ovarian, urinary, skeletal or other organs' associated malformations are among the malformations of the female genital tract. Most of the malformations affect the uterus, and are, therefore, referred to as mullerian anomalies, but sometimes they are of mesonephric or wolffian origin, apart from the fact that many alterations of the mullerian system also have their origin in a mesonephric or gubernaculum anomaly.

The malformations of the female genital tract are frequent but not always detected. Uterine anomalies have been reported in 0.1–3 % of women, in 4 % of infertile women and in 15 % of those with recurrent miscarriage [58]. Most likely, an increase in the use of the ultrasound, hysterosalpingography, hysteroscopy, laparoscopy and magnetic resonance has led to an apparent increase in their incidence. In a previous study [10] we observed that if we included minor uterine anomalies (hypoplastic and arquate uterus) among the malformations, the frequency of those uterine malformations reached 7–10 % in all women. But even just considering those uterine malformations properly recognized clinically, they were observed in 2–3 % of fertile women, 3 % of infertile ones and 5–10 % of those with recurrent miscarriages [10].

Complex malformations of the female genital tract (and not only the uterine or müllerian malformations with their impact on fertility) are not as common, but they do appear and are often incorrectly identified, inappropriately treated, and sometimes incorrectly reported. The main reasons for the frequent diagnostic delay and/or inappropriate surgery are: (1) Not considering the malformation as a cause of the patient's clinical symptoms and (2) Not considering the embryological origin of the different constituent elements of the genito-urinary tract [8].

However, given that these anomalies frequently cause very important clinical problems in very young women, with specific symptoms and an important impact in their quality of life, an appropriate knowledge of the embryology of the

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female genital tract is essential to solve the symptoms and start the treatment adequately [5, 9, 11, 54]. And though it is true that embryological hypotheses vary [28, 34, 39, 43, 52, 54, 55, 59, 60, 63, 67, 75] and that the direct cause of the majority of anomalies is not known, the pathogenesis of the majority of these malformations can be correctly explained and understood through our embryological hypothesis that likewise, provides the guidelines for its appropriate correction.

Etiology of the Malformations

The direct cause of genital malformations is unknown despite the many different theories and hypotheses in this area. The familiar incidence is difficult to research though it is clear that it does exist [50]. The karyotype is generally normal [22] but sometimes there are mosaicisms or other anomalies that do not seem related to the malformation; and the environmental causes can only explain some cases. Apart from the DES-syndrome (Diethylstilbestrol syndrome), other teratogenic drugs, malnutrition, metabolic alterations, viral infections and placental anomalies have been implied.

And association between didelphys uterus and trisomies 13–15 has been described, some familiar cases seem to be linked to a recessive autosomal gene and others to a dominant autosomal one [26]. Discordant congenital anomalies of the reproductive system in monozygotic twins have been described [44]. In cases with hereditary renal adysplasia (HRA) (a rare autosomal dominant condition frequently associated to pulmonary hypoplasia and renal agenesis [15, 64]) a balanced 6p/19q traslocation has been described, supporting the assignment of one of the loci for HRA to chromosome 6p [65] but with incomplete penetrance and variable expressivity and not always being present [15].

In other cases, the anomaly is part of a more general malformative syndrome, such as the MURCS association (Müllerian duct, renal and cervicothoracic somite aplasia/dysplasia association), the uterus-hand-foot syndrome with characteristic dermatoglyphics [73], the Klippel-Feil anomaly (fused cervical vertebrae), the Winter syndrome (middle ear anomalies), and Fraser, Meckel, Rudiger and Edwards and Gale's syndromes [24]. Duncan et al. [35], Greene et al. [42] speculated that the combination of müllerian duct, renal and skeletal anomalies seen in the MURCS association is due to a teratogenic event late in the fourth week of fetal life, when the cervicothoracic somite mesoderm and pronephric duct are in close proximity thus, due to a damage of the para-axil mesoderm. Others [78], also believe that a teratogenic event occurring before the end of the first fetal month is the best explanation for other major anomalies sometimes linked to MURCS association.

Specific mutations of several genes, such as WT1 (Wilms tumour 1 gene), PAX2 (Paired box gene 2), HOX A7-HOX A13 (Homeobox A7/A13 genes), PBX1 (Pre-B-cell leukemia homeobox 1) and WNT4, which are involved in the earliest stages of embryonic development, or TCF2 (HNF1B) (Hepatocyte nuclear factor-1beta encoded by the TCF2 gene) and LHX1 (LIM homeobox protein 1), which are involved in determinism, could play a key role in the etiopathogenesis of MRKH syndrome (Mayer-Rokitansky-Kuster-Hauser syndrome) [31, 53, 69].

Another study has shown that vaginal agenesis might be associated with reduced activity of the GALT enzyme (Galactose-1-phosphate uridyl transferase enzyme) [32]. And it has also been suggested that a very strong hyperincretion of AMH (Anti-müllerian hormone) or an anomaly in its receptor, caused by genetic mutation, could lead to Müllerian athresia or agenesis [25, 48]. In most genital malformations, however, there is no evident cause or association with gene mutations [77].

It seems then that genital malformations are influenced by multifactorial, polygenic and familiar mechanisms that together can create a favorable environment for the anomaly. But in most cases there is no evident cause or association. However, the embryological development of the female genital tract and the chain of anatomical events leading to the production of the malformation are better known [3, 8, 12, 17, 20, 21, 28, 72], and therefore, we must analyze the embryology for a better understanding of the pathogenesis.

Normal Embryological Development

The Gonads

The gonads begin to develop when the embryo has a crown-rump length of 5–7 mm, in the fifth week of pregnancy. Their formation begins as swellings located on either side of the dorsal mesentery, at the ventromedial surface of the mesonephros (Wolff's body), and they become prominent in the coelomic or peritoneal cavity [66].

The longitudinal swelling on both sides of the primitive mesentery, which encloses the mesonephros and the primitive gonad internally, is the urogenital ridge. The protrusion of the gonad forms the gonadal or genital ridge as a part of the primitive urogenital ridge (Fig. 1.1).

The gonad is formed by the interaction between the primitive blastema in that area (somatic cells) and the gonocytes (germ cells) that migrate from the backside of the yolk sac. The somatic cells of the gonads are derived from mesonephric cells, which migrate into the area of the genital ridge early in development, and also from the mesenchyme and overlying coelomic epithelium [30]. The gonocytes or germ cells arrive at the gonadal ridge from the yolk sac, attracted by a chemotactic factor [71] or teloferon. In addition, there is a close association between the primordial germ cells and fibronectin and other components of the extracellular matrix during the migration [40]. Since the XX gonocytes arrive at the gonadal ridge later than the XY gonocytes (around the 10th–12th week), the wave of primary sexual cords has already passed and form the rete ovarii in the medullary region of the gonad. Now, in the absence of the Y chromosome, the male HY histocompatibility antigen and TDF/SRY gene (Sex-determining region of the Y chromosome gene) (but probably in the presence of HX antigen), the secondary sexual cords individually include each gonocyte in the cortical region of the gonad, generating primordial follicles and the cells of those cords differentiate into granulosa cells [8, 27]. Follicles fail to form in the absence of oocytes or with precious loss of germ cells, and oocytes not encompassed by follicular cells degenerate (Fig. 1.1).

The Internal Genitalia

The internal genitals begin their formation in the sixth week. In the thickness of the urogenital ridge, the mesonephric excretory tubules converge in a mesonephric or wolffian duct that descends to the cloacae in the urogenital sinus. Meanwhile, a longitudinal invagination of the celomic epithelium is formed on the outer side of the urogenital ridge and originates the paramesonephric or Müller's duct. This one, at the top, opens into the celomic cavity, descends in parallel, and externally to the mesonephric duct, crossing it then ventrally, growing in the caudomedial direction until fusing and forming in the middle line a Y shape structure that is the uterine primordium, without reaching the urogenital sinus (Fig. 1.1).

Three portions can be distinguished in the müllerian ducts: a superior converging, a middle fused and an inferior diverging portion [72]. In any case, the most proximate part is the uterine isthmus at the internal cervical os level [13]. The lower diverging parts of these paramesonephric ducts fuse with the medial wall of the mesonephric ones inside a common basal membrane, and then, caudal to the end portion of the Müller ducts, over the dorsal wall of the urogenital sinus, an accumulation of paramesonephric cells which constitute the Müller tubercle [8] can be observed.

This Müller tubercle is then delimited laterally by the Wolff ducts [34, 43, 59]. These mesonephric or Wolffian ducts, close medially, do open into the urogenital sinus, and from the caudal tip of their opening, the ureteral buds sprout in each side and, growing laterally, anteriorly and cranially, move toward the metanephros to form the definitive kidney.

When the ovary is being formed, and therefore the testosterone and the AMH are absent, the Wolffian ducts become athretic and the Müllerian ones develop. The fused caudal parts of the paramesonephric ducts form the uterus, and the tubes come from the uppermost part that remains separated and opened into the celomic cavity. However, the adequate development and fusion of the paramesonephric ducts, the reabsorption of the middle septum and the correct formation of

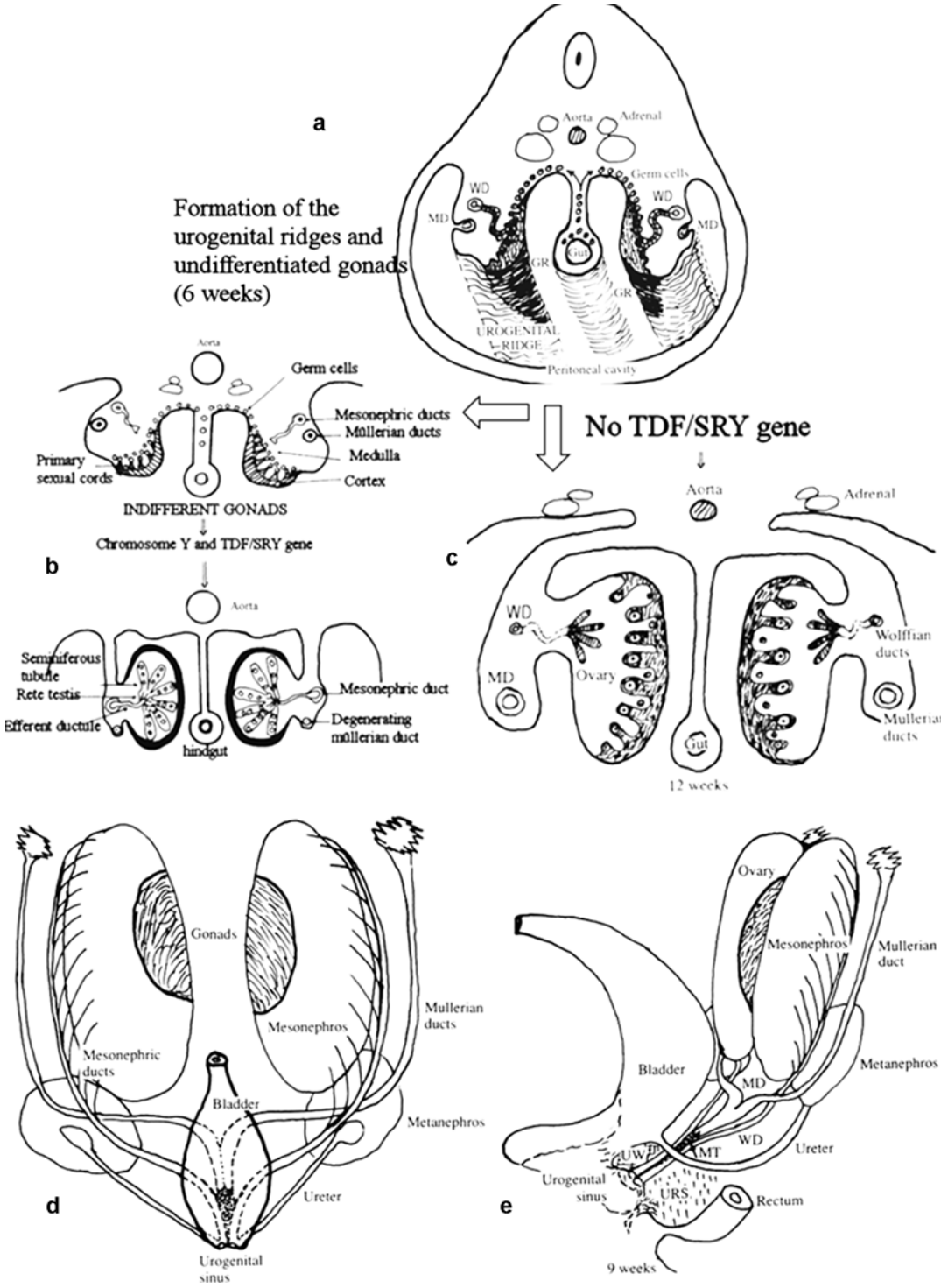

Fig. 1.1 (**a**) Urogenital ridge and undifferentiated gonads. (**b**) Development of the gonads and Wolffian ducts in the male, and the Müllerian ducts in the female in (**c**). (**d**) Development of the genital ducts in the female. The formation of the uterine primordia and opening of the mesonephric ducts to the urogenital sinus is shown. (**e**) Lateral view showing the urorectal septum (*URS*) and the urogenital wedge (*UW*) (Taken from Acién and Acién [17], with permission)

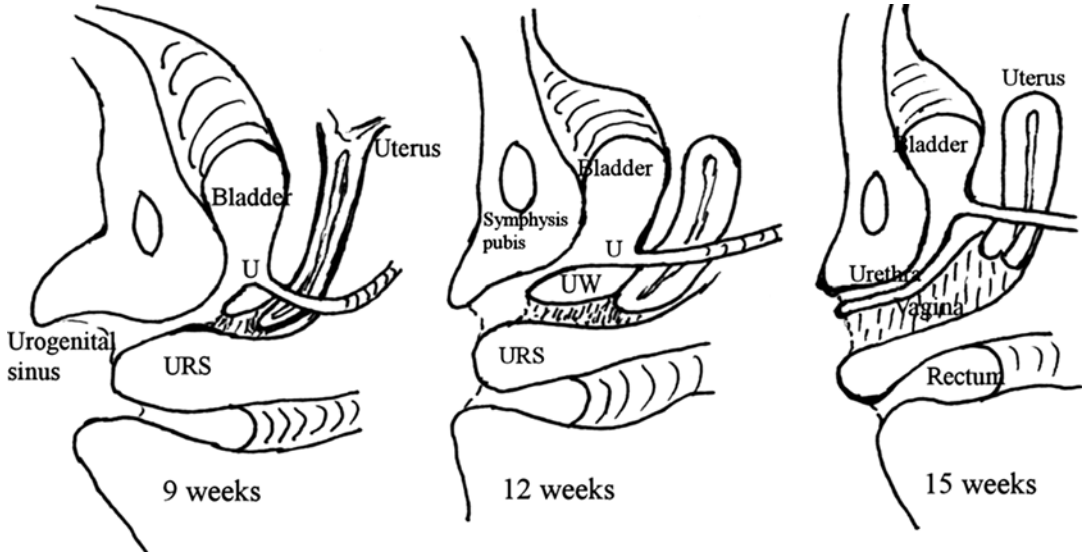

Fig. 1.2 Development of the urogenital sinus from 9 to 15 weeks. *U* ureter, *UW* urogenital wedge, *URS*, urorectal septum (Taken from Acién and Acién [17], with permission)

the normal uterus is induced by the laterally situated mesonephric ducts. The fusion and reabsorption processes begin at the uterine isthmus and progress simultaneously in both cranial and caudal directions [13, 67]. The mesonephric ducts act as guide elements for the paramesonephric ducts [43, 57].

The Müller tubercle's cells remain below the uterus, and at both sides of it, a peritoneal fold which from the fused paramesonephric ducts move laterally towards the lateral walls of the bony pelvis, are known as the broad ligaments. The ovaries are located on the posterior surface of the broad ligaments.

The Urinary System

The development of the urinary system is intimately associated with that of the genital tract and occurs between the sixth and ninth week [67].

The metanephrogenic mass is formed in the intermediate mesoderm, caudally to the mesonephros, and is induced by the metanephric diverticulum or ureteral bud that has sprouted from the dorsal side of the mesonephric duct in its opening into the urogenital sinus. The ureteral bud forms the ureter and from its cranial part it expands to form the renal pelvis in the metanephrogenic mass.

The bladder and the urethra sprout from the urogenital sinus and adjacent mesenquima, though the ventrocraneal part of the bladder comes from the allantoids. After the division of the cloacae by the urorectal septum, the formation of the rectum and superior anal duct dorsally and urogenital sinus ventrally occurs [56]. In the inferior part of the urogenital sinus, in front of the urorectal septum, the mesonephric ducts open, and the bladder is formed ventrally which incorporates the allantoids. Gradually, the bladder ascends and the most caudal part of the mesonephric ducts with the ureteral bud (what has been named the "Wolffian patch" – [72]) ends up incorporated into the dorsal wall. Like this, the ureters are incorporated and remain, opening themselves separately, in the adult vesical trigone.

Now, the growing of a new urogenital fold (the urogenital wedge) finally separates the bladder and the urethra anterior and ventrally, while the mesonephric ducts continue opening into the lower side of the urogenital sinus (Fig. 1.2).

The Vagina

The vagina is the female genital organ whose embryology is more controversial. There are theories that suggest it derives from the paramesonephric ducts [47, 75], from the mesonephric or Wolffian ducts [38], from the urogenital sinus [63], or from a combination of these structures [60, 62]. Until very recently, the most generalized theory about the embryology of the vagina suggested that its upper part comes from the Müller ducts (müllerian vagina) and the lower part from the urogenital sinus (sinus vagina) [33, 67], though always assuming the inducing function of the mesonephric ducts in the appropriate müllerian development [43, 57].

However, apart from the inducing role of the mesonephric ducts on the Müllerian ducts, different studies, some of them experimental, have proved their participation in the formation of the vagina, so that the "protrusions of the sinus" or the "sinuvaginal bulbs" observed during the development of the vagina would actually be the caudal segments of the Wolffian ducts [28, 29, 37, 60]. Certainly, Hart [46] had already adopted the term "Wolffian bulb" because the epithelial pockets that form the sinuvaginal bulbs keep remnants of the wolffian ducts. Witschi [76] reexamined the Koff's embryo and deduced that the sinuvaginal bulbs were identical to the lower segments of the Wolffian ducts. This observation was confirmed by Bok and Drews [28] in an experimental study with embryo cultures.

These findings, together with the analysis of published papers [23, 36, 41, 49, 61, 68, 70], as well as cases studied by us [1–4, 6, 7], especially those referring to patients with renal agenesis and ipsilateral blind hemivagina, led to our proposal of an embryological hypothesis [3, 8]: "The vagina seems to come completely from the fused mesonephric ducts, though the Müller tubercle would also take part and is fundamental for its adequate formation and cavitation".

According to this embryological hypothesis, the fused Müller ducts would form the uterus until the external cervical orifice, induced by the mesonephric ducts that descend at both sides and to which they caudally fuse after their divergence. Later, the mesonephric ducts regress cranially but from the level of the external cervical os, they enlarge and form the sinuvaginal bulbs, incorporating the Müller tubercle's cells to the vaginal plate formed by the fusion of both bulbs (Fig. 1.3). Likewise, the Müller tubercle would

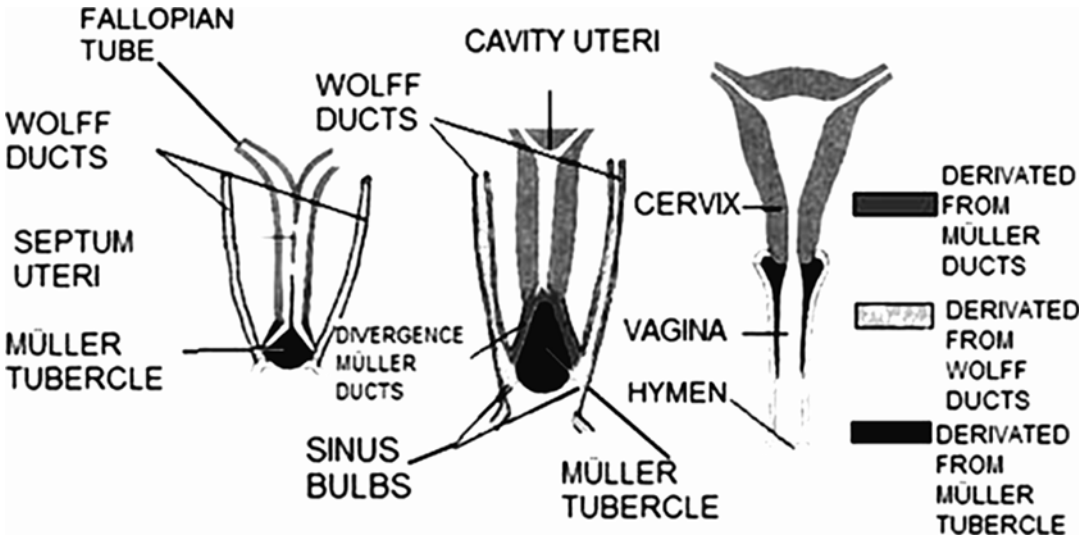

Fig. 1.3 Representative diagram of the evolution of the Wolffian and Müllerian ducts, the Müller tubercle and the formation of the vagina, according to the studies of Acién and Sánchez-Ferrer (Taken from Acién and Acién [17], with permission)

be delimited at the top and laterally by the diverging portion of the Müller ducts, more laterally by the Wolffian ducts, infero-laterally by the portion of the sinuvaginal bulbs and below by the urogenital sinus [72].

The posterior cavitation of the Müller tubercle lets the müllerian cells cover the primitive vaginal cavity with a cuboidal or paramesonephric epithelium. Then, by metaplasic induction or, more probably, by epidermization from the urogenital sinus, the vagina becomes lined by a flat, squamous, polystratified epithelium. Some mesonephric remnants may remain in the vaginal wall, which occasionally can give rise to Gartner cysts.

This hypothesis has also been proved experimentally in rat embryos by our group [72], as we observed that the protrusions of the sinus or the sinuvaginal bulbs are positive for specific inmunohistochemical markers for wolffian derivatives (GZ1 and GZ2) and that in posterior stages of the development, these markers show themselves all along the completely formed vagina.

Since the ureteral bud sprouts from the opening in the urogenital sinus of the mesonephric duct, the absence or distal injury of a duct would mean the absence of the ureteral bud and, therefore, the definitive kidney would not develop either, which will result in renal agenesis in that side and in blind or ipsilateral athretic hemivagina. In these cases, mesonephric and paramesonephric remnants are frequently found in the intervaginal septum and are identified as such by the characteristics of the epithelium that lines them [5, 7, 74].

Suidan and Azoury [74] pointed out that the epithelium of the vagina and of the transverse vaginal septum are from a mesonephric origin. Certainly, the epithelium that covers the blind hemivagina has müllerian characteristics (cuboidal) [45, 68] except when there is some communication with the permeable side or inflammation; in these cases, it is epidermoid, squamous, stratified and flat. And when the blind vagina is athresic, small, found in the anterolateral upper part of the normal hemivagina and lateral to the cervix (Gartner pseudocyst, Herlyn-Werner Syndrome and Wunderlich Syndrome), then the epithelium is of a mesonephric kind, probably due to the absence or non-participation of the Müller tubercle [4, 5, 7].

Besides, in cases of blind hemivagina there is generally an associated uterine malformation (normally a duplicity) because of a failure in the inducing function of the injured mesonephric duct.

The External Genitalia

The development of the external genitalia begins in the fourth week with the formation of the genital tubercle in the ventral portion of the cloacal membrane, but the final aspect is not established until the 12th week. Genital swellings and urogenital or urethral folds appear on each side soon after, and between both folds is the urogenital groove and membrane.

The genital tubercle forms the phallus, which in absence of male inductors becomes the clitoris, while the genital folds form the labia majora. The urogenital or urethral folds do not fuse and form the labia minora. The urogenital groove remains open hence forming the introitum, where the urethra, and later the vagina, will open after the fenestration of the urogenital membrane; and the remnants of that membrane will be the hymen [51].

The Gubernaculum

The gubernaculum forms from the caudal fold that provokes the mesonephros elevating the covering peritoneum (Fig. 1.4). It begins as a cord that extends from the gonadal ridge, to the future inguinal region and its insertion into the urogenital cord differentiates two portions of the Müller duct [18, 49].

In the absence of testicular differentiation that is, in the absence of androgens and AMH and presence of ovary formation, the paramesonephric or Müllerian ducts complete their invagination and development, interfering the connection of this tissular column that has arisen from the inguinal cone with the mesonephric duct and the caudal ligament of the gonad. The gubernaculum then grows over the paramesonephric ducts, and its muscular fibres incorporate into the wall of the

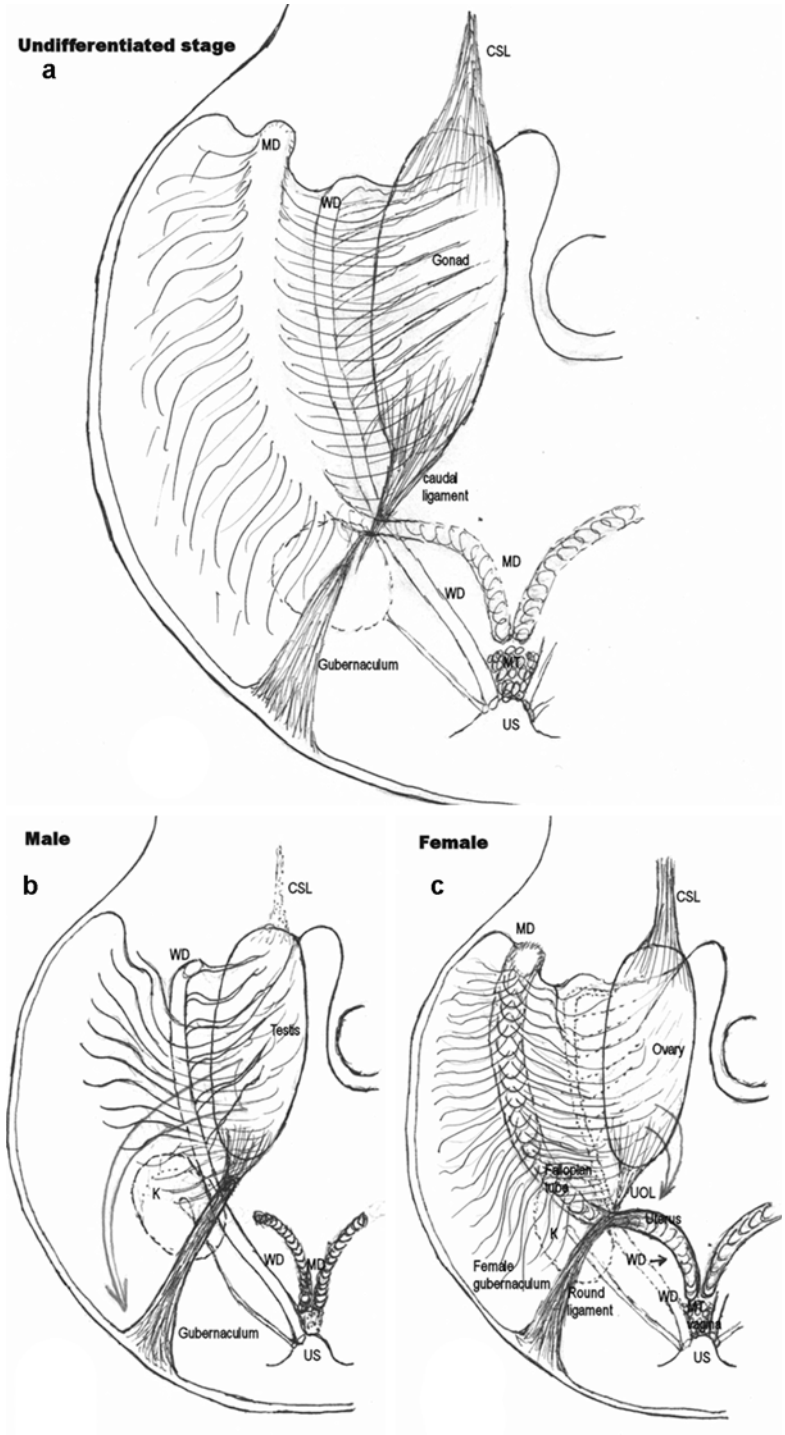

Fig. 1.4 Schematic illustration of the possible development of the gubernaculum. (**a**) At an Undifferentiated stage. (**b**) In Males. (**c**) In Females. *CSL* cranial suspensory ligament, *WD* wolffian duct, *MD* müllerian duct, *MT* müllerian tubercle, *US* urogenital sinus, *K* kidney, *UOL* uteroovarian ligament (caudal ligament of the gonad) (Taken from Acién et al. [18], with permission)

Table 1.1 Adult derivatives and female abnormalities of embryonic urogenital structures

Embryonic structure	Normal derivatives	Female abnormalities
Urogenital ridge with mesonephros and mesonephric ducts (Wolffian ducts) opening to urogenital sinus	1. Epoophoron, paroophoron (paraovarian cysts), mesonephric duct remnants (Gardner cysts)	1. Agenesis of all derivatives of one urogenital ridge (ovary, tube, hemiuterus, and kidney): unilateral renal agenesis and contralateral unicornuate uterus
	2. Ureteral bud (ureter, pelvis, calyces, and collecting tubules): normal kidney	2. Mesonephric distal anomalies: blind hemivagina or unilateral cervico-vaginal atresia with ipsilateral renal agenesis and Müllerian malformation (didelphys, bicornuate, or septate uterus)
	3. Inductor function on Müllerian ducts: normal uterus	3. Ectopic ureters
	4. In association to Müllerian tubercle: normal vagina	4. Paravaginal Gardner cysts (in mesonephric duct remnants)
Paramesonephric ducts (Müllerian ducts) and Müllerian tubercle (MT)	Fallopian tube and uterus. MT in association to Wolffian duct: normal vagina	Isolated Müllerian malformations Vaginal atresia Transversal vaginal septum
Female gubernaculum	Round ligament	Accessory and cavitated uterine masses Possible participation in uterine anomalies such as didelphys uterus
Urogenital sinus	Urinary bladder, urethra, urethral and paraurethral glands, greater vestibular glands, hymen and anorectal duct	Urachal anomalies, exstrophy of the bladder, bladder duplication. Blind hemibladder with renal adysplasia? Epispadias, hypospadias, imperforated hymen, cloacal disgenesis, including persistence of the urogenital sinus. Vesicovaginal and rectovaginal fistulae

Modified from Acién et al. [16], with permission

Müllerian ducts, becoming the round ligament. Behind and above, in the absence of androgens and AMH, only athretic remnants of the mesonephric duct remain; thus, the caudal ligament, uniting the gonad inferior pole to the posterior wall of the Müllerian ducts, constitutes the utero-ovarian ligament.

The Müllerian ducts continue their development, and induced by the mesonephric ducts, complete the fusion process, the reabsorption of the middle septum and the appropriate formation of the uterus. It remains unclear whether the growth of the female gubernaculum and its fusion with the developing Müllerian ducts could be one of the most important processes in the induction of the formation of the uterus, but it has been suggested that a gubernaculum anomaly could lead to certain genital malformations and a fusion defect between the müllerian ducts [14, 18, 19].

The interaction and correspondence between the analysed embrionary structures and its normal or abnormal adult derivates is shown in Table 1.1.

Conclusions

In **summary**, then:

1. The appropriate development, fusion and reabsorption of the separating wall between both Müller ducts is induced by the Wolffian ducts placed at both sides and which act as guide elements.
2. The fused Müller ducts form the uterus until the external cervical os, and the inducing mesonephric ducts regress cranially though they enlarge caudally from the level of cervical os, form the sinuvaginal bulbs, incorporate the Müller tubercle's cells and give rise to the vaginal plate whose cavitation is covered by müllerian cells with a cuboidal

or paramesonephric epithelium. Then, by metaplasic induction or by epidermization from the sinus, the vagina is covered by a flat, squamous, stratified epithelium.

3. Since the ureteral bud sprouts from the opening of the wolffian duct into the urogenital sinus, the absence or distal injury of one of these ducts will give rise to a renal agenesis and ipsilateral blind or athretic hemivagina and an uterine anomaly (fusion or reabsorption defect) due to a failure in the inducing function of the injured mesonephric duct.
4. In the absence of formation and caudal growth of the urogenital wedge, there is persistent urogenital sinus and then the opening of the vagina into the sinus can be seen as a vesicovaginal fistula just underneath and between both uretheral orifices.
5. The female gubernaculum is likely formed by muscle fibres that are not of a mesonephric or paramesonephric origin and their attachment to the Müllerian ducts allows or induces the fusion and adequate development of the uterus. Thus, dysfunction of the female gubernacula probably results in female genital tract malformations.

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Pathogenesis and Aetiology of Female Genital Malformations

2

Spiros A. Liatsikos

Normal development of the female reproductive tract is based on the proper formation, differentiation and fusion of the Müllerian or paramesonephric ducts. Those ducts are initially formed by an invagination of the coelomic epithelium and due to lack of Anti-Müllerian Hormone (AMH) secretion in genetic female embryos (46,XX) they normally develop into the oviducts, the uterus and the upper 2/3-part of the vagina [45, 79, 86]. It is not yet clearly known what determines the development of the uniform paramesonephric duct into the distinguishable genital tract organs. It is suggested that molecular mechanisms play a pivotal role [65]. Certain molecules functioning as transcriptional factors seem to act as determinants of segmental identity along the proximodistal axis of the developing Müllerian duct. These molecules are encoded by specific genes; hence the development of the female genital tract seems to have a genetic basis. Hormonal factors and especially sex steroids may also be well involved in this developmental process [3, 64].

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Pathogenesis of Female Genital Malformations

Congenital anomalies of the female genital tract are the result of four major developmental defects during fetal life: (i) failure of one or both Müllerian ducts to form results in hemi-uterus without rudimentary cavity (class U4b according to the new ESHRE/ESGE classification system) or aplastic uterus (class U5) respectively. Aplastic uterus is the most severe Müllerian defect. Cervical and vaginal aplasia commonly co-exist and this is known as Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome or Müllerian aplasia (MA); (ii) failure of the ducts to canalize results in hemi-uterus with rudimentary cavity (class U4a); (iii) failure of or abnormal fusion of the ducts results in bicorporeal uterus (class U3); (iv) failure of re-absorption of the midline uterine septum results in septate uterus (class U2) [1, 4, 5, 43, 74]. Dysmorphic uterus (class U1) can be attributed to abnormal formation of the ducts as a result of impaired segmental identity after drug exposure, as it will be analyzed later.

The role of the Wolffian or mesonephric ducts is also quite important in the pathogenesis of genital tract anomalies. Apart from their crucial role in renal development, they also act as inducer of Müllerian duct development. As a result, mesonephric anomalies may have a negative effect on female genital tract formation [2]. It is estimated that up to 60 % of women with unilateral renal

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agenesis present also with some type of genital tract agenesis, most commonly a hemi-uterus [8] and about 40 % of women with a hemi-uterus suffer from renal anomalies [37].

Some rare anomalies of the vagina result from failure of the urogenital sinus to contribute the caudal part of the vagina (vaginal atresia) or from failure of the urogenital sinus derivatives and Müllerian duct derivatives to meet and canalize (transverse vaginal septa) [86].

Aetiology of Female Genital Malformations

Although the pathogenesis of female genital malformations has been well established, the aetiology for virtually all such anomalies remains unknown, as for most developmental defects. This aetiology however seems to be multifactorial, with the involvement of chromosomal abnormalities, gene mutations and environmental factors, mostly in the form of endocrine disruptors. The aforementioned genetic and environmental factors could act individually but most commonly combined, resulting in the manifestation of abnormal phenotypes of the female genital organs.

The Role of Genetic Factors

The available genetic information regarding such malformations is still limited. However, the familial nature in a number of cases of genital anomalies suggests the contribution of genetic factors. It is estimated that about 10 % of all Müllerian defects are attributable to a familial association, with first-degree relatives having a 12-fold risk of developing an abnormality [48].

Chromosomal Abnormalities

In most reports, the karyotype of patients is that of a genetic normal (46, XX) woman. However, a number of chromosomal abnormalities have been sporadically found. Mosaicisms, rearrangements and deletions have been reported in association with MA [45] and trisomies 13 and 18, triploidy and various duplications and deficiencies in association with Müllerian duct fusion defects [86]. Due to lack of systematic clinical trials, the incidence of genital malformations in such conditions is not precisely known.

Structural or numerical abnormalities of the chromosome X could cause gonadal dysgenesis. Rarely this co-exists with absence of the uterus and the vagina [6, 46, 73]. A mos45,X/46,X,del(X)(p11.2) karyotype has been reported in a 17-year old girl with absence of uterus and ovaries and hypoplastic vagina [47].

An identical t(12;14)(q14;q31) translocation has been detected in two unrelated Indian females [56] and a maternally inherited 4q deletion in women with MRKH syndrome [10]. An identical 17q12 deletion has been reported in two MRKH patients [11]. However, no 17q12 deletions were subsequently detected in a larger group of 20 MRKH patients. Deletions and submicroscopic genomic inbalances affecting the 1q21.1, 16p11.2, 17q12, 22q11.21 and Xq21.31 chromosomal regions have been reported by Cheroki et al. [21, 22], Ledig et al. [58] and Nik-Zainal et al. [78] in patients with MA.

Certain genital tract anomalies could possibly be component of the DiGeorge syndrome. Deletions in chromosome 22q11.21, overlapping the DiGeorge syndrome region, have been described in association with MRKH syndrome [33, 89, 93] and didelphys uterus [85].

Sandbacka et al. [83] conducted a study to investigate possible role of Y chromosomal material in the aetiology of Müllerian duct anomalies. No Y chromosomal markers (TSPY1 or other male-specific fragments) were found in 110 patients with well diagnosed MA, suggesting that Y-specific fragments are not responsible for such anomalies.

Gene Mutations

A number of genes seem to be expressed on the developing genital tracts of both sexes, as early as the stage of gastrulation and the formation of the urogenital ridge until the final differentiation of the Müllerian and the Wolffian ducts to the individual genital organs (Fig. 2.1). It has been suggested that impaired expression of such genes as

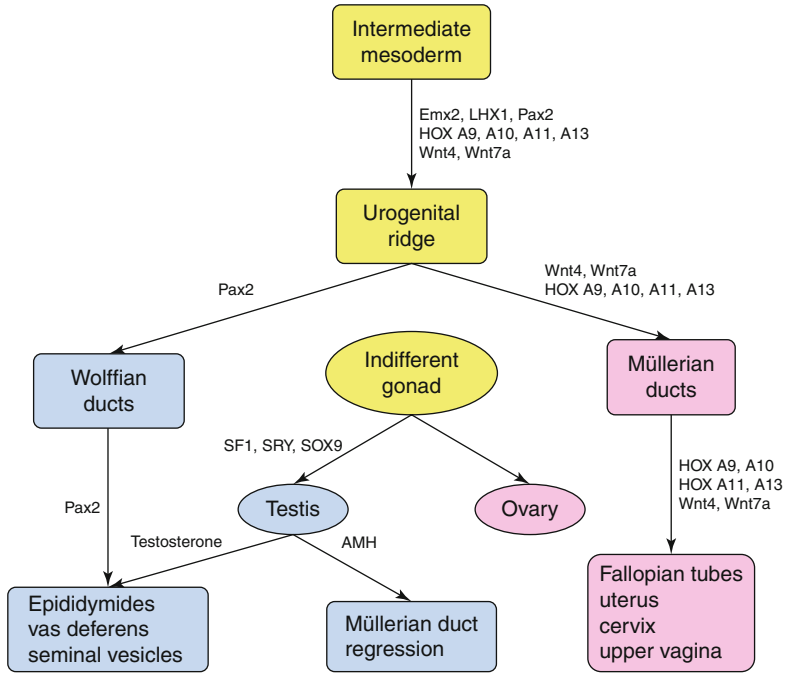

Fig. 2.1 Genes involved in the morphogenesis of the genital tracts in different stages of development

a result of mutations might be the aetiological basis of congenital genital tract anomalies. Those genes could be conventionally classified into six main groups: Those involved in the early development of the genital tracts, the genes associated also with other diseases, the Homeobox (HOX) gene family, the Wingless-type Integration Site gene family (Wnt), the Anti-Müllerian Hormone (AMH) and Anti- Müllerian Hormone Receptor genes and the Estrogen Receptor (ER) genes (Table 2.1).

Genes Involved in the Early Development of the Primordial Genital Ducts

Genes in that group mainly encode transcriptional regulators and have been identified as important for the development of the embryonic intermediate mesoderm and the initial formation of the ducts [86]. It is well known that the development of the Müllerian duct is induced and dependent on the presence of the Wolffian duct [82]; hence genes involved in the formation of the latter are also of great importance. Genes essential for the initial, biphasic process of Müllerian duct development are the Lim Homeobox 1 (LHX1), Paired box 2 (Pax2), Empty spiracles homeobox 2 (Emx2), Dachshund homologs 1 and 2 (Dach1, Dach2) and the GATA binding protein 3 (GATA3) [67]. Those genes have been suggested as candidates for genital tract malformations on the basis of similar phenotypes observed mainly in mutant mice.

LHX1 (chromosome 17q12) encodes a transcription factor which plays an important role in early mesoderm formation and later in lateral mesoderm differentiation. Absent Wolffian and Müllerian duct derivatives in LHX1-null mice reveal that the particular gene is required for the formation of both sexual ducts [55, 102]. LHX1 disruption results in reduced expression of Pax2, another transcription factor acting as marker of the Wolffian duct. In human, heterozygous LHX1 mutations have been reported in sporadic cases of MRKH syndrome [59]. Those findings however were not confirmed by other researchers studying similar anomalies [101].

Pax2 (chromosome 10q24) is involved in the formation of the epithelial components derived

Table 2.1 Genes that have been implicated in the aetiology of female genital malformations

Gene group	Genes studied	Relevant studies in human
Genes involved in early development of the ducts	LHX1	Ledig et al. (2012) [59]
		Xia et al. (2012) [101]
	PAX2	Van Lingen et al. (1998) [97]
		Wang et al. (2012) [99]
	EMX2	–
	DACH1, DACH2	–
	IGF1, RARs,	–
	GATA3	Hernandez et al. (2007) [51]
		Nakamura et al. (2011) [77]
Genes associated with other diseases	GALT	Cramer et al. (1996) [29]
		Bhagavath et al. (1998) [12]
		Klipstein et al. (2003) [54]
		Zenteno et al. (2004) [103]
	CFTR	Timmreck et al. (2003) [90]
	TCF2 (HNF1)	Lindner et al. (1999) [62]
		Bingham et al. (2002) [15]
	WT1	Van Lingen et al. (1998) [96]
The Homeobox (HOX) gene family	HOX A9, HOX A10, HOX A11	Burel et al. (2006) [17]
		Lalwani et al. (2008) [57]
		Liatsikos et al. (2010) [60]
		Ekici et al. (2013) [36]
	HOX A13	Mortlock and Innis (1997) [75]
		Stelling et al. (1998) [88]
		Devriendt et al. (1999) [34]
		Goodman et al. (2000) [42]
		Utsch et al. (2002) [94]
		Burel et al. (2006) [17]
		Ekici et al. (2013) [36]
	PBX1	Burel et al. (2006) [17]
		Ma et al. (2011) [63]
	SHOX	Gervasini et al. (2010) [39]
		Sandbacka et al. (2011) [84]
The Wingless-type Integration site gene family (Wnt)	Wnt4	Biason-Lauber et al. (2004, 2007) [13, 14]
		Clement-Ziza et al. (2005) [25]
		Chang et al. (2012) [19]
	Wnt5a	Wu et al. (2013) [100]
	Wnt7a	Timmreck et al. (2003) [91]
		Dang et al. (2012) [31]
Anti-Müllerian Hormone (AMH) and anti-Müllerian Hormone Receptor (AMHR) genes	AMH, AMHR	Resendes et al. (2001) [81]
		Zenteno et al. (2004) [103]
Estrogen Receptor (ER) genes	ERa, ERb	–

from the intermediate mesoderm. Homozygous mutant mice lack kidneys, ureters and genital tracts in both males and females [92]. In human however genetic analysis did not demonstrate any significant association between molecular variants at this locus and the occurrence of MRKH syndrome [97] or other Müllerian anomalies [99].

EMX2 (chromosome 10q26) encodes a transcription factor and is homolog to the "empty spiracles" gene in Drosophila. In humans, apart from its main expression on the developing dorsal telencephalon, it is also expressed on epithelial tissues of the developing urogenital system. Homozygous mutant mice completely lack the urogenital tract in both males and females. No such defects have been observed in heterozygous mice [67, 72]. However, there are no studies suggesting a similar association of Müllerian anomalies with mutations of the particular gene in human.

Dach1 (chromosome 13q22) and Dach2 (chromosome Xq21) encode transcriptional factors which participate in the molecular cascade of Müllerian duct development. Inactivation of each corresponding gene does not affect genital development. Combined knock-out mice however demonstrate drastic defects of Müllerian derivatives (hypoplastic oviducts, severely hypoplastic uterine horns, aplastic vagina) [32]. It is possible that those two genes act redundantly to control development of the female genital tract.

Insulin-like growth factors (IGFs) encode proteins similar to insulin in function and structure, involved in mediating growth and development. IGF1 (chromosome 12q23) is believed to have a role in the developing rat uterus, as loss of gene function in mice results in severe uterine hypoplasia [7, 44]. Retinoic Acid Receptors (RARs) regulate gene expression in several biological processes. Null mutations lead to various developmental anomalies, including severe urogenital defects. In particular, RARαβ2 double mutant mice lack Müllerian ducts [69]. Similar defects (cervical and vaginal aplasia) have also been described in Disks large homolog 1 (Dlgh1) mutant mice, though no relation has been established between those genes [52].

GATA3 encodes a transcription which is a regulator of T-cell development and plays an important role in endothelial cell biology. Mutations of this gene have been reported in women with Hypoparathyroidism-Deafness-Renal dysplasia (HDR syndrome) and Müllerian duct fusion defects (didelphys or septate uterus) or vaginal atresia [51, 77]. It is not clarified though, if the mutation is the aetiology of the HDR syndrome or the aetiology of the genital tract anomaly.

Although a number of cases with severe anomalies of the reproductive tract have been attributed to mutations in the genes involved in the early development of the ducts in mice, molecular progress in similar malformations has been disappointing in human. Indeed, no association has been identified with most of those genes.

Genes Associated with Other Diseases

Scientists were prompted to investigate the role of such genes based mainly on the association of MRKH syndrome with galactosemia and cystic fibrosis. The most well studied genes in this group involve the galactose-1-phosphate uridyl transferace (GALT), the cystic fibrosis transmembrane regulator (CFTR), the transcription factor 2 (TCF2) gene [formerly known as HNF1 homeobox b or hepatocyte nuclear factor 1-beta (HNF-1β)] and the wilms tumor 1 (WT1) gene.

The findings regarding a possible association of the N314D allele of GALT (chromosome 9p13) with MA have been contradictory. In a study by Cramer et al. [29], 46 % of the MRKH patients exhibited the N314D allele compared to 14 % of the control group. However these results were not confirmed by subsequent studies [12, 54, 103].

Mutations of the CFTR gene (chromosome 7q31) have been associated with congenital bilateral absence of vas deferens in some males. The incidence of such mutations in cases of MRKH syndrome (8 %) was found to be twice as high compared to the general population (4 %), but significantly lower than the incidence of CFTR mutations in men with aplasia of the vas deferens (80 %) [90]. Those results suggest that such mutations do not cause MA in women in a similar way that they cause vas deferens agenesis in some men.

TCF2 mutations have been associated with MODY-type diabetes, diabetes mellitus and renal defects. It is interesting that similar mutations were found in some familial cases of genital tract anomalies, mainly bicornuate uterus, didelphys uterus and MA, co-existing with renal anomalies [15, 62]. The heterogeneous genital malformations and the absence of a direct genotype/phenotype

correlation however do not suggest a straight aetiological association with TCF2 defects.

WT1 gene (chromosome 11p13) is involved in the development of both the internal and external genital organs. No mutations or polymorphisms have been found in a number of MRKH patients studied, suggesting that its expression is possibly required at a later stage of development, well after the initial formation of the ducts [96].

The Homeobox (HOX) Gene Family

HOX genes encode numerous transcription factors (Homeoproteins), which are expressed along various developmental axes of the body and control embryonic morphogenesis. Some of the HOX genes are involved in the formation of the genitourinary tract and their deletions seem to result in renal agenesis and reproductive tract malformations. The embryonic female genital tract could be considered a developmental axis; the initially uniform Müllerian duct will finally form the oviducts, the uterus, the cervix and the upper part of the vagina.

HOX genes belonging to paralogue groups 9–13 seem to provide the axis of the developing paramesonephric duct with a positional identity: HOX A9 is expressed in areas designated to form the future oviduct, HOX A10 is mainly expressed on the developing uterus, HOX A11 is expressed on parts of the Müllerian duct which will form the lower compartment of the uterus and the cervix and HOX A13 is expressed on the upper third of the vagina. There is no HOX A12 gene; this has been possibly lost during evolution [35]. As those genes provide regional identity and specify the segmental body plan, their defects could be involved in the aetiology of severe Müllerian anomalies.

Genital tract malformations have been observed in HOX A10, HOX A11 and HOX A13 mutant mice. Such mutations lead in region-specific defects along the female genital tract. In human though, apart from some non-specific, rare polymorphisms and mutations found in sporadic cases of Müllerian anomalies, most researchers did not find genetic perturbations of HOX A9 to HOX A13 genes in the vast majority of patients with MA or other severe genital tract anomalies studied [17, 36, 57, 60].

HOX A13 is the most well studied gene in anomalies resulting from abnormal fusion of the Müllerian ducts. A variety of HOX A13 mutations (nonsence, missence, polyalanine tract expansions) have been associated with a rare, dominantly inherited condition called Hand-Foot-Genital syndrome (HFGS), which involves skeletal and urogenital (incomplete Müllerian fusion) malformations [34, 42, 75, 94]. Female genital tract defects range from isolated vaginal septum to didelphys (bicorporeal) uterus [41]. Such mutations have only been found in the context of the syndrome and not in sole fusion defects of the paramesonephric ducts [88].

The Pre-B-cell leukemia homeobox1 (PBX1) gene (chromosome 1q23) encodes an essential co-factor for HOX proteins that is expressed on the Müllerian ducts. Inactivation of the gene in mice does not result in congenital anomalies. Similarly in human, no mutations have been found in cases of Müllerian aplasia or other genital malformations studied [17, 63].

Short stature homeobox (SHOX) gene (chromosomes Xp22 and Yp11.3) controls fundamental aspects of growth and development. In contrast to other genes of the HOX family, it is absent in the mice. No obvious role of this gene in the development of the female reproductive tract has been reported in the literature. Although partial duplications of the gene have been reported in sporadic cases of MA [39], no association was confirmed in an extensive cohort of patients with similar anomalies [84].

The Wingless-Type Integration Site Gene Family (Wnt)

Wnt genes seem to contribute significantly in the patterning and differentiation of the female genital tract [53]. They encode a number of cysteine-rich secreted growth factors and they guide the epithelial-mesenchymal interactions that direct uterine development. Wnt4, Wnt5a and Wnt7a are mainly expressed on the developing Müllerian duct and deficiency of those genes in mice results in a wide range of genital malformations [71].

Wnt4 (chromosome 1p36-p35) presents both an anti-testis function by repressing male differentiation and a pro-ovary function by supporting germ cells [14]. Homozygotic inactivation in mice results in total failure of Müllerian duct development [49, 95]. In human, homozygotic inactivation results in the SERKAL syndrome (female-to-male sex reversal, dysgenesis of kidneys, adrenals and lungs) which is embryonic lethal [66]. Recent studies suggest that there are no genetic alterations involved in the aetiology of MRKH syndrome or other Müllerian duct abnormalities [19, 25]. Interestingly, mutations have been described in two women presenting with absence of Müllerian duct derivatives, unilateral renal agenesis and androgen excess [13, 14]. It is possible that Wnt4 deficiency results in a phenotype that is similar but certainly different to the classic MRKH syndrome, as it is characterized by hyperandrogenism.

Wnt5a (chromosome 3p21-p14) mutated female mice present with a shortened uterus and poorly defined cervix and vagina [102]. Evidence from human studies is quite limited, however no causal Wnt5a mutations were recently observed among 189 Chinese women [100].

Wnt7a (chromosome 3p25) plays an important role in guiding uterine growth and hormonal responses. It is possible also that it mediates the expression of anti- Müllerian Hormone Receptor type II (AMHR2). Wnt7a mutations in mice result in severe changes in the size, the morphology and the cytoarchitecture of the uterus [18, 70, 91, 102]. In human, apart from some sporadic polymorphisms, no mutations have been detected in women with various malformations of the genital tract, suggesting no correlation [31, 91].

Anti-Müllerian Hormone (AMH) and Anti-Müllerian Hormone Receptor (AMHR) Genes

The genes for the AMH (chromosome 19p13) and its receptor (AMHR) have been considered as candidate genes for cases of aplasia, as they are responsible for Müllerian duct regression in male fetuses. In a similar way to the genetic males, activating mutations could cause Müllerian duct regression in a genetic female during embryogenesis [61]. Indeed, anomalies similar to those observed in the human MRKH syndrome were evident in female transgenic mice over-expressing AMH [9]. However, no mutations in those genes have been found in association with uterine aplasia or other anomaly of the genital tract in female mice. Possible role of other genes participating in the AMH signaling pathway (ALK2, ALK3) cannot be excluded from the aetiology of such anomalies [80]. Interestingly, Müllerian duct regression was evident in cases of ALK6 knock-out mice [24].

Apart from some rare polymorphisms (present both in patients and controls), no deleterious mutations of AMH/AMHR genes have been detected so far in women with MRKH syndrome [81, 103]. Other potential mechanisms have also been suggested, like high maternal AMH levels during pregnancy. Estradiol (E2) has been shown to induce AMH expression in vitro [20]. It can be assumed that high E2 levels or exposure to other estrogen-like substances in early pregnancy could induce AMH expression, resulting in Müllerian duct regression in the developing female fetus. On the other hand, over-expression of AMH would only justify a complete lack of Müllerian derivatives, which is not a common finding; the vast majority of anomalies correspond to partial rather than total agenesis.

Estrogen Receptor (ER) Genes

Estrogens seem to be involved in the organogenesis and differentiation of the female genital tract. It is well known the biologic responses to estrogens are mediated through the estrogen receptors. Both types of those receptors, ERa (chromosome 6q25) and ERb (chromosome 14q23), are expressed on the mesenchyme and the epithelium of the paramesonephric ducts and possibly function as ligand modulated transcription factors. As a result of estrogen binding, the ER undergoes a conformational change which allows dimerization, DNA binding and recruitment of co-factors. The final result is either transcriptional activation or regression of target genes, mainly HOX and Wnt [3]. ERa deficient mice commonly present with a hypoplastic uterus and vagina [26].

In human, there have not been ER mutations reported in relation to female genital tract malformations. However, other mechanisms of ER involvement in the pathogenesis of such anomalies could be suggested. Estrogen and progesterone regulate HOX gene expression in both the embryonic reproductive tract and the adult reproductive tract. HOX A10 and HOX A11 expression is up-regulated by 17β-estradiol and progesterone. The regulation is direct and is achieved by the estrogen or the progesterone receptor binding to regulatory areas of the genes [16]. Wnt-7a mediates normal growth in the absence of estrogenic activity but is also required at the time of the initial estrogenic response which induces increased cellularity of the uterine tissues [18]. It is possible that altered expression of ER genes leads to impaired expression of certain HOX and Wnt genes along the developing Müllerian ducts, which in turn results in abnormal phenotypes of the female genital tract.

The Role of Endocrine Disruptors

A number of chemicals released in the environment can bind to the ERs and exhibit estrogenic activity similar to 17β-estradiol. Epidemiological studies have shown that those chemicals, known as environmental endocrine disruptors or xenoestrogens, had an adverse impact on the woman's health and fertility over the past few decades. Apart from carcinogenesis, they have also been implicated in the pathogenesis of the congenital anomalies of the female genital tract [79]. It seems that the carcinogenic and teratogenic defects of such endocrine disruptors are caused after binding to the ERa [27, 28]. Moreover, it is not unlikely that those adverse effects might have been transmitted to subsequent generations through epigenetic modifications [67].

Diethylstilbestrol (DES) is a non-steroidal estrogen and the most well known example of a chemical compound with an adverse effect on the woman's reproductive health. Millions of women had been prenatally exposed to DES in the past, until the increased incidence of genital tract malformations and tumors became evident [50].

DES-induced malformations (T-shaped uterus, class U1a) were the result of abnormal morphogenesis of the Müllerian ducts and were similar to anomalies observed in HOX A10 mutant mice, with transformation of the upper part of the uterus into an oviduct-like morphology. According to developmental studies, prenatal DES administration shifts the expression of HOX A9 from the oviducts to the uterus and decreases both HOX A10 and HOX A11 expression on the uterus. Decreased expression of the genes that provide uterine identity and increased expression of a gene providing oviductal identity seems to be the cause of the T-shaped uterus, characterized by branching and narrowing into a tube-like form. The uterus in not fully transformed into an oviduct possibly due to the redundancy provided by other HOX genes [35].

Targeted mutations of ERa in mice prevent the effects of DES on HOX expression. It is possible that DES impairs the conformation of the ER, so as the receptor to interact selectively with atypical coactivators or corepressors, inducing differential HOX gene activation which in turn leads to genital tract malformations [28]. DES shifts the expression pattern of HOX genes also in human uterine cell cultures, suggesting a similar role in human uterine malformations [40].

Apart from HOX genes, DES seems to cause structural changes through a variety of genetic pathways. The morphological characteristic of the uterus in mice exposed to DES are almost identical to those observed in Wnt7a mutant mice. Wnt7a gene expression in the DES-exposed uterus was found to be significantly repressed when examined at birth [18]. Similarly in human, the expression of Wnt7a in Ishikawa cells (endometrial adenocarcinoma cell line) was reduced after exposure to DES [98].

Apart from DES, several other endocrine disruptors alter the expression of basic developmental genes, such as HOX and Wnt, potentially resulting in severe malformations of the female reproductive tract. Methoxychlor (MXC) represses HOX A10 expression on the uterus of mice, and Bisphenol A (BPA) increases HOX A10 expression in adult mice. Both cause a severe reduction in the reproductive performance

of the mice [38, 87]. Clomiphene citrate (CC) is a chemical widely used nowadays to induce ovulation for fertility treatment. This could also be considered an endocrine disruptor, as it interferes and alters the function of the ER. There is no evidence that the typical use of CC for ovulation induction affects the expression of developmental genes or the normal development of the reproductive tract in the female embryo. Some studies however suggest a possible role for CC in the pathogenesis of congenital uterine malformations in animals when administered in pregnancy or even after birth [23, 30, 68, 76].

Clinical Implications

Despite a number of potentially attractive candidate genes, no association has been so far established between a particular gene mutation and a genital tract anomaly in human. Apart from some sporadic cases of MA, mutations have been observed in women with fusion defects only in the context of rare syndromes and not solely in anomalies of the Müllerian ducts. The lack of findings does not support mutation screening for women with genital tract congenital anomalies or their relatives.

A thorough clinical investigation should be offered for every woman diagnosed with a genital tract defect, as it is well known that such malformations are often accompanied by renal, skeletal and cardiovascular abnormalities. In that case, genetic analysis is recommended for the woman, her siblings and her female offsprings only if the coexistent anomalies suggest the presence of a syndrome. Finally, a thorough investigation of the anatomy of the reproductive tract is recommended for every woman when prenatal exposure to endocrine disruptors is suspected, especially if there is a history of infertility or recurrent miscarriage.

Conclusions and Future Insights

A variety of genes, encoding mainly transcriptional regulators have been identified as important for the proper development and differentiation of the female reproductive tract. Mutations of those genes have been associated with serious defects of the Müllerian ducts in mice in a number of studies. The expectation however that analogous mutations would be related to human genital tract anomalies was not confirmed. Apart from some rare polymorphisms found in sporadic cases of MA, studies have failed so far to establish a direct relationship between a particular mutation and a genital tract malformation in women. Mutations and chromosomal abnormalities associated with such malformations have only been recognized in the context of rare syndromes. On the other hand, exposure during embryogenesis to endocrine disruptors may result in female genital tract anomalies, due to alterations in the expression pattern of certain genes on the developing Müllerian ducts.

Undoubtedly, the development of the female reproductive tract has a genetic basis. The pathogenesis of Müllerian duct anomalies, as of most developmental defects, seems to be multigenic and multifactorial. The phenotype is the result of the additive effects of miscellaneous proteins encoded by a number of genes, under the influence of hormonal factors.

Future research should not focus only in the role of individual genes, but mainly in the genetic pathways that orchestrate a highly organized developmental process. As genomic sequence has failed so far to establish a strong association between a gene mutation and a human genital malformation, scientists should now aim in expression screening, in order to identify differential gene expression along the developing paramesonephric duct. Finally, unidentified environmental disruptors (xenoestrogens) may dysregulate the developmental fate of Müllerian progenitor cells. Human are exposed to a variety of chemicals with estrogenic activity which potentially affect the expression of estrogen responsive genes. Further investigation is required for the identification of additional exogenous estrogenic factors which alter the expression pattern of fundamental developmental genes in women, leading possibly to congenital malformations.

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3 Implantation in Women with Uterine Congenital Malformations

Antonis Makrigiannakis

Introduction

The female reproduction tract development consists of several steps involving the elongation, fusion, canalization and septum absorption of the paramesonephric duct (Mullerian duct) [36]. During the 12th week, the two mullerian ducts fuse to the uterovaginal canal. Subsequent canalization of each individual duct leads to a septate uterovaginal precursor. At the 20th week, the septum is absorbed, yielding the uterus and the upper vagina. The lower vagina is formed out of the absorption of the vaginal plate which in turn came out of the sinovaginal bulbs after the fusion of the caudal part of the mullerian ducts [36].

The incidence of congenital malformations in fertile women is extremely low (1 in 594 women or 0.16 %). In women diagnosed as infertile the incidence rises up to 3.5 % (approximately 21-fold increase) [32]. This implies that congenital malformations have an impact on fertility.

Endometrial Receptivity and Implantation

Infertility is markedly related to endometrial receptivity and decidualization. Decidualization is the functional result of the progesterone effect on the endometrium. In humans, decidualization is spontaneous -after an estrogen priming of the endometrium- and progresses in case of pregnancy. On the contrary, in mice and rats, decidualization occurs only in the presence of a blastocyst [37]. Decidualization can be defined as the transformation of the endometrial tissue to the morphologically and functionally distinct decidua [37]. This transformation involves both the epithelial and the stromal cells, as well as the further infiltration of the decidual stroma by immune cells.

Uterine sensitivity to implantation is programmed into three phases: pre-receptive, receptive and post-receptive. Blastocysts implant only in the receptive phase, which is characterized by unique molecular and morphological changes of the endometrium. Implantation can occur only during the "window of implantation", between days 19 and 23 of a 28-day menstrual cycle [33]. Recently, it has been suggested that the decidualized endometrial stromal cells serve as biosensors of embryo quality, thus introducing a novel functional window: "the window of natural embryo selection", which allows maternal recognition and elimination of compromised pregnancies [43].

The trophoblast invasion is performed by the small spindle-shaped extravillous trophoblast cells [18, 20, 23]. By infiltrating the decidual part of the spiral arteries, the intravascular trophoblast replaces both their endothelium along with the corresponding smooth muscle cells. Controlled invasion of extravillous trophoblast cells into maternal uterine tissues is essential

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for successful progression of pregnancy. Crucial regulators of blastocyst implantation include cell adhesion molecules, cytokines [such as leukaemia inhibiting factor (LIF) and interleukin (IL)-11] and chemokines, growth factors, signal intermediates and downstream transcription factors (such as STAT3, HOXA10, p53) [11, 42, 46]

Congenital Uterine Malformations and Implantation: Clinical Evidence

Congenital uterine malformations have been traditionally associated with poor obstetric outcome, mainly due to the increased risk for infertility, recurrent pregnancy loss, preterm delivery and fetal malpresentation [16]. However, the poor obstetrical outcome was mainly so far attributed to the abnormal anatomical shape of the malformed uterus rather than to problems related to deranged implantation.

Despite the well-established relationship between congenital malformations and increased risk for recurrent pregnancy loss, preterm delivery and fetal malpresentation, the clinical question whether uterine malformations could be aggravating factors in terms of fertility was attempted to be replied, especially in the context of assessing assisted reproduction efficacy. Several groups have published their results many of which being in discordance.

Recently a meta-analysis, aiming to clarify this issue, was published [8]. It included 9 studies referring to 3,805 patients. According to the meta-analysis performed, canalization defects (septate or sub-septate uteri) present with significantly reduced clinical pregnancy rate (RR, 0.86; 95 % CI, 0.77–0.96) [8]. On the contrary, unification defects (unicornuate, bicornuate and didelphic uteri) did not exert any effect on pregnancy rate [8]. To the same direction, canalization defects presented a significant risk for first trimester miscarriage (RR, 2.89; 95 % CI, 2.02–4.14) [8]. This significance was also maintained during subgroup analysis referring to septate and sub-septate uteri respectively. In case of unification defects, although the overall relative risk was not significant, subgroup analysis revealed a significantly increased risk for first trimester miscarriage in case of bicornuate (RR, 3.40; 95 % CI, 1.18–9.76) or unicornuate RR, (2.15; 95 % CI, 1.03–4.47) uteri [8].

By considering clinical pregnancy rate as a means to assess implantation, this meta-analysis is the only evidence, so far, regarding a possible impact of congenital malformations on implantation. It seems that the impact of congenital uterine malformations on implantation is restricted to cases with canalization defects, justifying the effectiveness of hyperplastic metroplasty in increasing clinical pregnancy and live birth outcomes [2, 30, 34]

Genetic Basis of Reproductive Tract Development – Common Pathways with Implantation

The genetic basis of the female reproductive tract development has been recently reviewed [26, 49]. Lim1, Pax2, Emx2 and Wnt4 are essential since knock out of these genes in mice results in no FRT development [24, 29, 44, 45]. Disruption of members of the Wnt family (5a, 7a and 9b) is associated with posteriorization of genital tract or uterine and vaginal aplasia [6, 27, 28]. Absence of Dlgh1 is associated to cervical and vaginal aplasia [21], while knockout of β-catenin was reported to result to hypotrophic uterine horns and defective tubal coiling [10]. The HOXA genes down-regulation may lead to homeotic transformation of the anterior part of the uterus to an oviductal morphology, hypoplastic uterus and cervical/vaginal agenesis [3, 14, 47]. From all the genes reported to be involved in UCM only the HOXA genes have been described so far to be involved in implantation [5] (Fig. 3.1). Thus, further presentation of the role of HOXA genes will follow aiming to delineate a possible connection between reproductive tract development and implantation.

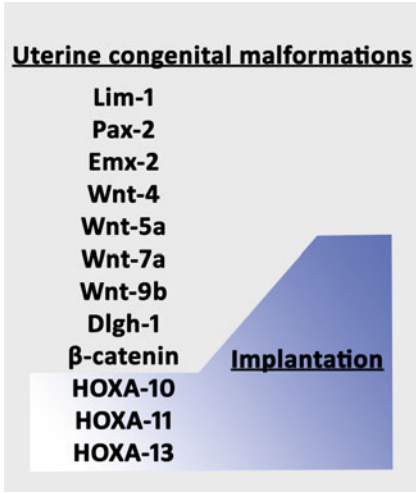

Fig. 3.1 Presentation of the genes involved in uterine congenital malformations. Only the HOXA genes have been reported to be involved in implantation as well

The Potential Role of HOX Genes on Reproductive System Development and Function

Despite the diversity of species, embryonic development is regulated by highly conserved gene clusters. Initially described in the drosophila species [25], as homeotic genes (HOM), the homeobox genes were found in many different species. Homeobox genes were organized in two classes: the first containing a HOM-box with more than 80 % identity to the initial drosophila HOM genes -designated as Hox-, and the second containing a HOM-box with less than 80 % identity to the initial drosophila HOM genes – designated as non-Hox [13, 39]. The HOX genes in humans are organized in four clusters, namely, HOXA, HOXB, HOXC and HOXD, located in four distinctive loci [12]. Each of the HOX genes contains a highly conserved sequence encoding for a 61-aminoacid domain designated as homeodomain [17, 35]. This homeodomain due to its specific three-dimensional conformation interacts with the DNA, as a transcriptional factor, regulating a significant number of genes involved in embryonic development.

HOX genes have been reported as major contributors to the axial pattern development. During axial development HOX cluster genes are selectively expressed in a uni-directional pattern: caudad. HOX genes are involved, among others, in nervous system and skeletal development [12]. Mutations on HOX genes have been associated to certain (neuro)-developmental syndromes [7, 15, 22, 31].

The female reproductive system (except from the ovaries), is developed following an axial pattern. The paramesonephric ducts gradually fuse forming the uterus, the cervix and the vagina. Interestingly, the HOXA genes are sequentially expressed in the areas of the reproduction system to be: HOXA-9 is expressed in the area that will develop into the fallopian tubes, HOXA-10 is expressed at the segment of the developing uterus, HOXA-11 is expressed in the primordial segment of the cervix and in the uterus, while HOXA-13 is expressed in the part that will lead to the formation of the vagina [12]. A possible direct impact of HOXA genes in female reproductive tract development was shown by studying the model of diethylsilvestrol (DES) in mice. In utero exposure to DES was found to alter significantly the topography of HOXA genes' expression [4, 40]. HOXA9 expression was significantly reduced in the fallopian tube and was shifted to the uterus where HOXA10 and HOXA11 expressions were also significantly reduced. This deregulation of the expression sequence and topography due to DES could probably explain the DES-related congenital abnormalities (ASRM classification class VII)

The same distribution of HOXA genes' expression found during reproductive tract development is also found in adults of reproductive age. HOXA-10 and −11 are expressed by the endometrium under the influence of estradiol and progesterone, presenting a major peak expression at the mid-secretory phase during the "window of implantation" [5].

Although lower HOXA10 and HOXA11 have been reported in case of lower implantation rates [41], no mutation on HOXA genes has ever been described in humans. Thus, evidence, regarding the importance of HOXA genes on reproductive

system development and function, stems mainly from mouse physiology. HOXA10 or HOXA11 knock-out mice can produce normal embrya but are incapable of efficient implantation, since wild-type embrya cannot implant in the HOXA10 (−/−) or 11 (−/−) mice [3, 19, 38]. HOXA11 knock-out leads to reduced leukemia inducible factor (LIF) and reduced numbers of endometrial glands [14]. In vivo transfection of HOXA10 (+/+) mouse endometrium with HOXA10 antisense, blocked implantation [1]. HOXA10 was reported to directly regulate β3-integrin (being well known for its involvement in early implantation) since β3-integrin promoter has HOXA10 binding sites [9]. Moreover HOXA10 was reported to regulate pinopode formation and IGFBP-1 [5]. Recently, other members of the HOXA cluster have been reported to contribute in implantation, strengthening even more the role of the HOXA cluster in human reproduction [48].

All the above, taken together, reveal an important role of HOXA genes in the development of the reproductive organs and in implantation physiology. HOXA genes seem to act as transcription factors regulating embryogenesis of fallopian tubes, uterus and vagina. The same genes under the influence of estradiol and progesterone regulate implantation. However, since HOXA10 or HOXA11 knockout mice do not present with major congenital malformations but rather with minor histological changes, and since at the same time other major factors are involved in regulating implantation, HOXA genes have to be considered as part of a complex developmental mechanism.

However, by taking together the clinical data of reduced clinical pregnancy rates in case of canalization defects, along with the HOXA genes' role in embrogenesis and implantation, it can be hypothesized that reduced HOXA genes' expression could be one possible mechanism explaining impaired implantation in such patients. Further properly designed studies are needed in order for this issue to be clarified.

Conclusion

The role of the congenital uterine malformations in implantation is still an area of controversy. The clinical evidence is rather weak stemming from a recent meta-analysis reporting that canalization defects can have an impact on clinical pregnancy rates. The pathophysiologic approach of both congenital malformations and impaired implantation reveals that the HOXA genes are the common ground on both entities. Further research is necessary in order to clarify whether endometrial HOXA cluster gene deregulation occurs in women with canalization defects and whether this can explain their, so reported, reduced clinical implantation rate.

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Classification of Female Genital Malformations

4

Grigoris F. Grimbizis and Rudi Campo

Introduction

Definition and Pathogenesis of Female Genital Anomalies

Female genital anomalies represent benign deviations from normal anatomy resulting from embryological maldevelopment of the Mullerian or paramesonephric ducts between the 6th and 18th week of gestation. Three distinct embryological defects underlie to the creation of female genital anomalies: abnormal formation with failure of Mullerian ducts development or canalization, abnormal fusion of the caudal parts and/or abnormal absorption of the midline septum [1, 2, 16]. They are common benign entities with an estimated prevalence in the general population ranging from 4 to 6.7 % depending on the method used for their diagnosis [8, 15, 30].

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It is important to note that although some of anomalies are the result of an embryological defect in only one stage of embryological development, others are the result of a combined defect in more than one embryological stages and, making the issue more complex, of different embryological defects in the different parts of the female genital system [16]. This gives rise to a wide range of anatomical variations and combinations from the more simple ones to the more complex ones (more than one organ plus more than one embryological defect). Furthermore, the clinical presentation of the patients is closely associated to the combined anatomical status of the female genital tract and not to the isolated defects of its different parts: e.g. vaginal aplasia in the present of a normal uterus is an obstructing anomaly whereas vaginal aplasia in the presence of uterine aplasia it is not. Even more importantly, treatment requirements are different depending on the clinical presentation and/or the possible effects on the reproductive potential of the women [6, 9, 16, 24].

The Value of the Classification Systems

Classifications are used widely in all scientific areas aiming to organize knowledge in a systematic way and helping the process of understanding (e.g. Mendeleev's periodic table of chemical

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elements has an immense contribution in the systematic appraisal and better understanding of nature consistency). It is obvious that in medicine classification systems play a crucial role enabling the better understanding of the disease processes by their users since pathogenesis is usually taken into account for their development, helping the diagnostic work-up of patients and the therapeutic decision-making process as well [16].

Classification systems are based on the systematic categorization of patients into classes having similar characteristics. It is important to note that the selection of the basic characteristic and how it is used for the patients' categorization are crucial for patients' grouping [16, 17]. Furthermore they are the key points for the differences observed between the different classification systems. It is also obvious that the acceptance of a system is mainly correlated to its effectiveness to fulfill the clinicians' needs in understanding, diagnosing and treating patients.

The parameters that a system has to fulfill in order to be clinically ideal are the following: (1) to have clear and accurate definitions enabling clinicians to make the diagnosis and differential diagnosis easily and objectively, (2) to be comprehensive incorporating all possible variations that could be observed, (3) to be correlated with clinical presentation and prognosis of the patients, (4) to be correlated with the treatment helping the therapeutic decision-making process and, equally important, (5) to be as simple as possible and users' friendly. It should be noted that the degree of accomplishing those criteria by a classification proposal is the unbiased way for its creative criticism [16].

Aims

The aims of this chapter are to critically review the current proposals for the classification of female genital tract anomalies and to present the new ESHRE/ESGE classification system. It is obvious that the effective management of women having an anomaly requires a representative classification system.

Current Proposals for the Classification of Female Genital Anomalies

Historically, the first attempts to describe and classify female genital anomalies go back to the mid-nineteenth century and continued in the beginning of the nineteenth century [1]. However, it was the American Fertility Society [5], based on the previous work of Buttram and Gibbons [5, 7], which published the first classification system for the categorization of, mainly, congenital uterine malformations. The AFS system has been widely used and, until recently, it was the most accepted categorization of the anomalies.

Another option for the classification of female genital anomalies was proposed by Acien et al. [2] 15 years later; the major contribution of this proposal is the shift in the basis of the classification from anatomy to embryology. One year later, Oppelt et al. [25] published their option for the classification of female genital anomalies; the contribution of this classification system was the introduction of the independent vagina, cervix, uterus, adnexae and associated malformations (VCUAM) categorization of the female genital organs in proportion to the tumor-node-metastases (TNM) principle used in oncology.

It is important to note that, in addition to these proposals a lot of subdivisions for certain categories of anomalies have been also published, in an effort to overcome clinical problems resulting from the management of patients having those anatomical variants [10, 21, 22, 28, 29, 31, 34].

AFS Classification

The basic characteristic selected for the categorization of the anomalies is the anatomy of the female genital tract and, mainly, the uterine anatomy (Table 4.1). The degree of uterine deformity was used for the design of the system's subclasses [5, 16]. As the majority of congenital malformations are uterine ones, the AFS system was proven to be effective in categorizing most of them receiving wide acceptance by the scientific community. Another notable advantage of the

Table 4.1 AFS classification system [5]

Main classes		Subclasses	
Class I	Hypoplasia/Agenesis	(a) Vaginal	(b) Cervical
		(c) Fundal	(d) Tubal
Class II	Unicornuate	(a) Communicating horn	(b) Non-communicating horn
		(c) No cavity	(d) No horn
Class III	Didelphys		
Class IV	Bicornuate	(a) Complete	(b) Partial
Class V	Septate	(a) Complete	(b) Partial
Class VI	Arcuate		
Class VII	DES Drug related		

system, explaining its acceptance from another point of view, is the correlation of the system's classes with the patients' prognosis and, mainly, the pregnancy outcome [16].

However, it is a reality that this system is associated with the following very serious disadvantages: (1) there are reported anomalies that could not be classified with the AFS system; (2) the definitions of the system's categories are not clear raising serious problems in the differential diagnosis between the different classes, with the more obvious one that of defining the "margins" between arcuate and partial septate; (3) class I of the AFS system seems to be a "potpourri" of patients with different clinical presentations of varying severity, including mainly cases of complex anomalies often needing difficult surgical treatment, and their ineffective categorization consists a great problem for their management and, (4) obstructive anomalies are not clearly represented in the AFS system placing them in the potpourri of the first class or in other classes of the system but without any clear distinction [16].

It seems, therefore, that the AFS classification system "could function as a framework for the description of anomalies rather than an exhaustive list of all possible anomaly types" [16, 30].

The Embryological-Clinical Classification

The embryological origin of the different elements of the genitourinary tract is selected as the basis for the development of this system [1, 2] (Table 4.2). The embryological-clinical classification has the theoretical advantage that it is closely related to the pathogenesis of the anomaly enhancing the explanation and understanding of the resulting anatomical status of the female genital organs. It has also the potential advantage that it might be more effective at classifying complex anomalies, a hypothesis that needs to be tested.

However, this system has not received wide acceptance. This seems to be due to the following reasons: (1) female genital anomalies are by definition deviations from normal anatomy and clinicians difficultly accept the shift from anatomy to embryogenesis, (2) it is quite complex classifying not only anomalies of the female genital tract by of the genitourinary tract in general which is not the requested issue for gynecologists, (3) patients' clinical presentation, prognosis and treatment are closely related to the anatomical status and, it seems to be more functional to design the classes of a system on that basis and (4) most therapeutic interventions tend to restore anatomical deviations from the norm emphasizing the need to use anatomy per se as the basis of the system [16].

On the other hand, the contribution of this system and of its inventors to the better understanding of the pathophysiology of female genitourinary malformations could not be ignored representing a step forward in their interpretation. As a general statement, the embryological-clinical classification system could, probably, better explain pathogenesis of congenital malformation but it could not act as a functional framework for the description and treatment of the anomalies.

Table 4.2 Embryological clinical classification system [2]

Class	Embryological defect	Clinical presentation
1	Agenesis or hypoplasia of a urogenital ridge	Unicornuate uterus with uterine, tubal, ovarian, and renal agenesis on the contralateral side
2	Mesonephric anomalies with an absence of the Wolffian duct opening to the urogenital sinus and ureteral bud sprouting (and, therefore, renal agenesis). The "inductor" function of the Wolffian duct on the Mullerian duct also fails, and there is usually uterovaginal duplicity plus blind hemivagina ipsilateral with renal agenesis	(a) Large unilateral hematocolpos (b) Gardner's pseudocyst on the anterolateral wall of the vagina (c) Partial reabsorption of the intervaginal septum, seen as a "buttonhole" on the anterolateral wall of the normal vagina, which allows access to the genital organs on the renal agenesis side (d) Vaginal or complete cervico-vaginal unilateral agenesis, ipsilateral with renal agenesis, and with [1] no communication or [2] communication between both hemiuteri (communicating uteri)
3	Isolated Mullerian anomalies affecting	
	(a) Mullerian ducts	The common uterine malformations as unicornuate (generally with uterine rudimentary horn), bicornuate, septate, and didelphys uterus
	(b) Mullerian tubercle	Cervico-vaginal atresia and segmentary anomalies, such as transverse vaginal septum
	(c) Both Mullerian tubercle and ducts	Mayer-Rokitansky-Kuster-Hauser (uni- or bilateral) syndrome
4	Anomalies of the urogenital sinus	Cloacal anomalies and others
5	Malformation combinations	Wolffian, Mullerian, and cloacal anomalies

The VCUAM Classification System

The basic characteristic selected for the design of this proposal is also the anatomy of the female genital tract [25] (Table 4.3). However, the new and important element in the design of this system is the independent classification of each organ of the female genital tract and of the associated malformations according to the TNM classification for breast cancer. This approach has the theoretical potential of classifying the anomalies in a detailed, representative and precise way; each anomaly, even the more complex, could be theoretically described giving the clinician an accurate description of female genital tract anatomy.

However, the inventors of this system, focusing mainly in its design ignored the need to discuss in details and define the groups for each separate organ, which is extremely important for the users and the accuracy of each classification system. Furthermore, each anomaly has the same independent importance in the classification of the patients; frequency is not taken into account and extremely frequent uterine anomalies e.g. septum have the same importance as the rare ones e.g. cervical aplasia [16]. Hence, it seems that there is a non-functional overestimation of the anatomy. Moreover, patients could only be classified with the use of the system's tables and, reversely, description of the patient' clinical condition (e.g. "V5b, C2b, U4b, A0, MR", which is a patient with Mayer-Rokitansky-Kuster-Hauser syndrome) could not be done without the use of those tables.

Thus, it seems that the main restriction for the acceptance of the VCUAM system is that it is not simple and user's friendly. Thus, "although the VCUAM classification system may serve as an exhaustive list of all possible anomalies, it could not easily serve as a functional framework for describing the anomalies" [16].

The ESHRE/ESGE Classification System

The European Society of Human Reproduction and Embryology (ESHRE) and the European Society for Gynecological Endoscopy (ESGE),

Table 4.3 The Vagina Cervix Uterus Adnexa and associated Malformations (VCUAM) classification system [25]

Vagina (V)	0	Normal	Uterus (U)	0	Normal
	1	(a) Partial hymenal atresia		1	(a) Arcuate
		(b) Complete hymenal atresia			(b) Septate <50 % uterine cavity
					(c) Septate >50 % uterine cavity
	2	(a) Incomplete septate vagina <50 %		2	Bicornuate
		(b) Complete septate vagina			
	3	Stenosis of the introitus		3	Hypoplastic
	4	Hypoplasia		4	(a) Unilaterally rudimentary or aplastic
	5	(a) Unilateral atresia			(b) Bilaterally rudimentary or aplastic
		(b) Complete atresia			
	S	1. Sinus urogenitalis (deep confluence)		+	Other
		2. Sinus urogenitalis (middle confluence)			
		3. Sinus urogenitalis (high confluence)			
	C	Cloacae		#	Unknown
	+	Other			
	#	Unknown			
Cervix (C)	0	Normal	Adnexa (A)	0	Normal
	1	Duplex cervix		1	(a) Unilateral tubal malformation, ovaries normal
					(b) Bilateral tubal malformation, ovaries normal
	2	(a) Unilateral atresia/aplasia		2	(a) Unilateral hypoplasia/ gonadal streak
		(b) Bilateral atresia/aplasia			(b) Bilateral hypoplasia/ gonadal streak
	+	Other		3	(a) Unilateral aplasia
					(b) Bilateral aplasia
	#	Unknown		+	Other
				#	Unknown
Associated malformations (M)		0	None		
		R	Renal		
		S	Skeleton		
		C	Cardiac		
		N	Neurologic		
		+	Other		
		#	Unknown		

has recently published the new ESHRE/ESGE classification system of female genital tract congenital anomalies [18, 19] (Fig. 4.1). This was the result of an effort based on the preparatory scientific work done within the European Academy for Gynecological Surgery (EAGS), which was adopted by the CONUTA (CONgenital Uterine Anomalies) common ESHRE/ESGE Working Group [16, 17]. The development of the new system was done using DEPLHI procedure for consensus assessment [13, 23, 35]; based on the results of the DELPHI procedure, consensus development by the CONUTA Scientific Committee was followed [18, 19].

ESHRE/ESGE classification
Female genital tract anomalies

Name **Birth Date:**

Diagnostic Method:

	Uterine anomaly		Cervical/Vaginal anomaly	
	Main class	***Sub-class***	***Co-existent class***	
U0	Normal uterus		***C0***	*Normal cervix*
U1	Dysmorphic uterus	**a.** T-shaped **b.** Infantilis **c.** Others	***C1***	*Septate cervix*
U2	Septate uterus	**a.** Partial **b.** Complete	***C2***	*Double "normal" cervix*
			C3	*Unilateral cervical aplasia*
			C4	*Cervical aplasia*
U3	Bicorporeal uterus	**a.** Partial **b.** Complete **c.** Bicorporeal septate		
			V0	*Normal vagina*
U4	Hemi-uterus	**a.** With rudimentary cavity (communicating or not horn) **b.** Without rudimentary cavity (horn without cavity/no horn)	***V1***	*Longitudinal non-obstructing vaginal septum*
			V2	*Longitudinal obstructing vaginal septum*
U5	Aplastic	**a.** With rudimentary cavity (bi- or unilateral horn) **b.** Without rudimentary cavity (bi- or unilateral uterine remnants/aplasia)	***V3***	*Transverse vaginal septum and/or imperforate hymen*
			V4	*Vaginal aplasia*
U6	Unclassified malformations			
U			***C***	***V***

Associated anomalies of non-Müllerian origin:

Fig. 4.1 The ESHRE/ESGE classification scheme of female genital anomalies

Design of the System

Anatomy is the basis for the systematic categorization of anomalies of the ESHRE/ESGE classification system. Uterine anatomy is the basic characteristic selected for the design of the main classes; embryological origin has been adopted as a secondary basic characteristic. Thus, deviations of uterine anatomy deriving from the same embryological origin are represented in the main classes.

Anatomical variations of the main classes expressing different degrees of uterine deformity and being clinically significant are the basis for the design of the main sub-classes. Cervical and vaginal anomalies are classified in independent co-existent sub-classes.

Uterine Main Classes and Sub-classes

There are five main classes in the ESHRE/ESGE system based on the classification of uterine anomalies; furthermore, normal uterus is adopted as class 0, and potentially unclassified cases could be categorized in class 6 (Fig. 4.2). A new and significant element of the new system is the definition of uterine deformity as proportions of uterine anatomical landmarks (e.g. uterine wall thickness) due to the fact that uterine dimensions and, more specifically, uterine wall thickness could normally vary from one patient to another.

Class U0 or normal uterus

It is defined as any uterus having either straight or curved interostial line but with an internal inden-

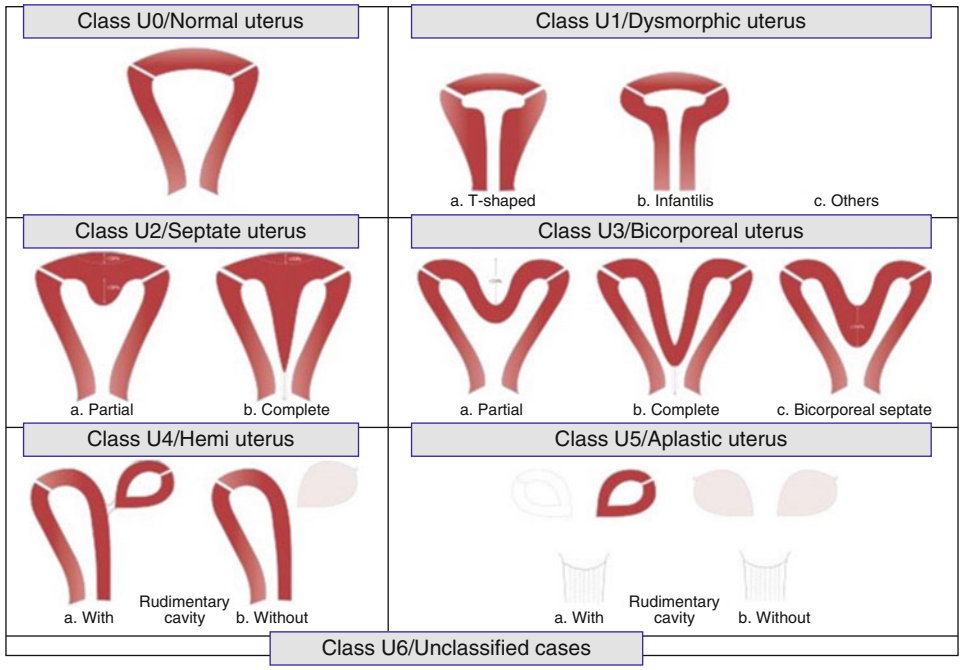

Fig. 4.2 The ESHRE/ESGE classification of uterine anomalies: schematic representation (Adapted from Grimbizis et al. [18, 19])

tation at the fundal midline not exceeding 50 % of the uterine wall thickness. The addition of normal uterus as class 0 was decided in order to give the opportunity for an independent classification of cervical and vaginal congenital malformations when the uterus is normal [20, 29, 31].

Class U1 or Dysmorphic uterus

It is defined as any uterus having normal uterine outline but with an abnormal shape of the uterine cavity excluding septa. Class U1 is further subdivided into three categories: ***Class U1a or T-shaped uterus***, having normal correlation 2/3 uterine corpus and 1/3 cervix, and characterized by a narrow uterine cavity due to thickened lateral walls (giving to it the characteristic T shape). ***Class U1b or uterus infantilis***, having an inverse correlation 1/3 uterine body and 2/3 cervix, and characterized also by a narrow uterine cavity but without lateral wall thickening. ***Class U1c*** or others, including all minor deformities of the uterine cavity and incorporating also those with an inner indentation at the fundal midline level of <50 % of the uterine wall thickness. This aims to facilitate clinical research for patients with minor deformities and to clearly differentiate them from patients with septate uterus [14, 33].

Class U2 or septate uterus

It is defined as any uterus with normal outline and an internal indentation at the fundal midline exceeding 50 % of the uterine wall thickness. Septate uterus is an absorption embryological defect of the midline septum; fusion is normal. The midline indentation is characterized as septum and it could divide partly or completely the uterine cavity. Class U2 is further divided into two sub-classes according to the degree of the uterine corpus deformity: ***Class U2a or partial septate*** uterus characterized by the existence of a septum dividing partly the uterine cavity above the level of the internal cervical os and, ***Class U2b or complete septate uterus*** characterized by the existence of a septum fully dividing the uterine cavity up to the level of the internal cervical os. Patients with complete septate uterus (Class U2b) could have or not cervical (e.g. bicervical

septate uterus) and/or vaginal defects (see cervical/vaginal anomalies) [17].

Class U3 or bicorporeal uterus

It is defined as any uterus with an external indentation at the fundal midline exceeding 50 % of the uterine wall thickness; it is an embryological fusion defect. The external indentation could divide partly or completely the uterine corpus including or not the cervix and/or vagina; it is obvious that it is, also, associated with an inner indentation at the midline level that divides the cavity as happens also in the case of septate uterus. Class U3 is further divided into three subclasses according to the degree of the uterine corpus deformity: ***Class U3a or partial bicorporeal uterus***, characterized by an external fundal indentation partly dividing the uterine corpus above the level of the cervix. ***Class U3b or complete bicorporeal uterus***, characterized by an external fundal indentation completely dividing the uterine corpus up to the level of the cervix. Patients with complete bicorporeal uterus could, also, have co- existent cervical (e.g. double cervix/AFS didelphys uterus) and/or vaginal defects (e.g. obstructing or not vaginal septum). ***Class U3c or bicorporeal septate uterus*** characterized by a width of the midline fundal indentation exceeding 150 % the uterine wall thickness due to the presence of an absorption defect in addition to the main fusion defect. These patients could be partially treated by hysteroscopic cross section of the septate element of the defect.

Class U4 or hemi-uterus

It is defined as the unilateral uterine development; the contralateral part could be either incompletely formed or absent; it is a formation defect. Class U4 is further divided into two subclasses depending on the presence or not of a functional rudimentary cavity since this is the only clinically important factor for complications such as hemato-cavity or ectopic pregnancy [11, 32]: ***Class U4a or hemi-uterus with a rudimentary (functional) cavity*** characterized by the presence of a communicating or non-communicating functional contralateral horn. ***Class U4b or hemi-uterus without rudimentary (functional) cavity*** characterized either by the presence of non-functional contralateral uterine horn or by full aplasia of the contralateral part.

Class U5 or aplastic uterus

It is defined as the absence of any fully or unilaterally developed uterine cavity. It is a formation defect incorporating all cases of uterine aplasia [4, 26]. Patients with aplastic uterus could have co-existent defects (e.g. vaginal aplasia/Mayer-Rokitansky-Kuster-Hauser syndrome) [26]. Class U5 is further divided into two sub-classes depending on the presence or not of a functional cavity in an existent rudimentary horn [12, 18, 19, 26, 27] since this is the only clinically important factor for the presence of health related problems such as cyclic pain and hemato-cavity: ***Class U5a or aplastic uterus with rudimentary (functional) cavity*** characterized by the presence of bi- or unilateral functional horn, ***Class U5b or aplastic uterus without rudimentary (functional) cavity*** characterized either by the presence of uterine remnants or by full uterine aplasia.

Class U6 is kept for still unclassified cases

The system is designed to include, hopefully, all cases resulting from formation, fusion or absorption embryological defects. Duplication defects or ectopic Mullerian tissue anomalies [3], if existing, could not be described; these anomalies or any other that might not be classified with the use of the main classes could be put in this class.

Cervical Sub-classes

Cervical anomalies are categorized into four supplementary classes; furthermore, normal cervix is adopted as class 0.

Sub-class C0 or normal cervix

This sub-class incorporates all cases of normal cervical development. The addition of normal cervix as class C0 allows the independent classification of uterine and vaginal congenital malformations when the cervix is normal.

Sub-class C1 or septate cervix
It is a cervical absorption defect characterized by the presence of a normal externally rounded cervix with the presence of a septum.

Sub-class C2 or double cervix
It is a cervical fusion defect characterized by the presence of two distinct, externally rounded, fully divided or partially fused cervices. In combination with complete bicorporeal uterus, as a ESHRE/ESGE Class U3b/C2 consists the formerly AFS didelphys uterus.

Sub-class C3 or unilateral cervical aplasia
It is a cervical formation defect characterized by the unilateral, only, cervical development; the contralateral part could be either incompletely formed or absent. This sub-class allows the classification of rare anomalies such as complete bicorporeal uterus with unilateral cervical aplasia (Class U3b/C3), which is a severe obstructing anomaly. Although patients with hemi-uterus always have unilateral cervical aplasia, this is not necessary to be mentioned in the final classification report (Class U4 instead of Class U4/C3) as being apparent.

Sub-class C4 or cervical aplasia
It is a cervical formation defect characterized by the absolute absence of any cervical tissue or by the presence of severely defected cervical tissue such as cervical cord, cervical obstruction and cervical fragmentation. The inclusion of all these variants [20, 28, 29] in sub-class C4 makes the cervical classification simple and users' friendly. This sub-class in combination with a normal or deformed uterine corpus allows the classification of obstructing anomalies due to cervical defects.

Vaginal Sub-classes

Vaginal anomalies are categorized into four supplementary classes; furthermore, normal vagina is adopted as class 0.

Sub-class V0 or normal vagina
This sub-class incorporates all cases of normal vaginal development. The addition of normal vagina as class V0 allows the independent classification of uterine and vaginal congenital malformations when the cervix is normal.

Sub-class V1 or longitudinal non-obstructing vaginal septum
The described anomaly in this sub-class is clear allowing the classification of variants of septate or bicorporeal uteri together with septate or double cervices.

Sub-class V2 or longitudinal obstructing vaginal septum
The described anomaly in this sub-class is also clear and, its utility for the effective classification of obstructing anomalies due to vaginal defects is obvious.

Sub-class V3 or transverse vaginal septum and/or imperforate hymen
This sub-class incorporates obviously different vaginal anomalies and their variants (mainly those of transverse vaginal septa); they are usually present as isolated vaginal defects and they have the same clinical presentation (obstructing anomalies).

Sub-class V4 or vaginal aplasia
It is a fusion defect incorporating all cases of complete or partial vaginal aplasia.

Future Perspectives

The new ESHRE/ESGE classification system seems to be a reliable tool for the categorization of female genital anomalies. Nowadays, a lot of newer non-invasive, high accuracy diagnostic techniques are available allowing the more objective estimation of uterine anatomy. Hence, the new classification system with its accurate and clear definitions could be used as the working basis for their diagnostic work-up. Furthermore, it could be used as the working basis for the study of the clinical consequences

of the different types of female genital anomalies facilitating the development of guidelines for their management.

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Part II

Screening and Diagnosis of Female Genital Malformations

Hysterosalpingography

5

Anne P. Hemingway and Geoffrey H. Trew

Introduction

Hysterosalpingography (HSG), a radiological procedure undertaken to delineate the uterine cavity and fallopian tubes, involves the introduction of iodinated radiographic water-soluble contrast medium into the endocervical canal, uterine cavity and fallopian tubes under x-ray fluoroscopic control.

The chapter will describe in detail the indications, contraindications, technique used, and complications of hysterosalpingography, illustrate the range of HSG appearances seen in female genital tract anomalies (FGTA) and critically appraise the value of the technique in the management of patients with FGTA.

Over a century has elapsed since Rindfleish [1] reported the first HSG performed by injecting a bismuth solution into the uterine cavity. By 1914 collargol, an oil soluble agent was being used by Cary [2] to determine tubal patency but its use was abandoned secondary to adverse side effects. Lipiodol, another oil-soluble contrast medium, was first used in 1925 for hysterosalpingography [3], when one of the indications for its use was to confirm the diagnosis of pregnancy! [3, 4] Lipiodol remained in routine use until the 1980s when it was largely replaced by water-soluble contrast agents [5]. The vast majority of HSGs are now performed using non-ionic water-soluble iodinated radiographic contrast agents such as Omnipaque 300 (Iohexol- GE Healthcare).

A variety of imaging techniques is employed to demonstrate the uterus and fallopian tubes including hysterosalpingography (HSG), 3D ultrasound, sonohysterography and magnetic resonance imaging (MRI). The number of these procedures performed has risen significantly over the last two decades with the dramatic developments in infertility management [6, 7].

Indications and Contraindications [5, 6, 8, 9]

Investigation of infertility is the commonest indication for hysterosalpingography, other indications are shown below.

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Common Indications for Hysterosalpingography

- Primary or secondary infertility
- Recurrent pregnancy loss
- Post –operative assessment following:
  - Caesarean section
  - Myomectomy
  - Division of intrauterine adhesions
  - Reconstructive tubal surgery
  - Hysteroscopic sterilization
- Assessment of congenital abnormalities
  - Delineation of anatomy
  - Following corrective surgery

Hysterosalpingography, performed correctly, is a remarkably safe and well tolerated procedure however some absolute contraindications such as pregnancy, active pelvic infection and bleeding exist:

Contraindications to Hysterosalpingography

- Pregnancy
- Untreated pelvic infection
- Bleeding
- Uterine or tubal surgery within last 6 weeks
- Immediate pre-menstrual phase
- Allergy to contrast medium

Recent or current untreated pelvic infection will be exacerbated by hysterosalpingography and can result in serious morbidity.

Performing an HSG whilst there is bleeding increases the risk of infection, may result in endometrial tissue being flushed into the peritoneal cavity and can lead to an incorrect diagnosis as intrauterine blood may be mistaken for pathology such as polyps.

Technique [6–9]

Hysterosalpingography is ideally undertaken in the follicular phase of the menstrual cycle after bleeding has stopped and prior to ovulation (day 6 to day 14), although this window may be extended in women with longer or irregular menstrual cycles.

Pregnancy in the cycle in which the HSG is performed is excluded by requesting the patient to avoid unprotected intercourse from day 1 of the cycle and by performing a urine ß hCG pregnancy test immediately prior to the examination. Women with amenorrhea or oligomenorrhea are asked to abstain from intercourse for a minimum of 14 days prior to the examination and a urine ß hCG pregnancy test is performed.

A calm environment, respect for the woman's privacy and dignity, and experienced personnel are prerequisites for a successful examination [5, 9].

HSG is an intimate examination, many women are apprehensive either because of a previous traumatic speculum examination or because they have read worrying descriptions of the examination on the internet. The number of staff in the examination room should be limited wherever possible to the radiologist, radiographer and nurse and, if requested by the patient, only female staff should be present.

The radiologist undertaking the HSG takes a brief obstetric and gynaecological history, this is followed by a detailed explanation of the procedure together with an opportunity for questions. Written consent is obtained and oral antibiotic prophylaxis administered. The woman lies on her back on the x-ray examination couch, heels together, knees and hips flexed. Some authorities advocate an initial vaginal examination [5], however this is not routine in our department and is reserved for the very few patients in whom visualisation of the cervix is problematic.

Hysterosalpingography is an aseptic rather than a sterile procedure, however all staff involved must observe strict aseptic technique and all equipment used must be sterile for single use only. The introitus is cleaned with 0.1 % chlorhexidine and a well lubricated, warmed metal or plastic speculum introduced gently into the vagina. The cervix is visualized and cleaned with 0.1 % chlorhexidine solution. Some authors describe the use of tenaculum forceps to grasp the cervix to facilitate insertion of the catheter and traction on the cervix and uterus [7, 8] however this increases patient discomfort [5]. In author's experience of in excess of 10,000 HSGs the use of tenaculum forceps has not been required.

The cervical canal is cannulated; the choice of cannula depends on the size of the cervical os. It is essential to have a wide range of equipment available to enable catheterization of any os, [9] (Fig. 5.1). The most frequently used catheters in our unit are the 5 F Catheter with a 2 cc balloon (Rocket Medical) or a Margolin (Cook Medical) catheter. The catheter must be primed with contrast medium prior to insertion and careful attention to remove all air bubbles is essential.

The tip of the catheter is placed in the high cervical canal and once the chosen catheter is securely placed, if possible, the speculum is removed, however if visualization of the cervix has been difficult or to remove the speculum may dislodge the catheter then it is left in situ.

Before any contrast is introduced into the uterine cavity the radiologist should review the pelvic cavity fluoroscopically for radio-opaque densities such as calcified fibroids, dermoid cysts or surgical clips and, if indicated, take a control image. A radio-opaque side marker is placed on the image intensifier.

Non-ionic iodinated water-soluble radiographic contrast medium (Omnipaque 300) is infused slowly and gently by hand injection into the uterine cavity under intermittent fluoroscopic control. It is crucial to infuse the contrast slowly in order to minimize discomfort. Forcible or rapid infusion causes significant pain, which in turn may limit the investigation and cause tubal spasm. Mechanical injection devices should not be used.

An early filling image of the uterine cavity is taken to visualize small intrauterine filling defects, such as polyps or fibroids, which may be obscured by contrast medium in later images. This is followed by right and left anterior oblique images to demonstrate the uterine cavity and the fallopian tubes throughout their length. These images may be acquired by either turning the patient and/or utilizing the rotational capability of the image intensifier. A fourth image is obtained in the frontal projection to show intra-peritoneal spill from the fallopian tubes. It is essential to obtain at least one true en-face image of the uterine cavity (Fig. 5.2) if significant pathology is not to be missed, this may require gentle traction or upward pressure on the cannula combined with patient rotation and/or angulation of the image intensifier. These 4 images are the minimum required – it may be necessary to acquire more and the examination can be supplemented

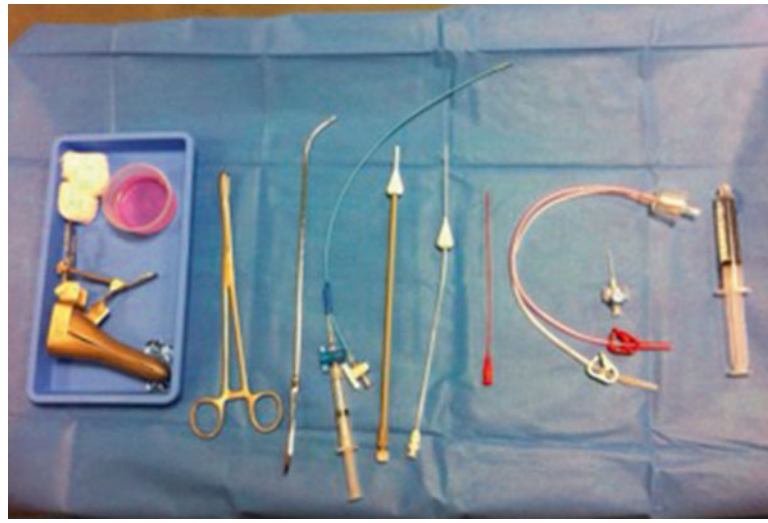

Fig. 5.1 Examination trolley & range of equipment. Examination trolley showing from *left* to *right*: a tray with 0.1 % chlorhexidine cleaning fluid, a cusco speculum and lubricating jelly; sponge forceps, Uterine sound, 5Fr balloon HSG catheter, Margolin acorn catheter, Goldstein HyCoSy catheter, 4Fr vessel dilator, Rocket 27 mm suction cup, 21 g plastic venous cannula and 10 cc syringe with contrast medium

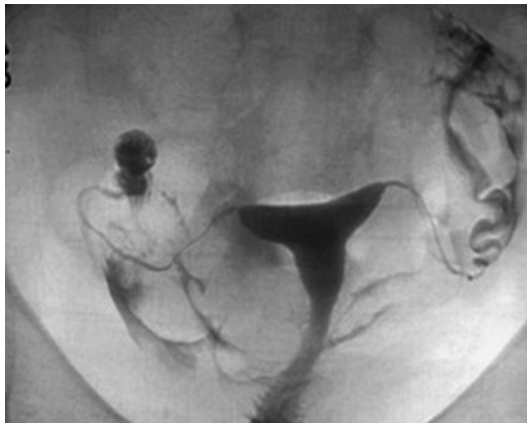

Fig. 5.2 Normal HSG enface view. A normal HSG showing the cervical canal, uterine cavity en-face and both fallopian tubes with free intraperitoneal spill. U0 C0 V0

by fluoroscopic grab images. Tilting the patient head down on the examination couch, rotating the patient through 360 degrees and taking delayed images may also be necessary to adequately demonstrate the fallopian tubes [5, 9].

Usually a maximum 10 cc contrast medium is sufficient to demonstrate the cavity and tubes but in a very enlarged cavity up to 50 cc may be required.

If the catheter has been introduced into the lower segment of the uterine cavity it is essential that any balloon is deflated and the catheter is withdrawn whilst continuing to infuse contrast medium under fluoroscopic control at the end of the procedure in order to adequately visualize the lower uterine segment and upper cervical canal (Fig. 5.3a, b). Hoffmann [10] observed that common causes for misdiagnosis in HSG include failure to obtain an en-face view, failure to deflate an intra-uterine balloon and failure remove a speculum obscuring the cervical canal.

In our unit we employ a Siemens Axiom Artis C arm x-ray machine. As in all investigations involving ionising radiation it is essential to keep the dose to the patient as low as practicable. In our department the mean screening time is 1 s and the DAP (dose area product) is 0.48 Gy cm^2. The national DRL (dose reference level) for HSG is 2 Gy cm^2 & 0.7 min (42 s) [11].

Complications [6, 9]

As with any procedure HSGs may be associated with complications, these can be minimized by good technique and observance of the contraindications.

Complications of Hysterosalpingography

- Infection
- Pain
- Intravasation
- Pregnancy irradiation
- Failure
- Vasovagal episode
- Contrast medium allergic reaction

A significant complication of HSG is pelvic infection, which is reported to occur in between 1 and 3 % of all cases and up to 10 % in the presence of tubal pathology [12–14]. In women with a medical history of pelvic infection the risk of infection is reduced by the use of prophylactic antibiotics [7, 13]. Whilst some centres routinely screen all women for Chlamydia prior to HSG some authors advocate prophylactic antibiotics in all women before uterine instrumentation without preliminary screening [15]. The author's practice is to administer 1 g of Azithromycin immediately prior to the procedure. It is impossible to completely exclude the risk of infection. Aseptic technique, prophylactic antibiotics, additional antibiotic therapy in the presence of hydrosalpinges and the avoidance of undertaking an HSG in the presence of active or recent PID (pelvic inflammatory disease) will help minimize the incidence.

An HSG is an invasive and intimate examination however by paying attention to the environment, establishing a rapport with the patient and with experience and good technique the patient may experience mild discomfort but it should rarely be a painful examination. We do not advise the use of analgesia before the procedure as this increases the expectation, and therefore the experience, of pain. Patients are advised that they

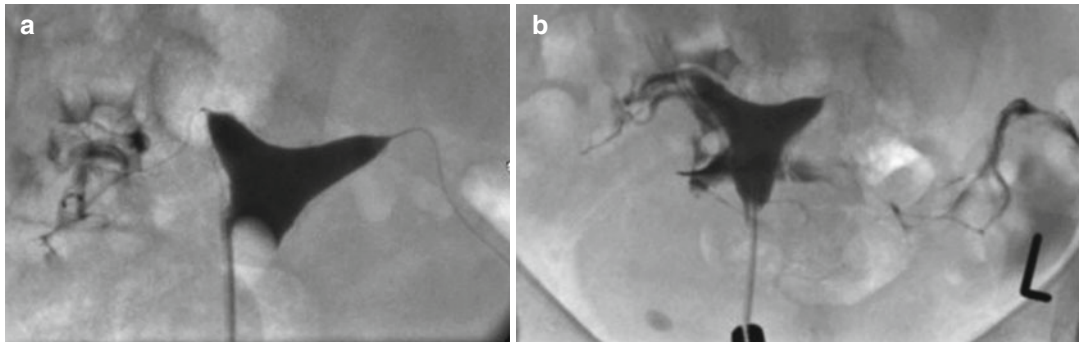

Fig. 5.3 Balloon in LUS inflated & deflated. (**a**) HSG showing a balloon catheter inflated in the lower uterine segment (LUS). (**b**) The same patient following deflation of the balloon and a normal LUS. U0 C0 V0

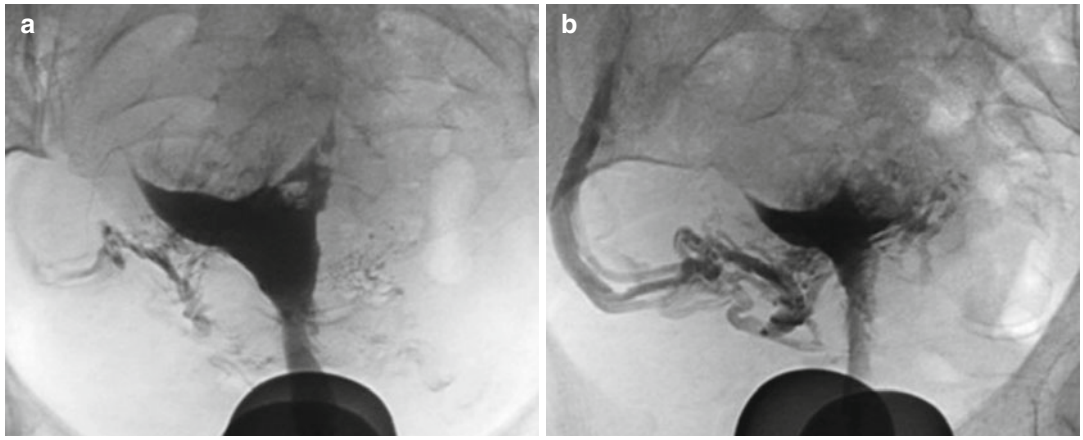

Fig. 5.4 Intravasation; HSG a woman who suffered a miscarriage and has undergone an ERPC. (**a**) The study reveals a uterine cavity that has an arcuate configuration, evidence of intra-uterine synechiae in the left fundal and cornual region and early venous intravasation. (**b**) A later image shows extensive venous intravasation

may experience some discomfort post procedure and to take analgesia if necessary.

Intravasation is usually indicative of uterine pathology. If it occurs it is of no clinical significance but may limit the study as it may not be possible to accurately identify the fallopian tubes (Fig. 5.4a, b) [7].

Irradiation of an early pregnancy is avoided by abstinence from intercourse from the first day of the menstrual cycle and until after the HSG has been performed and by performing a urine ß hCG pregnancy test on the day of the examination.

Failure to perform an HSG is usually due to severe vaginismus and consideration should be given to mild sedation if this occurs.

Vasovagal episodes are usually mild but may, on occasion, be severe and can occur at any stage during the procedure. Good technique dramatically reduces the incidence of vasovagal reactions. Conservative treatment is usually all that is required, tilt the head of the examination couch down (Trendelenberg position), reassure the patient, provide ice-cold water to drink and allow the patient to rest until recovered. Rarely the reaction may be more severe and warrant intravenous fluids and/or atropine.

Allergic reactions following the use of water-soluble contrast agents for HSG are rare. The authors would not undertake an HSG in someone with history of a previous severe reaction to

iodinated contrast medium as an HSG is an elective procedure and the information required can be obtained in other ways if necessary for example by HyCoSy, MRI, or hysteroscopy.

Hysterosalpingographic Demonstration of Female Genital Tract Anomalies

In the evaluation of congenital anomalies HSG is complementary but it cannot be wholly diagnostic. The HSG demonstrates the uterine cavity and fallopian tubes but it cannot accurately characterize the external contour of the uterus which is essential for the proper definition of FGTAs /Mullerian Duct Anomalies (MDA) [16, 17]. Accurate delineation and classification is essential for determining treatment and reproductive prognosis. 3D Ultrasound and MRI are the modalities of choice for full the anatomical evaluation of MDAs [18].

The HSG may be the first examination to detect a congenital anomaly. The HSG report should be descriptive. The radiologist may be able to suggest which ESHRE/ESGE [19] class any demonstrated anomaly falls into but cannot give a definitive answer and must therefore provide a differential diagnosis and suggest additional imaging such as MRI and/or 3D ultrasound for full characterisation of the abnormality [20]. For example the HSG cannot distinguish between a septate and a bicornuate (bicorporeal) uterine cavity and it cannot exclude a non-communicating rudimentary horn in a hemi or unicornuate uterus.

The HSG is useful in demonstrating concomitant pathology affecting the cavity and fallopian tubes including intrauterine synechiae, endometrial polyps, leiomyomata, salpingitis isthmica nodosa (SIN), tubal occlusive disease and hydrosalpinges. Demonstration of all relevant abnormalities is essential if fully informed consent is to be obtained preoperatively that allows the removal or correction of all pathology detected at surgery. Hysterosalpingography is also of significant value in post-operative assessment following surgical correction of operable congenital anomalies [21].

Normal Uterus, Cervix and Vagina (ESHRE/ESGE U0, C0 V0)

A normal HSG reveals a triangular shaped uterine cavity with the fundus representing the base of the triangle and the apex the lower segment extending into the endo-cervical canal. The walls of the cavity should be smooth, the filling pattern even and the fundal margin should be straight or showing minimal convexity or concavity. The fallopian tubes, which arise from the uterine cornu, are divided into four parts the short intramural portion, the long narrow isthmus, the wider ampulla with prominent mucosal folds and the infundibulum, a series of fimbriae, which radiate round the tubal ostium (Figs. 5.2, 5.3 and 5.5). Free intraperitoneal spill from the fallopian tubes disperses around bowel loops and may flow over the fundus indicating clearly the thickness of the myometrium (Fig. 5.6).

Dysmorphic Uterus (ESHRE/ESGE U1)

Whilst the HSG can suggest a dysmorphic uterine cavity it cannot distinguish between the sub-classes specified in the ESHRE/ESGE classification. Figure 5.7a, b demonstrate patients with uterine cavities that can be described radiologically as “t-shaped” but may be determined on other imaging modalities as being U1a (t-shaped) or U1b (infantilis).

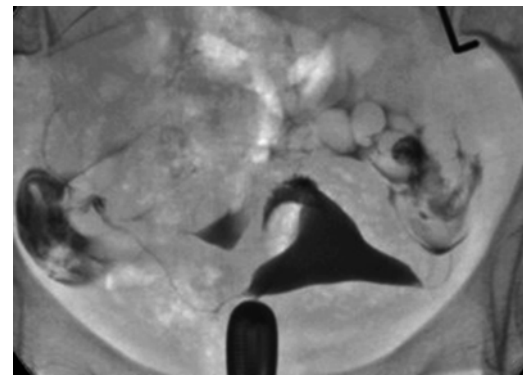

Fig. 5.5 Normal HSG. Enface view in steeply ante-verted uterine cavity U0 C0 V0

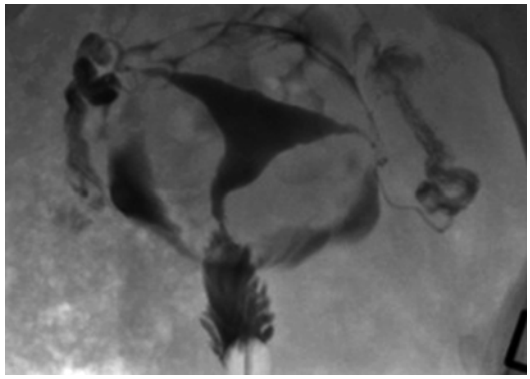

Fig. 5.6 Normal HSG demonstrating spill over the uterine fundus Intraperitoneal spill is seen arching over the uterine fundus demonstrating normal myometrial thickness U0 C0 V0

Under this classification it seems likely that some cavities previously described as arcuate might now fall into class *U1c or others* i.e. 'all minor deformities of the uterine cavity including those with an inner indentation of the fundal midline level of less than 50 % of the uterine wall thickness' [19], although arcuate uteri do not necessarily fit with the specification that dysmorphic uteri are usually smaller (Fig. 5.7c).

The arcuate uterus is described as a single cavity with a broad saddle shaped indentation of the fundus where the ratio of the fundal indentation is less than 10 % of the inter-cornual distance [22], however there is debate as to whether the arcuate uterus represents an anomaly at all but is rather just a normal variant [20].

Septate Uterus (ESHRE/ESGE U2) and Bicorporeal Uterus (ESHRE/ESGE U3)

These categories include all of those HSGs that would have been described as septate, sub-septate, bicornuate and didelphys under previous classifications. It is not possible to distinguish between these two categories at hysterosalpingography and examples will be illustrated together.

Figure 5.8a, b illustrate two very similar HSGs. Figure 5.8a is an HSG in a 38 year old woman suffering primary infertility, the study revealed a single vagina and cervix with a uterine cavity divided into two distinct uterine horns, polyps in the right horn and a patent left fallopian tube. Figure 5.8b shows the HSG of a 29-year-old woman who had 7 pregnancies, three live births delivered by caesarean section, a left ectopic pregnancy and 3 miscarriages. Figure 5.8a was found on MRI to be a septate cavity (U2a C0 V0); Figure 5.8b was known to be a bicornuate (bicorporeal) cavity (U3a C0 V0).

Figure 5.9 illustrates a woman who presented with recurrent miscarriage who had been told elsewhere that she had a bicornuate cavity. The HSG shows a single cervix and vagina and two smooth widely separated uterine horns. The MRI shows very clearly that this is in fact a septate cavity (U2a C0 V0).

HSG is of particular value in the post-operative follow-up in those women found to have a septate cavity who undergo corrective surgery (Fig. 5.10a, b).

If a patient has two vaginas and/ or two cervices it is important to catheterise both in order to assess the true extent of the anomaly. Figure 5.11a, b illustrate the importance of technique. An initial HSG (Fig. 5.11a) revealed what could easily be mistaken for a right unicornuate or hemi-uterus, however careful examination of the vaginal vault revealed a second cervix on the left. This was separately catheterised and revealed two cervical canals and two completely separate uterine horns joined only at the level of the internal os. Previous classifications would have called this bicornuate bicollis; the ESHRE-ESGE classification is of a bicorporeal uterus U3b C2 V0.

Figure 5.12 on the other hand is taken from an HSG series in a 37-year-old woman who had previously undergone surgery to relieve a right heamatocolpos secondary to an obstructing septum. Examination revealed that the patient had two separate vaginas, two cervices and contrast media injected into the left side revealed the left horn of the uterus, contrast medium crossed a bridge of tissue into the right side where some contrast refluxed down the right cervix and some enters the right cavity and tube. The cavities were divided by a thick septum U2b C2 V2.

Figure 5.13 demonstrates the HSG in a bicorporeal system with the appearances of

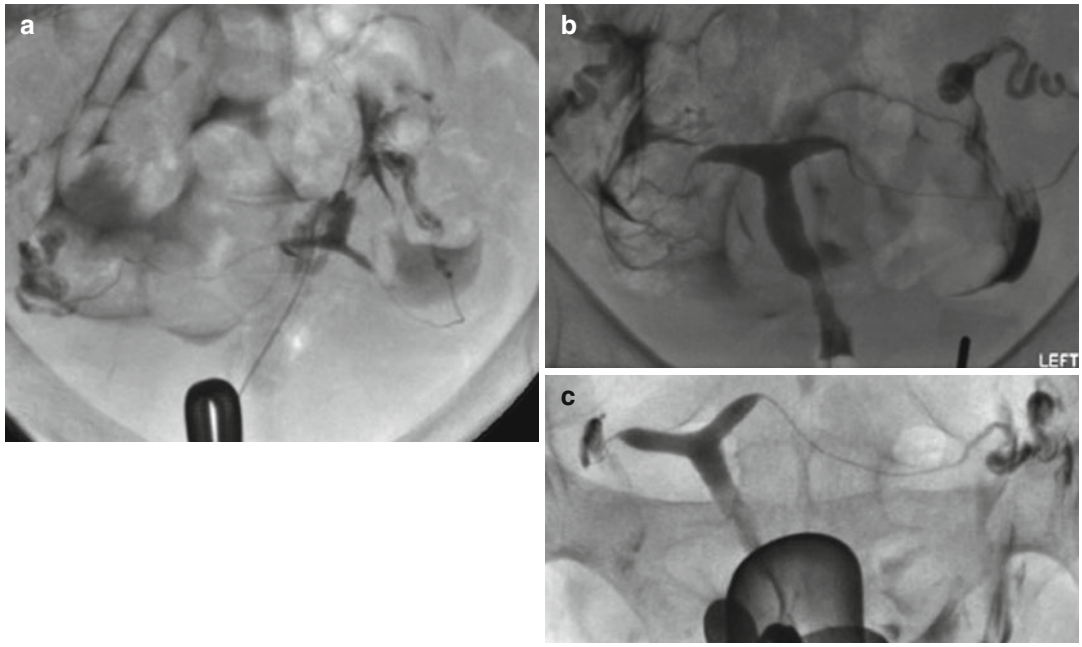

Fig. 5.7 (**a**) Dysmorphic uterus (U1). HSG demonstrates a dysmorphic uterine (U1) cavity in a 34-year woman presenting with primary infertility. HSG would describe this as t-shaped but cannot differentiate between U1a and U1b. (**b**) Dysmorphic uterus (U1). 'T-shaped' uterine cavity in a 34 year old woman presenting with PCO and primary infertility which may represent either subclass U1a or U1b. (**c**) Dysmorphic uterus (U1c). A T-shaped cavity with a concave 'arcuate' fundal margin, which would probably be classified as U1c

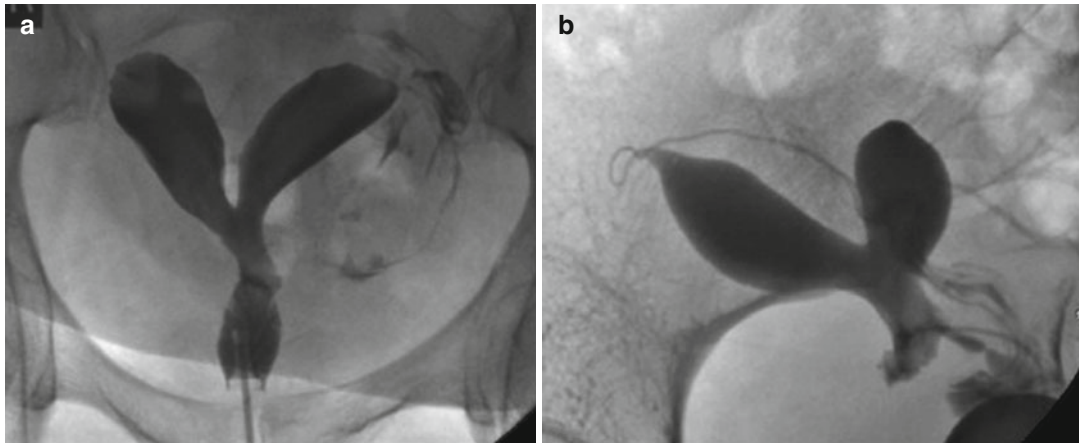

Fig. 5.8 HSG cannot differentiate between a septate and bicorporeal uterine cavity. (**a**) A 38 year old woman with primary infertility proven on MRI to be a septate cavity U2b C0 V0. (**b**) A 29-year-old woman P3 + 4, previous left ectopic pregnancy with salpingectomy. Caesarian section x3 proven to be bicorporeal U3a C0 V0

uterus didelphys. Two completely separate vaginas and cervices were cannulated and demonstrated separate uterine cavities each with a singe fallopian tube and no communication between them. The ESHRE –ESGE classification is U3b C2 V2.

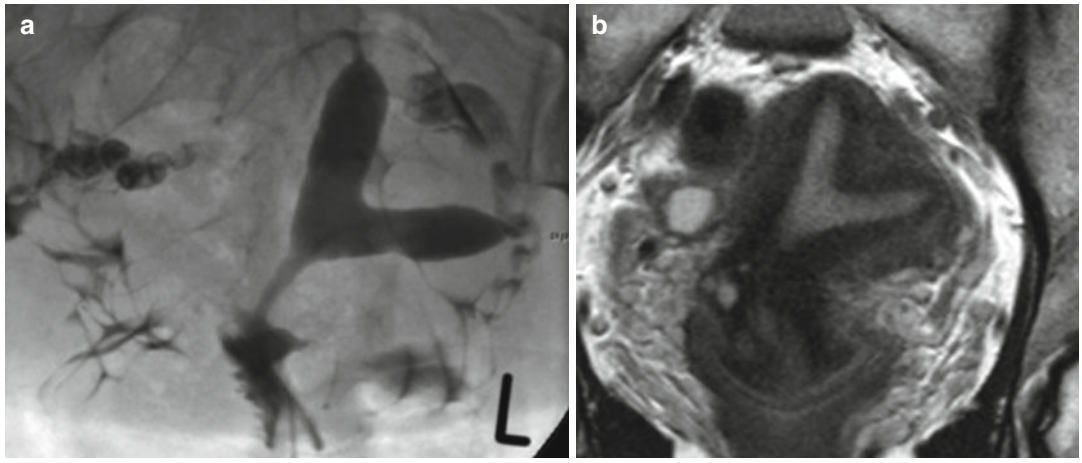

Fig. 5.9 (**a**, **b**) HSG and MRI in a woman suffering recurrent miscarriage. The HSG (8a) shows a single cervix and two widely separated uterine cavities The MRI shows that this is a septate cavity.U2a C0 V0

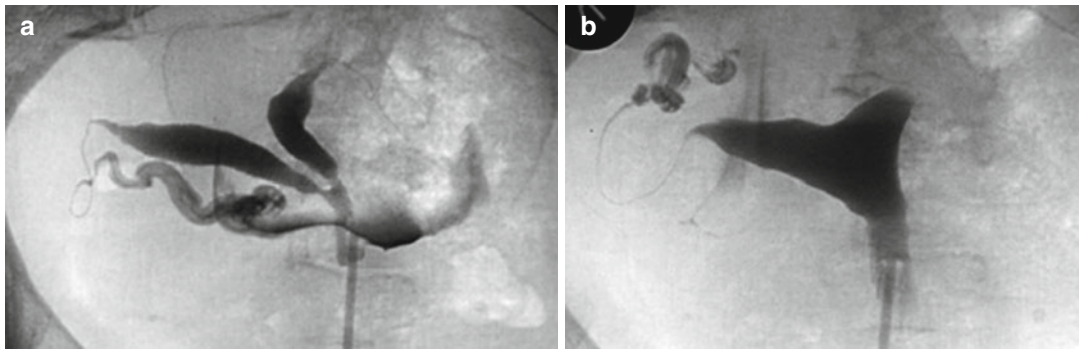

Fig. 5.10 Pre and post -operative HSG in a 37 year old woman found to have a septum. (**a**) Pre-operative HSG shows a single cervix and two separate uterine cavities shown on other imaging to be septate. The septum reaches the internal os but does not extend into the cervical canal U2b C0 V0. (**b**) Post-operative HSG shows a virtually normal uterine cavity only a minor indentation persists on the fundal margin

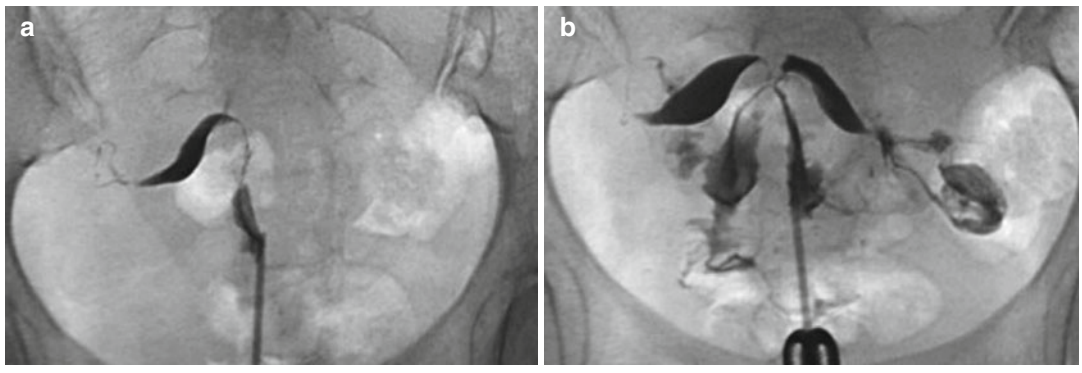

Fig. 5.11 Bicorporeal uterus. (**a**) Initial HSG showing a right sided uterine cavity and fallopian tube. (**b**) Catheterization of the left sided cervix fills both sides of this bicorporeal system U3b C2 V0

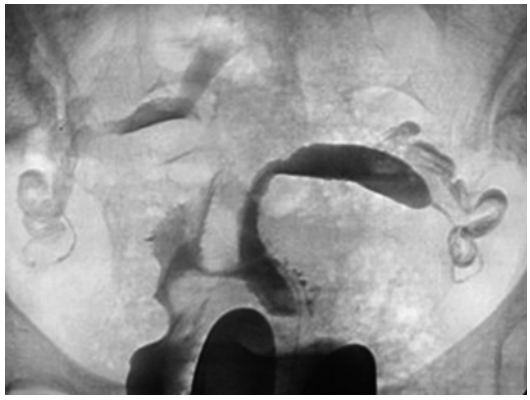

Fig. 5.12 Septate uterus. An HSG in a patient with a deep uterine septum extending to the internal os, two separate cervical canals and a vaginal septum which had been partially obstructing the right side resulting in a right haematocolpos. The uterine cavities communicate at the level of the internal os U2b C2 V2

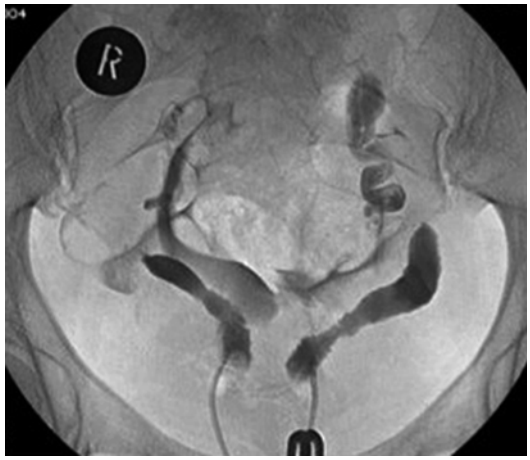

Fig.5.13 Bicorporeal uterus, uterus didelphys. Cannulation of two separate vaginas and cervices demonstrates two completely separate uterine cavities each with a single fallopian tube. U3b C2 V2

Patients with underlying congenital anomalies may present for investigation as a result of separate pathology. Figure 5.14 is from an HSG series in a woman who presented with an abdominal mass and was found on MRI & US to have fibroids for which she had had a previous open myomectomy and TCRF x2. The HSG revealed complete didelphys with both cavities full of fibroids (leiomyomata) (U3b, C2 V2).

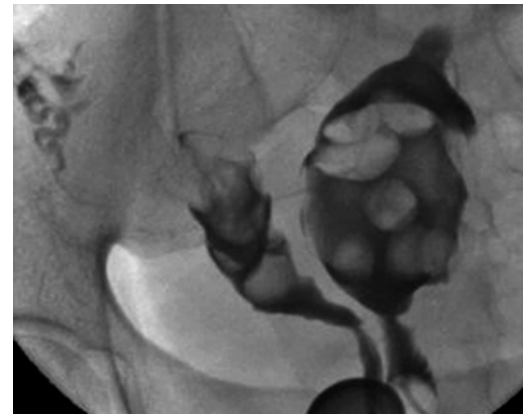

Fig. 5.14 Severe fibroid disease in a bicorporeal system. Extensive fibroid disease diagnosed on MRI and ultrasound. HSG confirmed the presence of a complete bicorporeal system, uterus didelphys U3b C2 V2

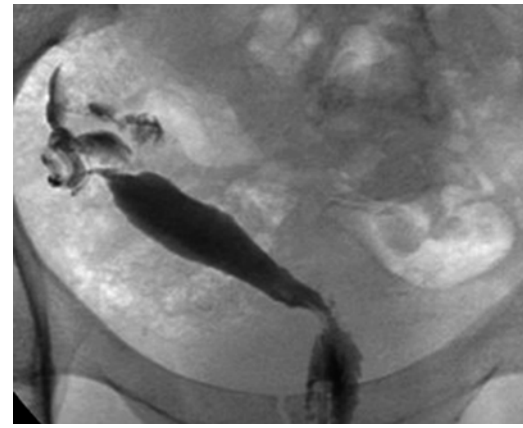

Fig. 5.15 Right hemi-uterus. HSG suggested a right unicornuate /hemi uterus, ultrasound confirmed that this represented an isolated system with no rudimentary horn and the presence of a single right kidney U4b C0 V0

Hemi Uterus (ESHRE/ESGE U4)

Previously described as unicornuate, there are four different types of hemi uterus. Isolated (35 %), communicating rudimentary cavity (10 %), non-communicating rudimentary cavity (22 %) and rudimentary non-cavitary horn (33 %) [23].

If the HSG suggests that there is a hemi-uterus, a small fusiform cavity deviated to one side with a single fallopian tube, the radiologist must look for any indication of a rudimentary horn (Fig. 5.15).

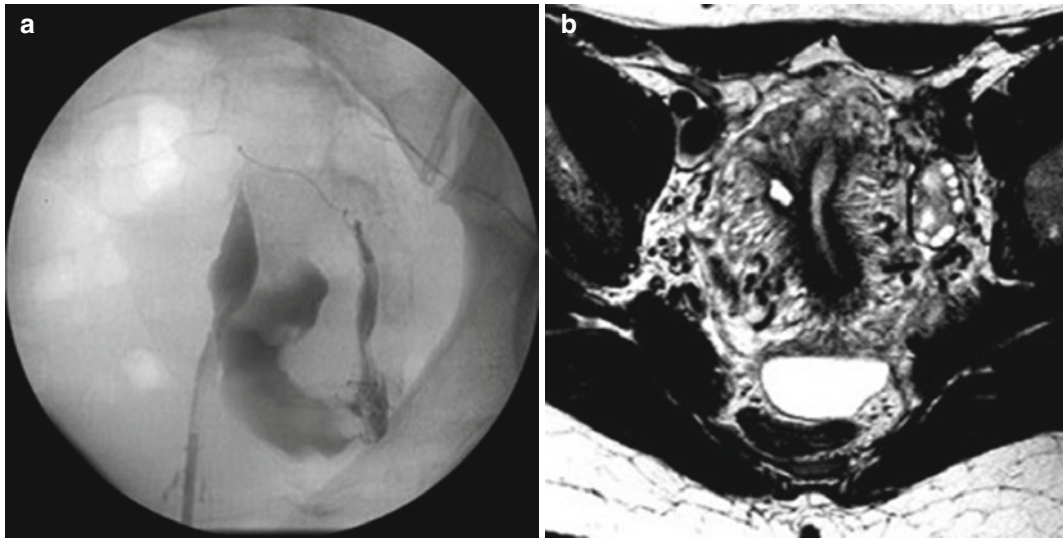

Fig. 5.16 (**a, b**) Left hemi- uterus with rudimentary horn. The HSG suggested a left hemi uterus; MRI confirmed the presence of a non-communicating functioning right rudimentary horn. U4a C0 V0

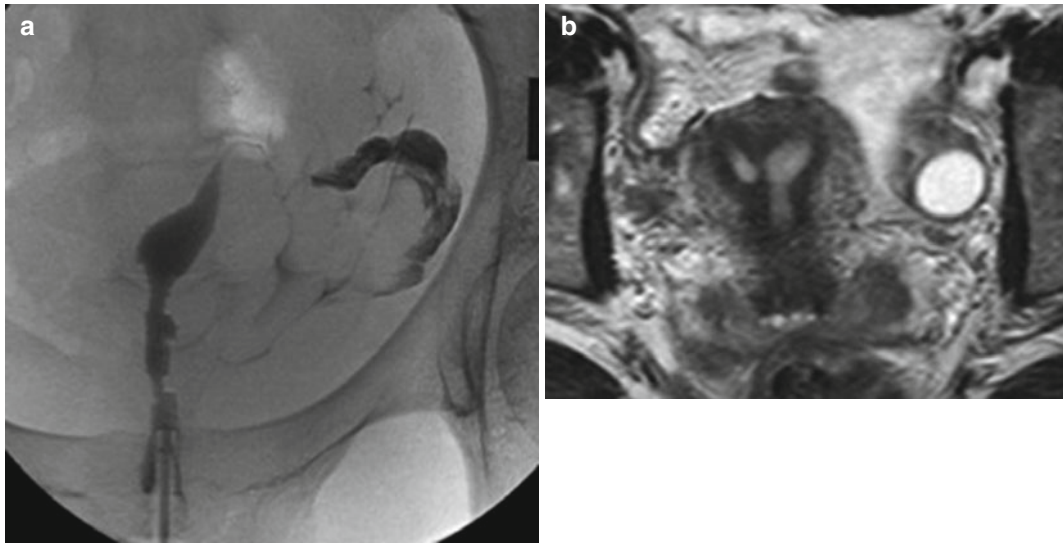

Fig. 5.17 Septate cavity with synechiae mimicking a hemi-uterus. HSG (**a**) in a woman who had suffered recurrent miscarriage suggests a left hemi uterus, MRI (**b**) and subsequent hysteroscopy confirmed that this represented a septate uterus with associated intrauterine synechiae U2a C0 V0

The catheter should be slowly withdrawn injecting continuously under fluoroscopic control. If a rudimentary cavity is not seen it does not exclude its presence and further imaging is required (Fig. 5.16a, b). The radiologist must also examine the patient carefully to determine if there is a second cervix and possibly vagina present that would suggest that what is seen is one half of a bicorporeal system (Fig. 5.11) [23]. The radiologist must also take into account any relevant history, which might suggest other causes for the HSG appearances (Fig. 5.17). Uterine synechiae must

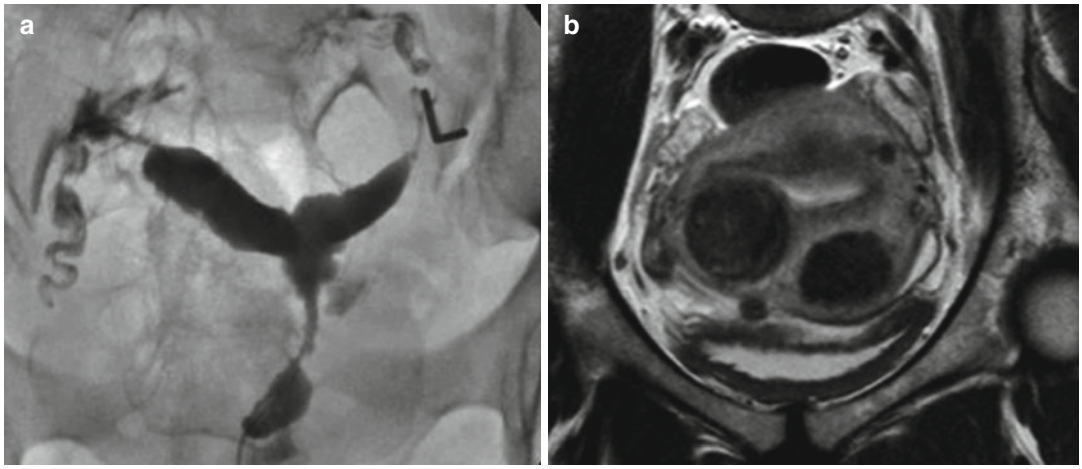

Fig. 5.18 (**a, b**) Fibroids mimicking a congenital anomaly. The HSG in a 38 year old woman with primary infertility suggested either a bicorporeal or septate uterine cavity. Ultrasound and MRI and subsequent myomectomy confirmed that this was a normal cavity distorted by the presence of large fibroids

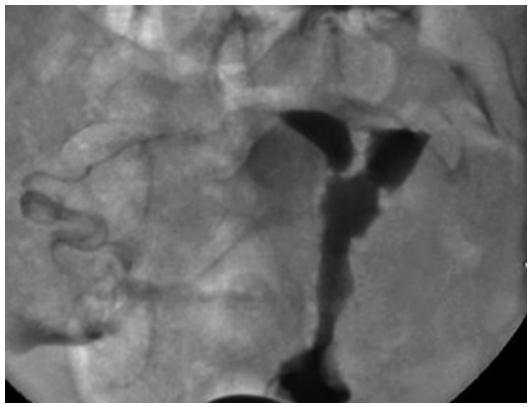

Fig. 5.19 Intra uterine synechiae mimicking a septate cavity. The HSG in a 39-year-old woman who had suffered two miscarriages and ERPC x2. The radiologist suggested synechiae (Asherman's syndrome) possibly associated with an underlying congenital abnormality. Hysteroscopy confirmed that all of the appearances were related to synechiae and adhesiolysis restored a cavity with a normal configuration

always be considered in the differential diagnosis in any patient who has previously undergone uterine instrumentation.

Pathology Mimicking Congenital Anomalies

The HSG may suggest a congenital anomaly but the radiologist must always provide a differential diagnosis that would account for the HSG appearances and suggest the appropriate additional imaging (Figs. 5.18 and 5.19). Figure 5.18 demonstrates how fibroid disease may mimic a bicorporeal cavity and Fig. 5.19 how synechiae can mimic a septum.

Conclusion

Whilst hysterosalpingography (HSG) is not able to fully characterise congenital anomalies of the female genital tract it has an important role in suggesting the presence of an anomaly and in the assessment of the uterine cavity and fallopian tubes both before and after any corrective surgery. It is also of value in detecting concomitant pathology, which may co-exist with or mimic a congenital anomaly.

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6 2D Ultrasound (2D US) and Sonohysterography (SHG) for the Diagnosis of Female Genital Anomalies

Caterina Exacoustos, Isabella Cobuzzi, and Valeria Romeo

Introduction

2D transabdominal (TAS) or transvaginal (TVS) sonography are the most available diagnostic tools used to detect the presence of congenital uterine anomalies [1]. The diagnosis of congenital uterine anomaly is usually made in patients with fertility problems or previous adverse obstetric outcomes while the prevalence in the general population is largely unknown [2]. 2D ultrasound (2D US) is used since many years for the assessment of uterine morphology because the appearance of the uterine cavity and the myometrium can be analyzed by 2D US in great details. The value of 2D US for the diagnosis of acquired uterine abnormalities, such as fibroids or endometrial cancer, is well known [3, 4]. However, in patients with congenital uterine anomalies, 2D TAS and TVS have been used with varying success. When used as a screening test, 2D TVS has provided sensitivity rates of up to 100 % [5]. However, the distinction between the different types of anomalies is often difficult [6]. Therefore, other diagnostic methods were usually required to complete the diagnosis evaluation. In the past, after a suspicious of female genital malformation based on gynecological examination and 2D US, several other diagnostic methods were performed such as hysteroscopy, hysterosalpingography, magnetic resonance and laparoscopy. Actually, with the introduction of 3D TVS, most of these diagnostic methods are not more required [7–10]. However, 2D US is still a very important diagnostic tool in evaluating uterine morphology and must be used in the first diagnostic approach in case of uterine congenital anomalies before other imaging or endoscopic techniques.

The 2D US, transvaginal approach is the basic imaging method and provides objective and measurable informations of the cervix, the uterine cavity, the uterine wall and the external contour of the uterus. It is simple, available, reproducible and non-invasive but its accuracy highly depends on the experience of the examiner and on the examination methodology followed [11, 12]. 2D US has a reported accuracy in diagnosing congenital uterine anomalies of approximately 90–92 % [2, 13]. Pooled data from reports comparing 2D US and hysteroscopy suggest low sensitivities of less than 60 % but high specificities of nearly 100 % [1].

The sonographic examination should be performed better during the secretory phase of the

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menstrual cycle. During this phase, the hyperechoic thick endometrium of the secretory phase is visible as a separated echogenic stripe representing the endometrium surrounded by a hypoechoic myometrial layer (inner myometrium or junctional zone) [14]. Imaging should not only focus on conventional longitudinal and transverse imaging of the pelvis but also include orthogonal (coronal or frontal) images along the long axis of the uterus to characterize the external uterine contour. In addition to 2D TVS, sonohysterography (SHG) can help to evaluate better the uterine cavity and the communications between different parts of the cavity. In combination with the previous techniques, Doppler evaluation in color, power or spectral imaging offers informations regarding blood flow to or within the pelvic organs.

Although 2D US is often the first imaging modality chosen because its availability, short scan time and low cost, several limitation are encountered during imaging. Image quality from TAS examination is often not appropriate and poor to make an accurate diagnosis of the type of genital tract malformations. 2D TAS may be performed, ideally through a distended bladder but offers reduced sensitivity and specificity because of increased distance from the uterus and of the often intervening bowel. TVS imaging, is superior to the transabdominal approach but had several limits in the evaluation of all pelvic structures together. It may have some technical problems in case of virgo patients and in patients with vaginal septa or atresia. In these cases, the transrectal approach with transvaginal probe can be performed with the similar diagnostic accuracy.

2D Ultrasound Techniques

Transabdominal Sonography (TAS)

Transabdominal US is usually best performed with a curved transducer. Although the TA US technique can be performed with an empty bladder, this technique is most effective if the patient has a full bladder. The full bladder provides an acoustic window as well as displaces the bowel away from the area of interest. Also, the uterine position is in a more perpendicular plane to the sound beam, which creates better axial resolution, producing a better image especially of the endometrium. A frontal (coronal) section of the uterus can be obtained by scanning transabdominally with a half-full-bladder and the probe positioned as much as possible parallel to the abdominal wall (half-full bladder technique) [15]. The frontal or coronal view of the uterus permits to visualize the fundal contour, myometrial thickness and conformation of the endometrial cavity. By scanning transabdominally, the sonographer has access to a global view of the pelvic region and the relationship between anatomic structures of the pelvis and upper abdomen (uterus, ovaries, bladder, kidneys, etc.) may be appreciated. TAS also has its limitations: overlying bowel gas and patient's body habitus can confound transabdominal imaging. Due to the fact that the TAS technique employs a lower frequency transducer, resolution is scarified to adequate penetration, thus sacrificing image quality.

Transvaginal Sonography (TVS)

The primary advantage of TVS over TAS lies in its ability to place a high-frequencies transducer next to the region of interest. This allows optimal visualization of the uterus, cervix, ovaries, adnexal regions and cul-de-sac, as well the urinary bladder and rectum. It is particularly useful in the evaluation of obese patients and in the evaluation of the retroverted or retroflexed uterus.

A systematic examination by 2D TVS of the pelvis included a detailed assessment of the uterine position, size and morphological characteristics. 2D TVS is able to evaluate the vaginal canal introducing the probe slowly by the external vaginal os, looking to the cervix and the cervical canal in longitudinal and in transverse section. Uterine cavities were examined systematically in the longitudinal plane from the right to the left uterine corner and in the transversal plane from fundus to cervix. Also the lateral parts of the uterine cavity close to the tubal origin can be evaluated.

The visualization of endometrial stripe from the cervix to the uterine fundus in longitudinal and in transverse section permits to evaluate the form of the uterine cavity, the presence of latero-deviation and the duplication of the cavity. The evaluation of the uterine fundus in transverse and longitudinal section can also give information about the type of uterine malformation. Intracavitary septa and cavity duplications can be detected especially on transverse section whereas in the longitudinal section alterations of the external profile of the uterus can be seen by moving the probe laterally and assessing the fundal position in different planes. Congenital uterine anomalies may be suspected in women who have an endometrial echo that is split from the fundus downwards or where the interstitial portion of one or other fallopian tube is not identified. These findings are suggestive of either a duplication anomaly or agenesis of one hemi-section of the uterus, respectively. The evaluation of adnexal regions is also very important, at first to visualize both ovaries and secondary to detect in the lateral parts of pelvis rudimentary cornua or abnormal tubal conformation. The major limitations of TVS are the inability to evaluate the external uterine contour adequately and the lack of global view of pelvis especially in patients with large uterus or with widespread horns.

The possibility to perform of a transrectal scan with the transvaginal probe is very useful to evaluate patients with congenital vaginal canalization defects or virgo patients. The TVS probe is inserted into the rectum and advanced until a midline image of the cervix is visualized in a longitudinal scan. The uterine cervix, parametria, vagina and rectum walls are evaluated by moving the transducer along the main axis in both transverse and longitudinal planes.

Sonohysterography (SHG)

Sonohysterography (SHG) is a diagnostic technique consisting of an intrauterine infusion of saline solution by means of an intrauterine catheter positioned in the cervical canal during TVS. The uterine cavity is often difficult to evaluate using ultrasound being a virtual space. Enlargement of the cavity with SHG can provide additional information and improves the imaging of the internal morphology of the uterine cavity. The expansion of the uterine cavity with the isotonic saline solution is directly observed through endovaginal sonography and the uterine cavities were examined systematically in the longitudinal plane from the right to the left uterine corner and in the transversal plane from fundus to cervix. Being the best phase to evaluate uterine cavities the secretory phase with thick endometrium, SHG could be useful to characterize better the uterine cavities in case of thin endometrium as in early follicular phase or if the endometrium stripe is unclear (myomas, contraceptive pills, irregular bleeding) [4].

SHG is a safe procedure and not particularly painful for the patient. The major limitations of the procedure are the ability to characterize only patent canals and, similar to 2D TVS, the inability to evaluate the external uterine contour adequately, but it appears that SHG provides more information about uterine abnormalities than hysterosalpingography or US alone [16]. Reports comparing SHG with hysteroscopy have suggested that SHG is highly accurate in both diagnosing and categorizing congenital uterine anomalies. The weighted mean sensitivity and specificity are 93 and 99 %, respectively [1].

Doppler

It has been suggested that uterine anomalies have different vessels distribution compared with normal uterus [17]. Inadequate vascularization and altered relationships between the endometrial and myometrial vessels are thought to be the cause of fertility problems [18, 19]. There are evidences that vascularity within uterine septa is altered. Color or power Doppler ultrasound allowed simultaneous visualization of uterine morphology and vascular network giving more information on the type of anomaly and the extent of the defect. Furthermore, Doppler imaging can detect deficient intraseptal vascularity and/or inadequate endometrial development in patients with a septate uterus [20].

In most situations, Doppler interrogation of pelvic vasculature is better appreciated utilizing endovaginal sonography versus the transabdominal approach using Power Doppler with low PRF (0.3–0.6 Hz). Due to the fact that the probe is closer to the area of interest, the sonographer is able to employ a higher frequency transducer creating improved image resolution.

2D Ultrasound and Genital Anomalies Types

Müllerian Agenesis and Uterine Hypoplasia/Aplasia (ESHRE/ESGE Class U5; Former AFS Class I)

Vaginal and uterine agenesis and hypoplasia can be easily detected by 2D US. In patients with Mayer-Rokitansky-Kuster-Hauser syndrome the absence of the uterus and the presence of both ovaries can be easily assessed by TVS (Fig. 6.1). The ovaries are normal in the majority of cases. In case of amenorrhea in Virgo patients or in the presence of vaginal agenesis, the transrectal approach (TRS) with transvaginal probe can be performed (Fig. 6.1). Being often the vaginal agenesis of the upper vaginal part and the injection of saline solution in the proximal vagina by means of a balloon catheter (Foley) can be useful to evaluate the length and morphology of the vagina and of the fibrotic agenetic tract. It is also possible to visualize the presence of rudimentary uterine tissue by TVS and TRS. In case of isolated vaginal agenesis with an obstructed or small rudimentary uterus a small or thin endometrial stripe can be detected. In case of uterine hypoplasia, the endometrial cavity is small with a reduced intercornual distance (<2 cm) [21]. Before corrective surgery of vaginal canalization defect a transrectal US should be performed to obtain information on all pelvic organs.

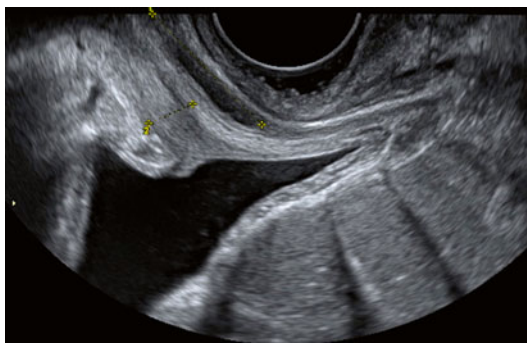


Fig. 6.1 Transrectal US with TVS probe imaging of a uterine agenesis with vaginal agenesis of the *upper vaginal* part: *1*+ ----+ normal hypoechoic lower vaginal tract with hyperechoic upper fibrotic agenetic tract. *2*+----+ uretra

Complete agenesis and hypoplasia without functioning endometrium could be observed in puberty with primary amenorrhea. Secondary sexual characteristics are present, which reflects the normal ovarian function with normal ovaries that can be seen during transrectal, transvaginal or transabdominal US. Primary amenorrhea with severe cyclic pelvic pain may reflect isolated vaginal agenesis and the presence of a uterus with functional endometrium secondary obstructed, resulting in hematometra. Hematometra appearance by ultrasound looks like a cystic structure containing dense fluid with ground-glass appearance (blood).

SHG has no role in the evaluation of müllerian agenesis and hypoplasia.

Hemi-uterus (ESHRE/ESGE Class U4) or Former AFS Unicornuate Uterus (AFS Class II)

On 2D TVS and TAS images, an isolated unicornuate uterus appears as a normal or slightly smaller than normal uterus and the characteristically asymmetric ellipsoidal shape is very difficult to be seen [22]. It can be suspected by an extremely laterodeviation of the uterus, an endometrial stripe in transverse section with circle shape and the visualization of only one intramural tubal part (Figs. 6.2 and 6.3a, b). A rudimentary horn in the presence of a small uterus could confirm the diagnosis. If a coronal section can be obtained transabdominally by a half-full bladder technique [23], the unicornuate uterus showed banana shaped endometrial cavity without the

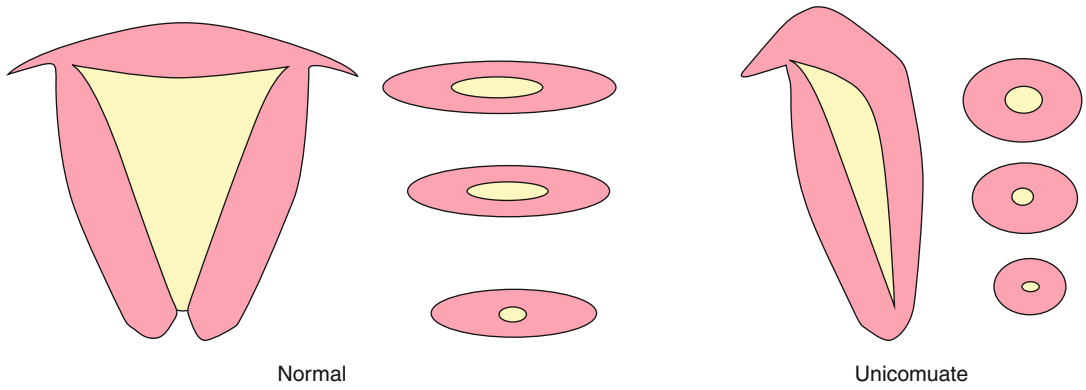


Fig. 6.2 Comparison in a schematic view of a normal and a unicornuate uterus by 2D US. The normal transverse section of the uterus shows a typical ovoidal endometrial stripe, whereas in the unicornuate uterus the endometrial stripe appears with *circle shape* and only one intramural tubal part is seen. If a coronal section can be obtained transabdominally by a half-full bladder technique (Fedele) or by 3D US the unicornuate uterus showed *banana shaped* endometrial cavity without the usual rounded or straight fundal contour and without the typical appearance of the fundal cavity in transverse section

usual rounded fundal contour and without the triangular appearance of the fundal cavity (Figs. 6.2 and 6.3a, b).

Unicornuate uterus could be associated with variable degrees of a rudimentary uterine horn. TVS can see a non-cavitary rudimentary horn without associate endometrium as a round shape myometrial structure near the single uterine corn and may be difficult to differentiate from a uterine peduncolate myoma. In case of rudimentary horn with endometrium a differential diagnosis in communicating or noncommunicating horn must be performed. The communication between the two horns can be evaluated by SHG.

On SHG images, speculum inspection of the cervix demonstrates a small cervix and a poorly developed contralateral vaginal fornix. After instillation of contrast material, the endometrial cavity assumes a fusiform shape, tapering at the apex and draining into a solitary fallopian tube. Filling of a small communicating rudimentary horn may be seen, although SHG cannot clearly delineate noncavitary and noncommunicating rudimentary horns [24].

The diagnosis of unicornuate uterus is usually incidental unless a non communicating rudimentary horn is present. Dysmenorrhea with hematometra may manifest at menarche in this subgroup. Unicornuate uterus is often diagnosed in infertile patients during the diagnostic workup by SHG or hysteroscopy. In addition, the incidence of endometriosis is increased in this subgroup, similar to the case of other uterine anomalies [25].

Renal abnormalities are more commonly associated with unicornuate uterus than with other müllerian duct anomalies and have been reported in 40 % of the patients [26]. The anomaly is always ipsilateral to the rudimentary horn. Renal agenesis is the most commonly reported abnormality, occurring in 67 % of cases. Ectopic kidney, horseshoe kidney, cystic renal dysplasia and duplicated collecting systems have also been described [26]. Therefore the evaluation by TAS is mandatory in these cases.

Complete Bicorporeal Uterus with Double Cervix (ESHRE/ESGE Class U3bC2) or Former AFS Didelphys Uterus (AFS Class III)

Uterus didelphys, which constitutes approximately 5 % of müllerian duct anomalies, is the result of nearly complete failure of fusion of the müllerian ducts. No communication is present between the two endometrial cavities and the two horns. A longitudinal vaginal septum is associated in 75 % of these anomalies

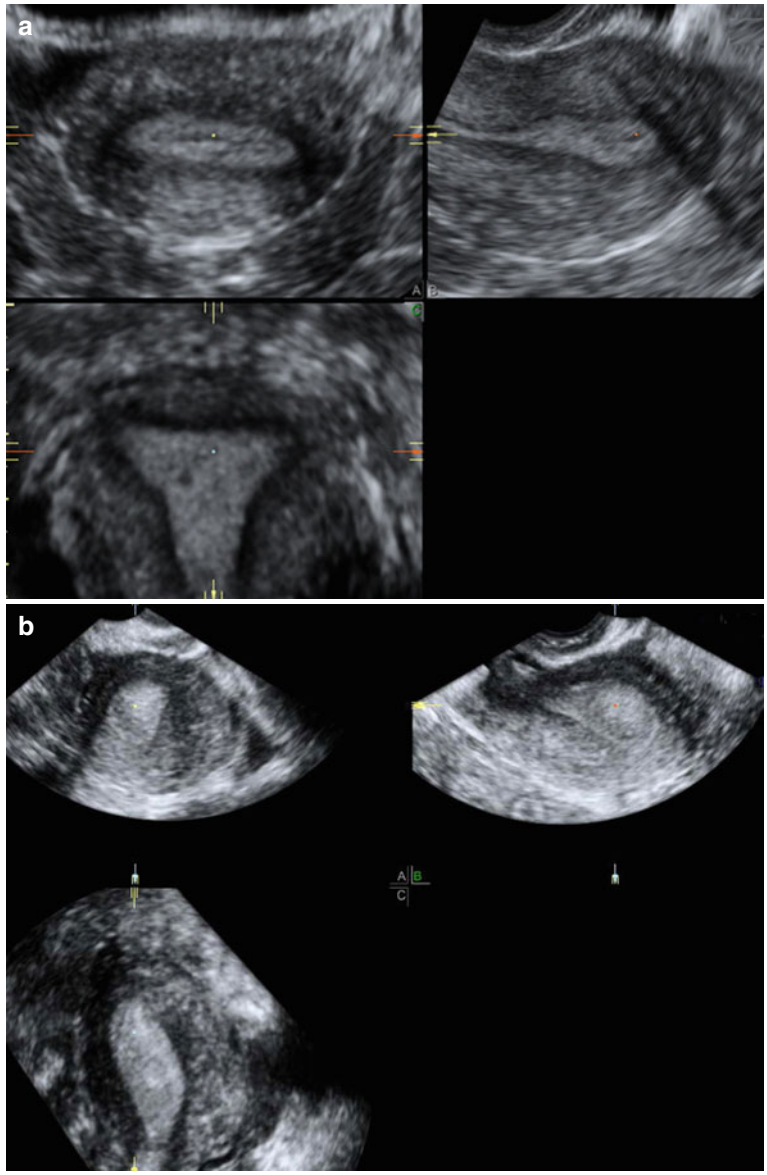


Fig. 6.3 Three planar (**A**) transverse section, (**B**) longitudinal section, (**C**) coronal section view of a normal (**a**) and unicornuate uterus (**b**). Note the *round shaped* endometrial stripe in the transverse section (**A**) of the unicornuate uterus (**b**) compared to the normal uterus (**a**). The coronal views (**C**) show also different morphologies (*banana shapeded*) in the unicornuate uterus (**b**) and fundal triangular in the normal uterus (**a**), where as the longitudinal sections (**B**) are quite similar

[27]. In this type of anomaly, two separate normal-sized uteri and cervices are observed. A vaginal septum may be difficult to visualize by 2D US.

On TA US images, two separate divergent uterine horns are identified, with a large fundal cleft (Figs. 6.4a, b and 6.5).

On TVS US two separate horns can be easily identify on the transverse section (Fig. 6.6). On the longitudinal section two endometrial cavities are seen uniformly separate, with no evidence of communication. The two uterine horns are usually widely displayed and endometrial and myometrial zonal widths are preserved. Two separate

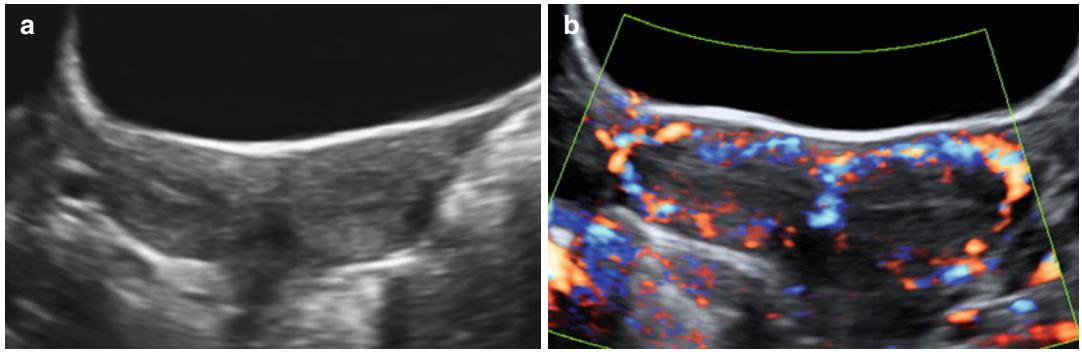


Fig. 6.4 TAS images of a dydelphus uterus in transverse section: (**a**) two separate uterine horns are seen (**b**) Color Doppler shows a typical uterine vascularization in each horn, arcuate and radial vessels in the myometrium around the endometrial layer

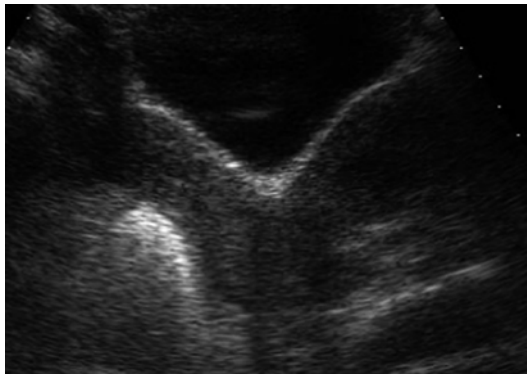


Fig. 6.5 Half full bladder TAS images of a dydelphus uterus, the coronal or frontal view shows two separate divergent uterine horns with a large fundal cleft

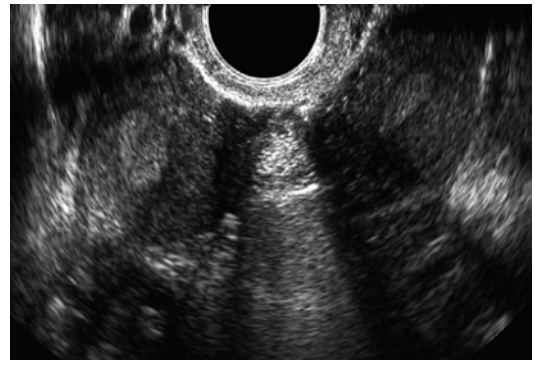


Fig. 6.6 TVS images of a dydelphus uterus, two separate uterine horns are seen transverse section completely separated from each other

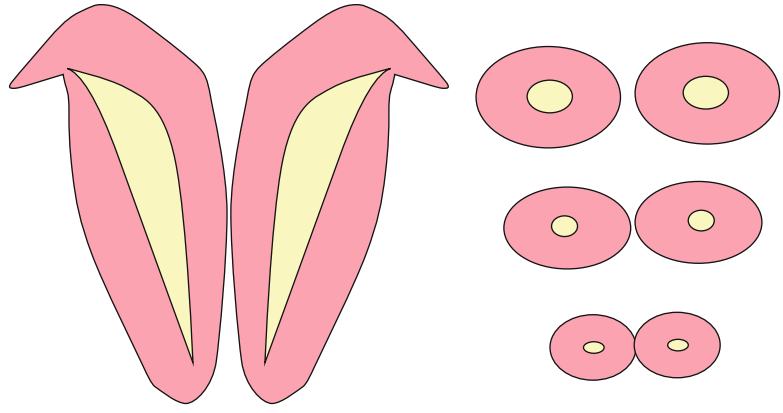


Fig. 6.7 Schematic view of a dydelphus uterus, two completely separate uterine horns are seen in the transverse and frontal planes of the uterus, only the two cervix can appear separated or fused medially together

cervices need to be documented by identifying in transverse section two separate cervical canals and on the longitudinal section two external cervical os (Fig. 6.7). Color Doppler shows a typical uterine vascularization in each horn, arcuate and radial vessels in the myometrium around the endometrial layer (Fig. 6.4a, b).

SHG demonstrates two separate endocervical canal, that open into separate fusiform endometrial cavities, with no communication between

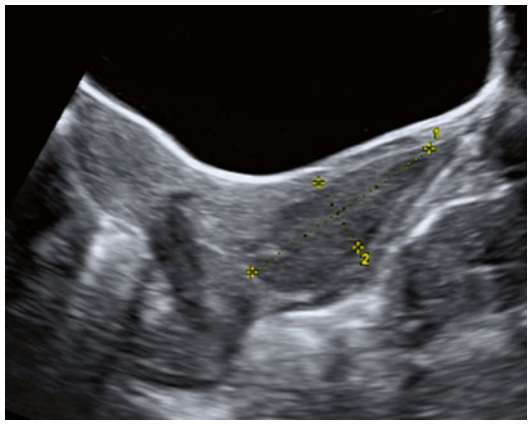


Fig. 6.8 TAS images of a hematocolpo in a young patient with didelphus uterus and an imperforated vaginal septum (Note the hypoechoic, dense fluid (blood) amount below the uterine cervix in the upper part of the vagina (1 longitudinal diameter, 2 anteroposterior diameter of the hematocolpo)

the two horns, the two cervical must be incannulated by two different catheters. However, if the anomaly is associated with an obstructed longitudinal vaginal septum, only one cervical os may be depicted, and it may be cannulated with the endometrial configuration mimicking a unicornuate uterus [28].

Non obstuctive uterus didelphys is usually asymptomatic, while uterus didelphys with unilateral vaginal obstruction may become symptomatic at menarche and manifest as dysmenorrhea. In case of obstructive vaginal septum, hematocolpo and hematometra can be observed on TVS and TAS (Fig. 6.8). Endometriosis and pelvic adhesions have an increased prevalence and are reported to be secondary to retrograde menstrual flow in the subset of patients with obstruction [25].

Bicorporeal Uterus (ESHRE/ESGE Class U3) or Former AFS Bicornuate Uterus (AFS Class IV)

The bicornuate uterus results from incomplete fusion of the uterovaginal horns at the level of the fundus and accounts for approximately 10 % of müllerian duct [13]. A bicornuate uterus consists of two symmetric cornua that are fused caudal with partial communication of the endometrial cavities, most often at the level of the uterine isthmus. The intervening cleft of the complete bicornuate uterus extends to the internal cervical os (bicornuate unicollis) while the cleft of a partial bicornuate configuration is of variable length. A bicornuate bicollis uterus is characterized by a cleft that extends to the external cervical os.

By 2D US, complete bicornuate uterus is very similar to the feature of the didelphus and only the assessment of one uterine isthmic cavity or cervical canal can made the diagnosis. In case of partial bicornuate uterus the length of the cleft between the two horns is important to be evaluated and several variations can be observed with different degree of communication between the two horns. The diagnosis of bicornuate bicollis uterus is very difficult by 2D ultrasound and probably the vaginal examination and hysteroscopy can be useful in evaluating two separate cervix.

In class IV or U3 anomalies, 2D US may demonstrate 2 uterine cavities with normal endometrium (Fig. 6.9a). The most important imaging finding is a concave fundus with a fundal cleft greater than 1 cm [5, 15, 29]. This has been shown to be a reliable means of distinguishing partial bicornuate uteri from septate uteri. 3D US plays actually the most important role in making this diagnosis. The cleft is visualized best on coronal or frontal image of the uterus that can be obtained by 2D TAS and half-full bladder technique (Fig. 6.5) or by 3D US. In case of partial bicornuate uterus on TVS transverse section near the fundus of the uterus, a double endometrial/myometrial view is seen whereas in the middle part of the uterus a double endometrial stripe is detected in one large uterine corpus (Figs. 6.9 and 6.10). On the longitudinal planes, the length of the corpus measured to each horn is greater than the length of the corpus taken through the midline (Fig. 6.10). This indentation between the two horns is much more easier to be detected by 3D US on the uterine coronal section. The cut-off level of this length of the indentation between the two horns to distinguish a partial bicornuate uterus from the septate uterus is 10 mm [15].

It is also important in case of partial bicornuate uterus to evaluate the length of the commu-

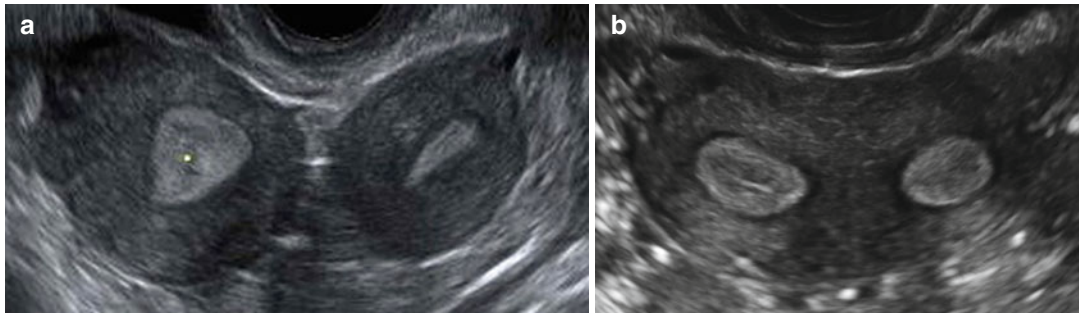


Fig. 6.9 TVS images of a bicornuate uterus (**a**) in comparison to a septate uterus (**b**): two separate uterine horns are seen the transverse section of the bicornuate uterus (**a**) whereas only double endometrial layer without doubling of the myometrium tissue around is seen in the septate uterus (**b**)

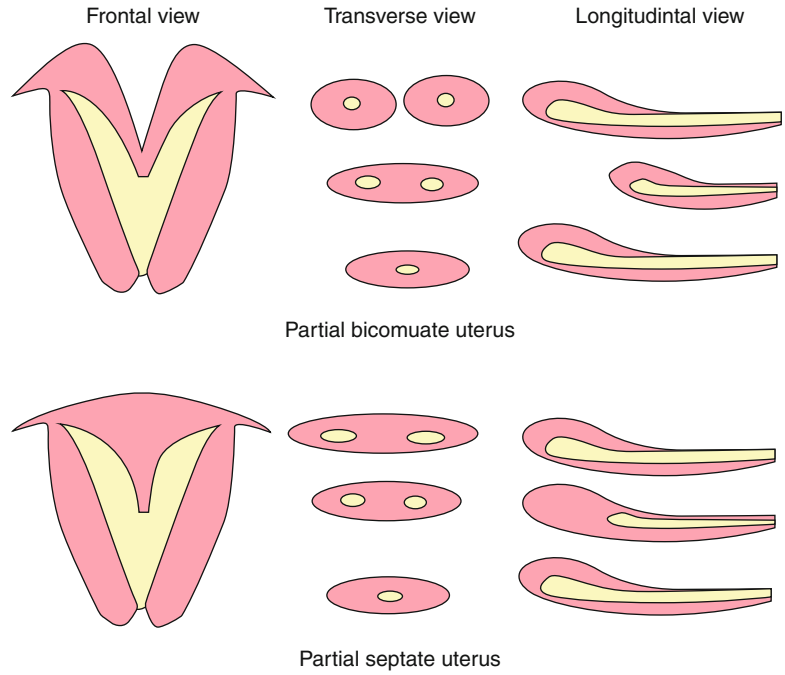


Fig. 6.10 Comparison in a schematic view of a partial bicornuate and a partial septate uterus by 2D US. In case of partial bicornuate uterus on TVS transverse section near the fundus of the uterus, a double endometrial/myometrial view is seen, whereas in the middle part of the uterus a double endometrial stripe is detected in one large uterine corpus. On the longitudinal planes, the length of the corpus measured to each horn is greater than the length of the corpus taken through the midline in case of bicornuate uterus, it is equal in case of septate uterus

nicating cavity and the presence of a partial septate cavity due to the fusion of uterine horns. In fact, in some partial bicornuate uterus, a hysteroscopy metroplasty can be performed in case of cavity with partial septum. It is therefore very important to measure the distance between the fundal indentation and the endometrial cavity. This can be done by 2D ultrasound in a longitudinal section calculating the difference of the distance of the residual myometrial tissue laterally on the horns and centrally at the level of the indentation and the common septum (Figs. 6.10 and 6.11). The septum separating the 2 horns demonstrates echogenicity identical to that of myometrium. The inferior portion of the septum (extending for a variable length inferiorly) may be fibrous [6].

SHG can be useful in evaluating the communication between the cavities. The presence of uterine septum may create some difficulties to perform SHG accurately. In this case, as in the didelphus uterus, the two cervical must be incan-

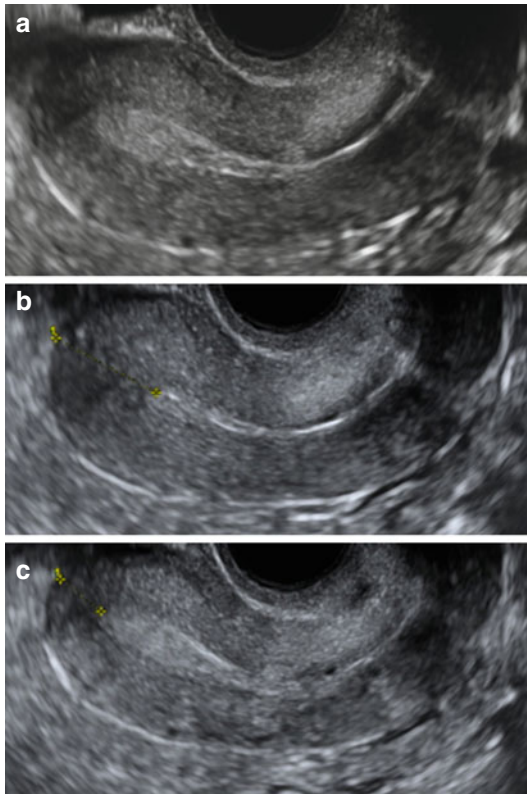


Fig. 6.11 TVS longitudinal view of a septate uterus in three different sections: (**a**) lateral on the left al the level of the tubal angle, (**b**) in the uterine middle at the level of the septum, (**c**) lateral on the right. Note the length of the corpus measured to each horn (diameter 1 in **c**) is equal to the length of the corpus taken through the midline (diameter 1 in **b**). Septum length can be obtained calculating the difference of the distance of the residual myometrial tissue laterally on the horns (**a** or **c**) and centrally at the level of the indentation and the common septum (**b**)

nulated by two different catheters. SHG gives also the opportunity to evaluate intracavitary anomaly such as polyps and fibroids.

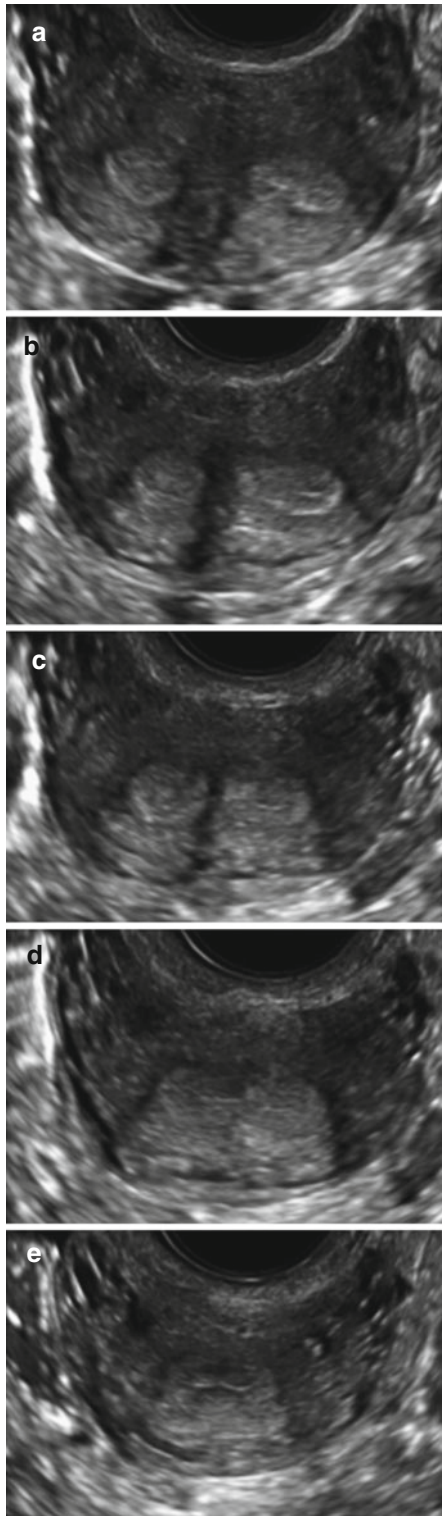
Longitudinal upper vaginal septa are reported to coexist in 25 % of bicornuate uteri. In presence of imperforated septa or vaginal septa a hematocolpo can be observed (Fig. 6.8) [5, 15]. Features such as extreme anteflexion or retroflexion and the presence and deformity caused by overlying leiomyomas made the differential diagnosis extremely difficult.

Septate Uterus (ESHRE/ESGE Class U2 or Former AFS Class V)

The septate uterus composes approximately 55 % of müllerian duct anomalies [30] and results from partial or complete failure of resorption of the utero-vaginal septum after fusion of the paramesonephric ducts.

A septate uterus is considered complete if the septum, which arises in the midline fundus, extends to the internal cervical os, otherwise it is considered partial. A partial septum is variable in length and may be mild or extend proximal to internal cervical os. Extension of the septum to the external cervical os and the upper vagina is seen in approximately 25 % of case [31]. Complete duplication of the cervix can occur and a double os can be detected (bicervical septate uterus). The external uterine contour may be convex, flat or mildly concave [32]. The depth of the fundal indentation is important for differentiation of a septate from a partial bicornuate. A cutoff of 1.0 cm was chosen after subjective evaluation by gynecologists at the time of laparoscopy and, while noted to be arbitrary, has been found to be reliable for differentiation from a bicornuate configuration [15, 33].

At 2D US a septate uterus is suspected when in transverse section double endometrial stripe without doubling of the myometrium tissue is seen (Fig. 6.9a, b). The endometrial cavities are separated at the fundus and, depending on septal length, double endometrial stripe is detected in the middle part of the uterus until the cervical canal (Figs. 6.10 and 6.12). In longitudinal planes, it is important for the diagnosis that the length of the corpus measured to each of the horns is equal or $\leq$10 mm than the length of the corpus taken through the midline (Figs. 6.10, 6.11 and 6.13). The measurement of the serosa-endometrial thickness of the uterus along its fundal border in longitudinal section is used as a diagnostic criterion; in the septate uterus the thickness should increase reaching the midline as the septate becomes apparent (Fig. 6.11) [34].



The external uterine contour must demonstrate a convex, flat or slightly concave configuration and may best be appreciated on transverse images of the uterus or coronal section obtained by TAS half full bladder technique; however, definitive characterization of the fundal contour remains a potential limitation of 2D US. The differentiation of a septate from a partial bicornuate uterus on a true frontal view of the uterus (coronal section) can be obtained only by 3D TVS or MRI. In this plane, the fundal indentation of the external contour can be accurately seen and measured to assess if the uterus is considered to be bicornuate or sepatate (Fig. 6.10). An intercornual distance of less than 4.0 cm has been also proposed to distinguish a septate from a bicornuate uterus [35]. However, this measurement is a residuum of hysterosalpingography (HSG) criteria that were created to compensate the inability of HSG to demonstrate the fundal contour.

The inferior segment of the complete septum is hypoechoic and reflects the caudal fibrous component. Multiple biopsies demonstrated increased amounts of muscular tissue and less connective tissue are present in the upper segment of septum [36]. Transvaginal color Doppler obtains information on vascularity of the septal region which may be important to distinguish the more vascularized myometrial component of the septum from the less vascularized fibrotic part and could be useful in determining treatment options (Fig. 6.14a, b).

SHG of a septate uterus can be used to evaluate the size and extent of septa [28] especially in case of thin endometrial stripe or in the presence of leiomyomas or adenomyosis within the septum causing secondary distortion of cavity. However, the diagnostic accuracy of SHG alone is low for differentiation of septate from bicornu-

Fig. 6.12 TVS transverse view of a septate uterus in 6 different sections of the uterus. Note the double endometrial layer at the uterine fundal (**a**), corpus (**b**, **c**) and isthmic level (**d**) and the single endometrial stripe at the internal cervical os (**e**) level

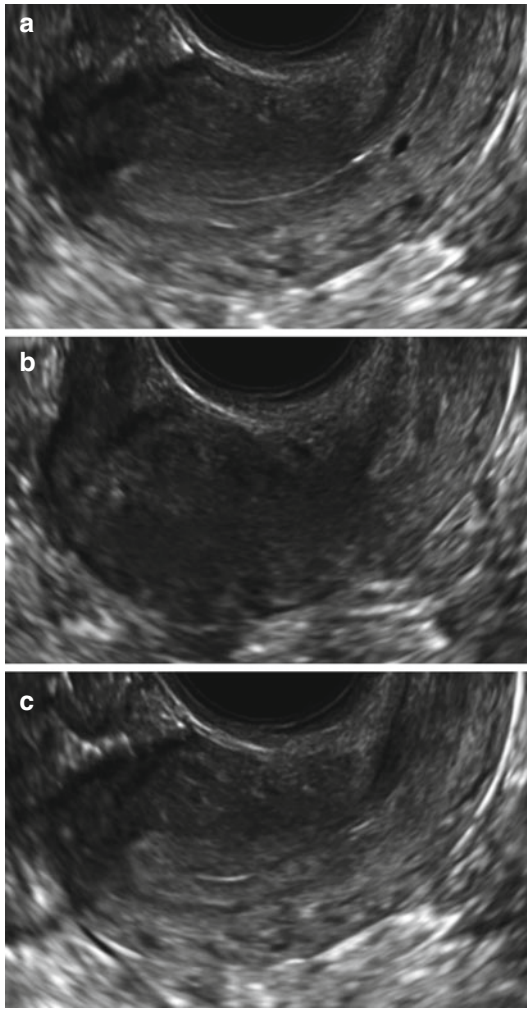


Fig. 6.13 TVS longitudinal view of a complete septate uterus in three different sections (**a**) lateral on the left; (**b**) in the uterine middle at the level of the septum note the total absence of the endometrial stripe, only the cervical canal is seen; (**c**) lateral on the right two separate uterine horns

ate uteri [37]. SHG gives also the opportunity to evaluate intracavitary anomaly such as polyps and fibroids (Figs. 6.15 and 6.16).

Arcuate Uterus (AFS Class VI)

The arcuate uterus is characterized by a mild indentation of the endometrium at the uterine fundus as a result of near complete resorption of the utero-vaginal septum. Classification has been problematic, because it remains unclear whether this variant should be classified as a true anomaly or as an anatomic variant of normal.

In the original Buttram and Gibbons classification, the arcuate uterus was subclassified with the bicornuate uterus because it "most closely resembled a 'mild' form of bicornuate uterus" [38]. On revision of the classification by AFS, a separate class was designated, because the arcuate uterus can be distinguished from a bicornuate uterus on the basis of its complete fundal unification [21]. Finally in the last ESHRE/ESGE classification arcuate uterus is no more considered as a distinct uterine congenital anomalies and some previous classified arcuate uterus are classified as septate uterus (U2 class) and others as normal or dysmorphic uterus (U0/U1 class).

On 2D US images, a normal external uterine contour is noted, with a broad smooth indentation on the fundal segment of the endometrium. The indentation may be best appreciated in the transverse plane with subtle, focal, superior duplication of the endometrial echogenic complexes. No division of the uterine horns is noted

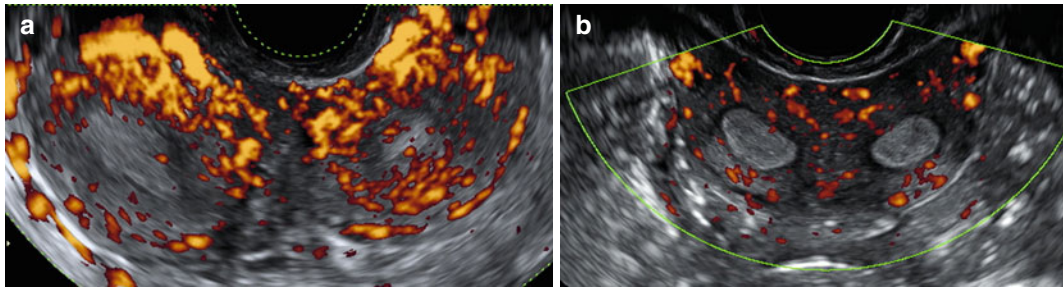


Fig. 6.14 Power Doppler TVS images of a septate uterus (**a**) in comparison to a bicornuate uterus (**b**). Note the typical vessel distribution in the myometrium of the bicornuate uterus around the endometrial layer (**b**) and the irregular vascularity between the two-endometrial stripes in case of septate uterus (**a**)

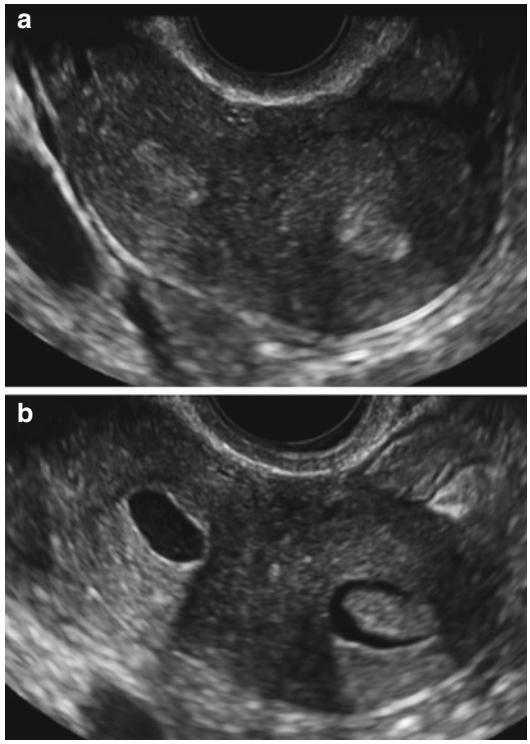


Fig. 6.15 SHG of a septate uterus: (**a**) transverse section of a septate uterus (**b**) the same transverse section after saline injection in the uterine cavity, note the presence of an endometrial polyp in the left horn, that can be missed at only 2D scan

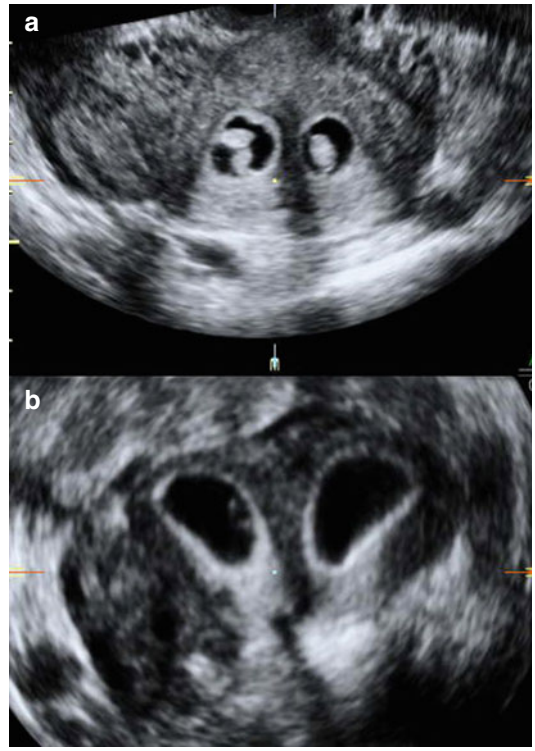
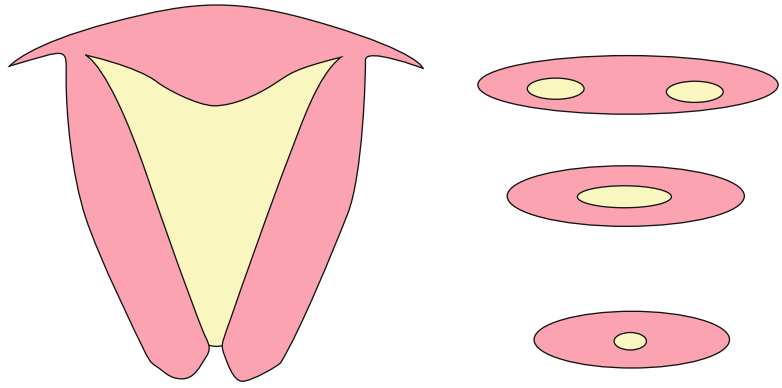


Fig. 6.16 SHG of a septate uterus can be used to evaluate better the size and the presence of polyps: (**a**) transverse section of a septate uterus with polyps at the isthmic level (**b**) coronal view of the two cavities during saline infusion note the better visualization of the septal myometrial tissue

Fig. 6.17 Schematic view of an arcuate uterus note the fundal transverse section very similar to this of the septate uterus of at fundal level (Fig. 6.10)



[5] (Figs. 6.17 and 6.18). For 2D TVS diagnosis of arcuate uterus, in transverse section double endometrial without doubling of the myometrium through the distal part of the uterus and a single endometrial stripe through the middle part of the uterus is detected (Figs. 6.17 and 6.18); In longitudinal planes, the length of the corpus measured to each of the horns is ≤10 mm longer than the length of the corpus taken through the midline. The differential diagnosis in 2D US of an arcuate uterus from a subseptate uterus in very difficult. The lateral parts of the uterine cavity

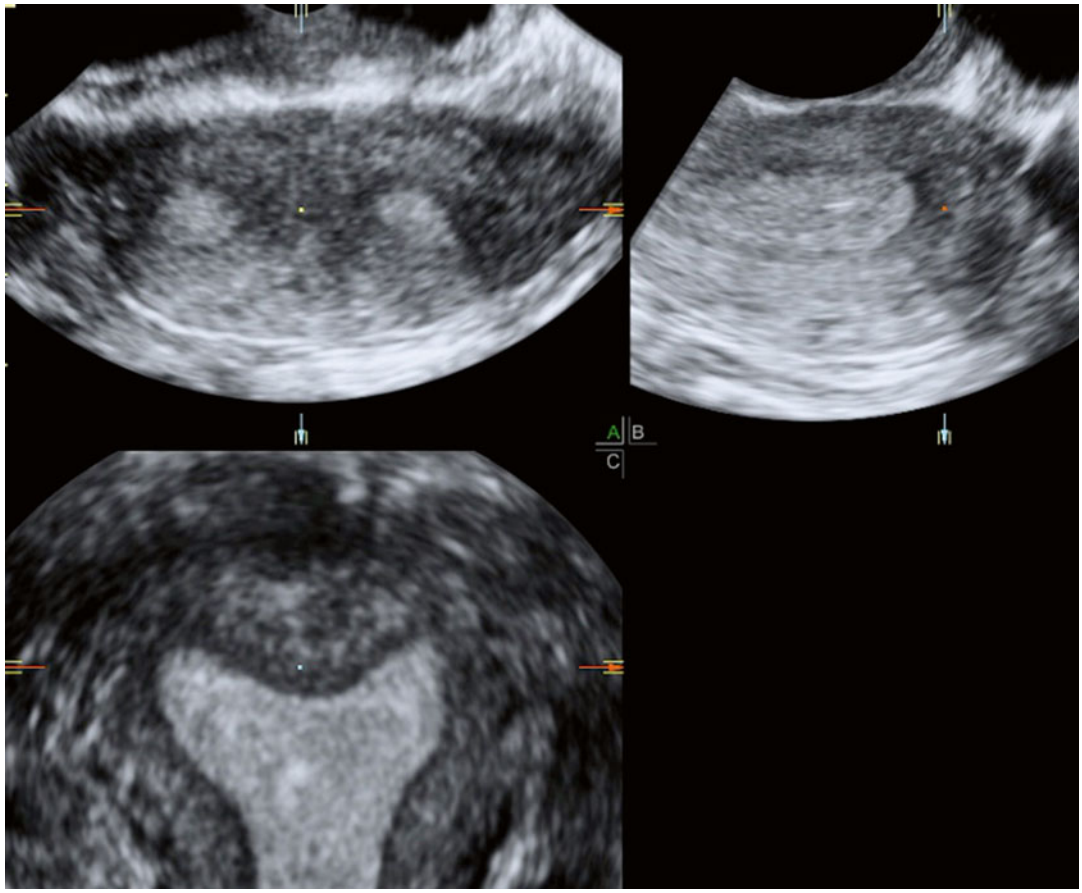


Fig. 6.18 Three planar view (**A** = transverse, **B** = longitudinal and **C** = coronal) view of an arcuate uterus, note how the transverse section (**A**) at fundal level is very similar to this of the septate uterus

close to the tubal origin often gave a false impression of an arcuate uterus. In both cases, a division of endometrial echo in the lateral uppermost part of the uterine cavity was seen. However, due to the inability to obtain frontal (coronal) sections of the uterine fundus, the distinction between a normal, septate and an arcuate uterus is often impossible on conventional 2D US. The 2D US evaluation and measuring are very similar to these of the septate uterus however a larger intercornual distance and shorter internal indentation (or septal length) are observed.

On SHG images, opacification of the endometrial cavity demonstrates a single uterine canal with a broad saddle-shaped indentation of the uterine fundus [5].

Other Types

Other uterine corpus anomalies include a small hypoplastic uterus, constriction bands, a widened lower uterine segment, and a narrowed fundal segment of the endometrial canal, irregular endometrial margins and intraluminal filling defects.

A **T-shaped configuration** of the endometrial cavity is the one of these uncommon abnormalities. T-shaped uterus was seen in the past in women exposed to DES [39, 40]. It has been shown that DES interferes with embryologic development of the mesenchyme of the genital tract. Structural anomalies of the uterine corpus, cervix and vagina were subsequently described [41]. T-shaped uterine cavities are observed now

also in not exposed DES patients and are associated to infertility, recurrent spontaneous miscarriages, premature deliveries and other pregnancy complication. A clearly definition of this T-shaped configuration is actually not present. It seems that not only the large and flat fundal cavity but also the tubular middle and isthmic part of the uterus needs a better definition to classify this uterine type (cut off for the thickness of the tubular part, of the lateral myometrial walls, and of the fundal myometrium are not defined). The classic T configuration is often extremely difficult to characterize by 2D US but is well seen on 3D coronal section of the uterus. On 2D US findings in case of T-shaped uterus can be nonspecific and definitive diagnosis may not be possible. 2D TVS could reveal a larger transverse section and an endometrial cavity length as well as endometrial thickness, notable smaller than normal in the middle part of the uterus. Cervical length is also markedly shorter [42].

Constriction bands are often seen at the midfundal segment, causing narrowing of interstitial segments of the fallopian tubes. In addition, Doppler US studies have shown in these anomalies an increased uterine artery pulsatility index, which reflects reduced uterine perfusion [43].

2D US rarely can detect anomalies of the fallopian tube such as sacculations and fimbrial deformities with fimbrial stenosis [44]. Also cervical anomalies such as hypoplasia, anterior cervical ridge, cervical collar and pseudopolyps [39] can not be accurately diagnosed. On 2D SHG images, cervical hypoplasia and cervical stenosis may make cannula insertion into the endocervical canal difficult.

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3D Ultrasound (3D US)

7

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Introduction

The first studies on 3D ultrasound in the diagnosis of congenital Müllerian anomalies were performed more than a decade ago, and the accuracy of 3D ultrasound imaging of uterine morphology has been demonstrated [4, 5, 8, 10, 13].

Magnetic resonance imaging (MRI) and 3D ultrasound are both non-invasive techniques and both perform equally well for uterine imaging [1, 3]. Associated renal anomalies can be detected with abdominal ultrasound as with MRI.

3D ultrasound has the advantages that it is readily available in centres dedicated to women's health such as gynaecological or fertility units and that abdominal as well as vaginal scanning are well known and accepted by women. 3D ultrasound volumes can be stored and manipulated later or elsewhere and an infinite number of sections through any plane in the volume can be obtained. From an economical point of view, MRI is the more expensive test.

3D ultrasound imaging has limitations. Children cannot be scanned by a vaginal approach nor can women with vaginal atresia. An abdominal ultrasound may be limited in those cases too due to e.g. the impossibility to obtain sufficient bladder filling, abdominal scarring or adiposity. Complex anomalies may prove particularly challenging. Although 3D ultrasound is the first line diagnostic test for congenital uterine anomalies, additional imaging with MRI and/or invasive tests such as laparoscopy or hysteroscopy may be useful or necessary to come to an accurate diagnosis.

3D Ultrasound in the Diagnosis of Female Genital Anomalies

Ultrasound examination of female genital organs may benefit from a full bladder in case of an abdominal approach whereas for a vaginal scan, a full bladder may push the uterus up and out of the field of vision.

3D ultrasound differs from 2D ultrasound in the use of a 3D probe and software only. 3D ultrasound evaluation of the female genital tract starts off with a standard 2D evaluation and these 2D images are obtained with the 3D probe in standard mode. A poor 2D image because of e.g. abdominal scarring, adipose tissue or bowel

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gasses for an abdominal approach or because of a pelvic mass or bowel gasses for a vaginal approach will result in a poor quality 3D volume.

A female genital anomaly may be detected on 2D imaging. 2D ultrasound only may be diagnostic in case of a major anomaly such as uterine agenesis, classified in class U5 b (aplasia) in the ESHRE/ESGE 2013 consensus classification (further referred to as ESHRE/ESGE) [6]. 2D ultrasound may show a hematocolpos secondary to an obstruction to menstrual flow in case of a transverse vaginal septum, ESHRE/ESGE class U0C0V3 or 2 hemicorpora with cervical agenesis (ESHRE/ESGE U3bC4) (Fig. 7.1).

However, for an accurate evaluation of the much more prevalent but less severe distortions of uterine morphology within the context of congenital malformations, a coronal image of the uterus perpendicular to its long axis is required. The reference image comprises the outer and inner contour of the fundal myometrium and the beginning of the interstitial portion of the Fallopian tubes (Fig. 7.2). Ultrasound imaging is based upon reflection of high frequency sound waves at interfaces between tissues with different characteristics and a distinct endometrial line is necessary to delineate the uterine cavity from the myometrium. The quality of the ultrasound image will be optimal if the endometrium is thick, thus in the secretory or late proliferative phase of the menstrual cycle [2] (Fig. 7.3). If the endometrial echo is not distinct enough, sonohysterography, also called fluid instillation sonography or FIS, will enhance contrast so that the uterine cavity becomes clearly delineated. Saline or gel are negative ultrasound contrast agents, while gel foam containing micro-air bubbles acts as a positive ultrasound contrast agent [11] (Fig. 7.4). Sonohysterography implicates a speculum examination and insertion of a catheter through or in the

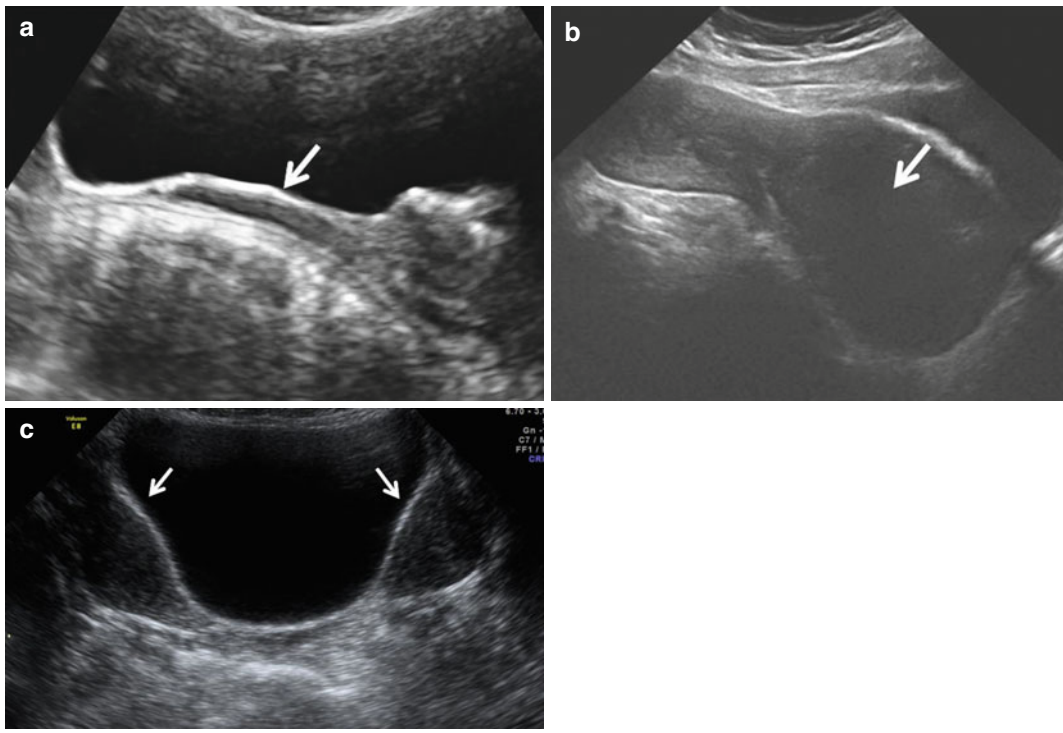


Fig. 7.1 Abdominal 2D ultrasound: (**a**) uterine agenesis: ESHRE/ESGE U5b C4 aplasia: vagina (*white arrow*), absent cervix and uterine body. (**b**) Transverse vaginal septum/imperforate hymen: ESHRE/ESGE U0 C0 V3: dilated proximal vagina (*white arrow*). (**c**) complete bicorporeal uterus and cervical aplasia: ESHRE/ESGE U3b C4: hemicorpora (*white arrow*)

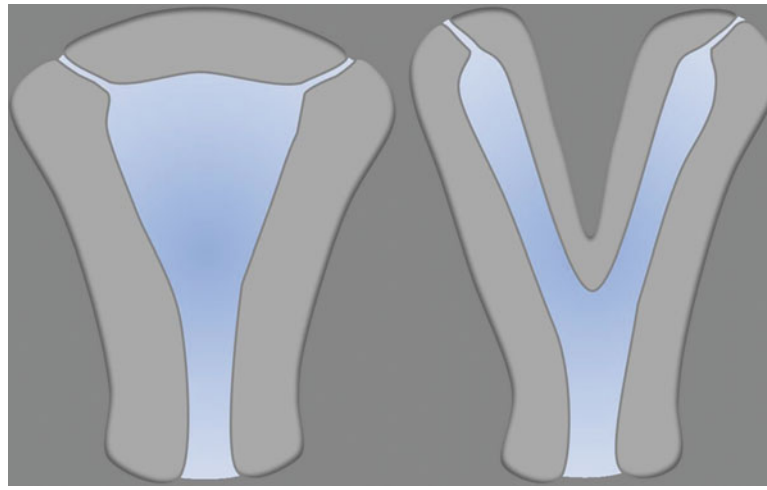


Fig. 7.2 Reference plane for uterine morphology assessment

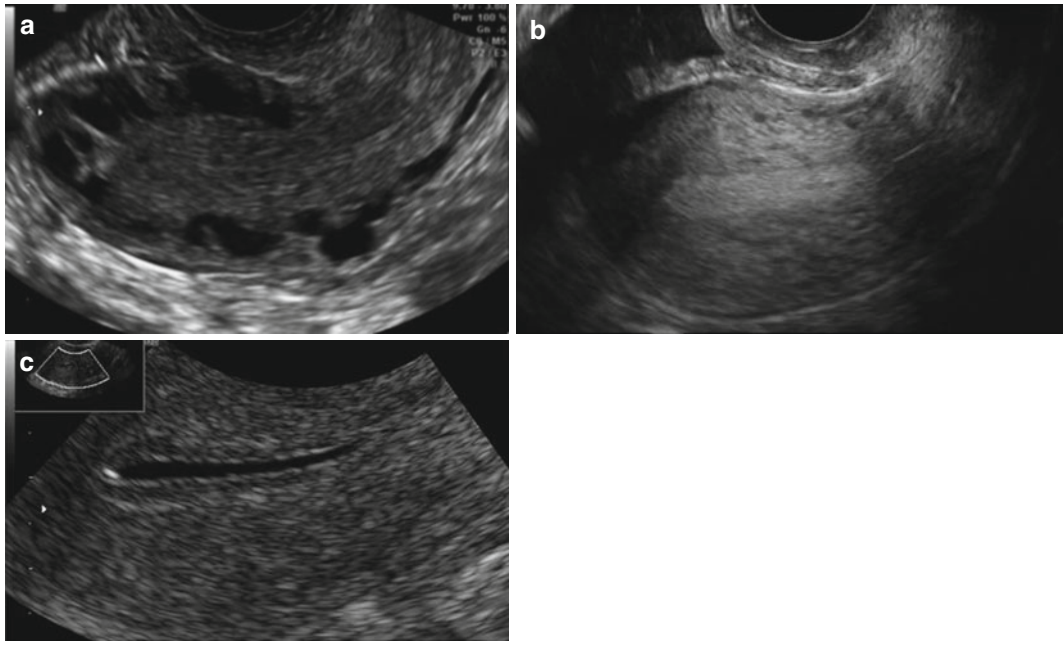


Fig. 7.3 The endometrial line needs to be visible for optimal ultrasound imaging. 2D sagittal image of the uterus: (**a**) the endometrium is not visible. (**b**) a well-defined endometrium. (**c**) contrast enhancement by fluid instilled in the uterine cavity

cervical canal and causes more discomfort compared to a vaginal ultrasound examination only [12]. Sonohysterography isn't an option if a vaginal approach is not possible or if the woman doesn't consent to.

Ultrasound imaging implies cross sections through the uterine cavity and cervical canal as well as through the endometrium, myometrium and cervical wall whereas the outline of the uterus should be visible too. Any change of

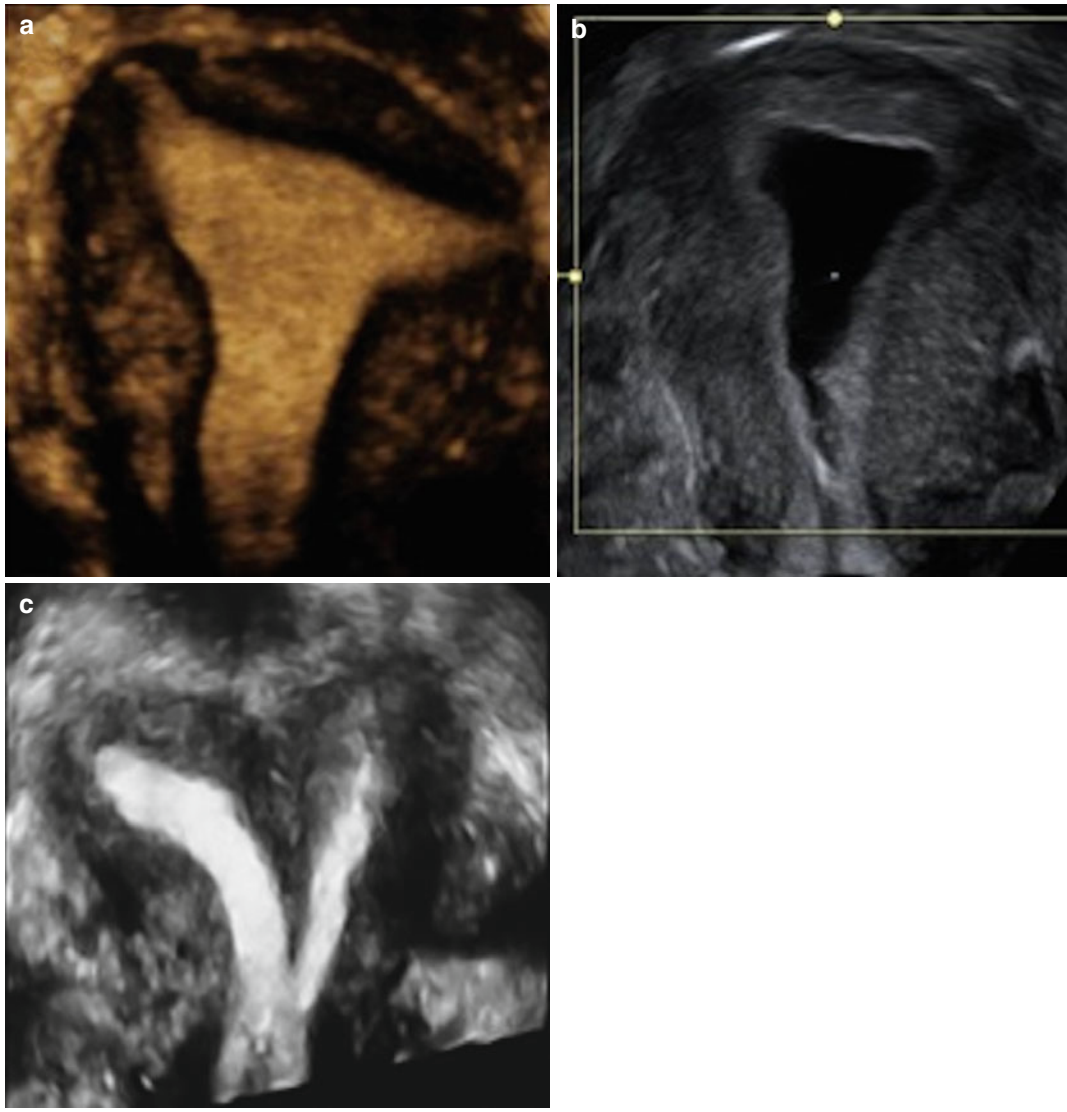


Fig. 7.4 Coronal image showing the outer uterine contour, the fundal outline of the cavity, the thickness of the fundal myometrium and the beginning of the interstitial segments of the Fallopian tubes. (**a**) Unenhanced rendered image. (**b**) Negative contrast enhancement by instilling gel or saline. (**c**) Positive contrast enhancement by instilling fluid containing small air bubbles (gel foam)

morphology is to be detected and the underlying cause should be elucidated too: e.g. a fibroid may distort the cavity and/or the uterine contour, an intracavitary structure may be a fibroid or a polyp, and a bulging wall may be due to adenomyosis (Fig. 7.5). A congenital anomaly can be evidenced too. To evaluate the more minor congenital uterine anomalies with 2D ultrasound, success in obtaining the reference image by an abdominal or by a vaginal approach, depends on the position of the uterus (Fig. 7.6). Transverse 2D images of the uterus can usually be obtained and an interrupted endometrial or cervical echo may be indicative of a fusion or a resorption anomaly. But these transverse images do not allow for a detailed evaluation of the degree of altered morphology (Fig. 7.7). With 3D ultrasound technology, the volume can be

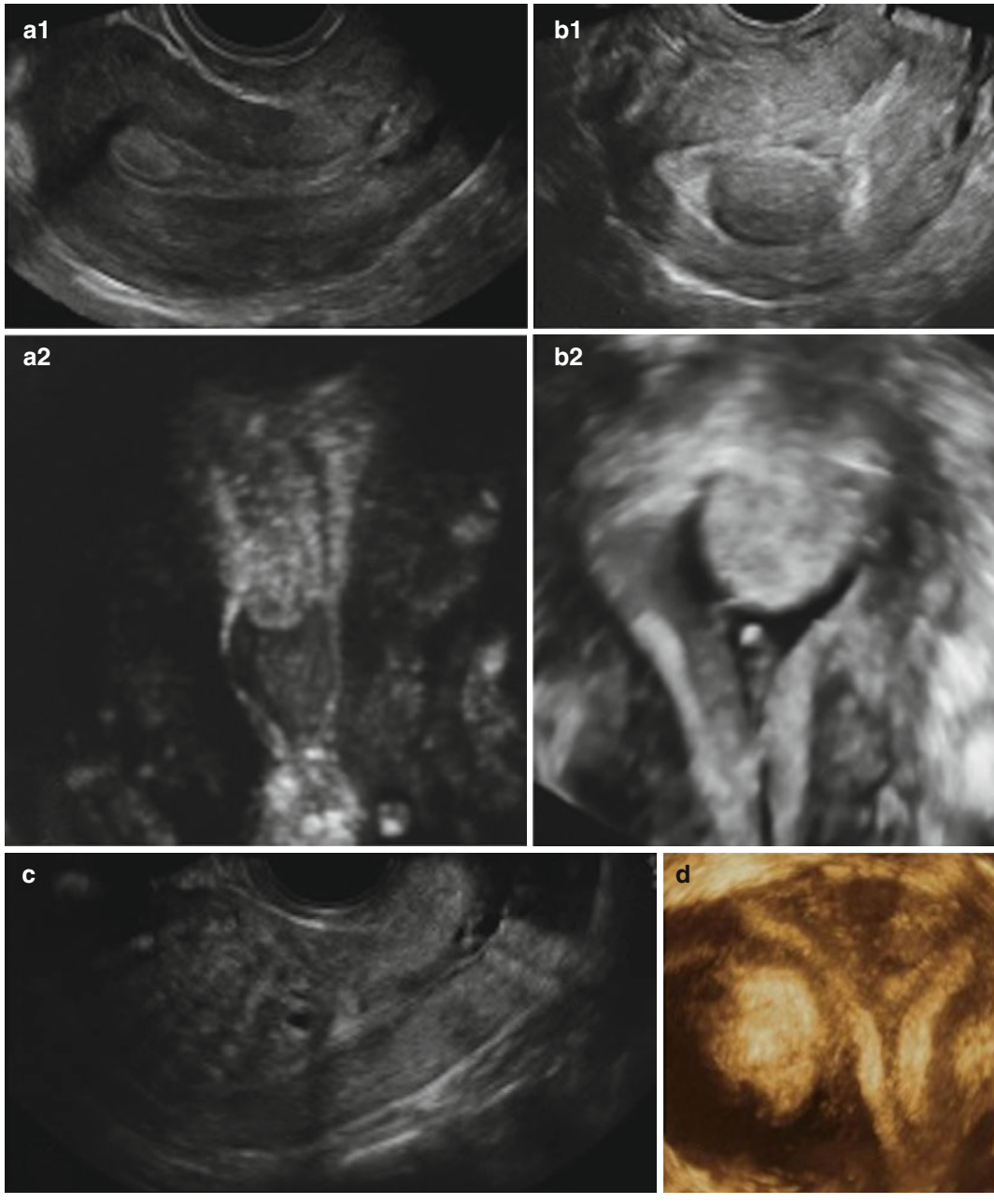


Fig. 7.5 Ultrasound provides additional information on changes in uterine morphology. (**a**) endometrial polyp, polyp, (**a1**) 2D, (**a2**) 3D-FIS. (**b**) intracavitary fibroid, (**b1**) 2D, (**b2**) 3D-FIS. (**c**) adenomyosis in the anterior myometrial wall (2D). (**d**) intramural fibroid and ESRE/ESGE U2b C2: complete septate uterus and cervical septum (3D)

manipulated and any section through the volume can be made. The reference image can be obtained, irrespective of the position of the uterus in the acquired volume (Fig. 7.8). This explains why 3D imaging is essential for an accurate evaluation of the majority of congenital uterine and

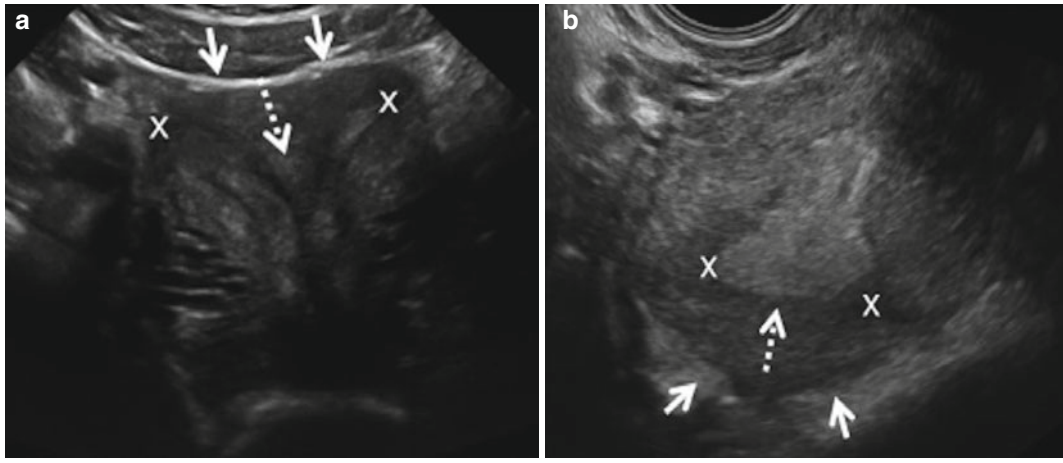


Fig. 7.6 2D coronal image of the uterus: (**a**) transabdominal image: ESHRE/ESGE U2b, complete septate. (**b**) Transvaginal image: retroverted uterus, ESHRE/ESGE U0, normal. *Full arrow*: external fundal contour. *Dotted arrow*: indentation (**a**), fundal outline of the cavity (**b**). *X* beginning of the Fallopian tubes

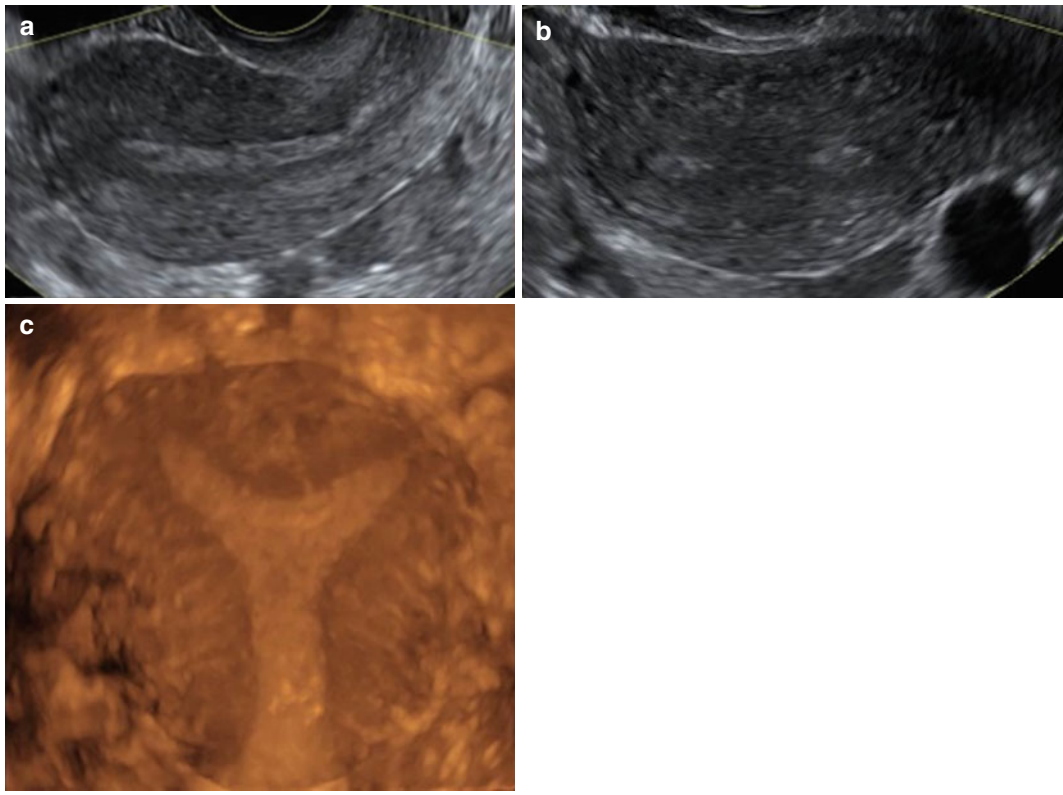


Fig. 7.7 Transverse 2D ultrasound does not allow for accurate assessment of the fundal myometrium. (**a**) Sagittal 2D image. (**b**) Transverse 2D image: an interrupted endometrial line is visible despite the poor contrast due to a thin endometrial line. (**c**) 3D coronal rendered image: ESHRE/ESGE classification: the indentation is >50 % of the thickness of the fundal myometrium: U2a C0 partial septate (AFS classification: arcuate uterus)

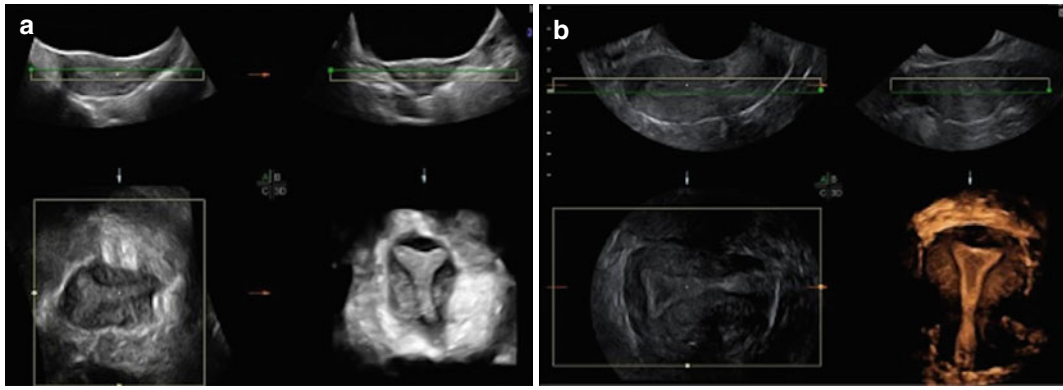


Fig. 7.8 3D sectional planes and rendered image of a normal uterus ESHRE/ESGE U0 C0. (**a**) abdominal ultrasound. (**b**) vaginal ultrasound

cervical anomalies by ultrasound. An important added value of 3D ultrasound is that a volume can be stored and exported allowing for reassessment, discussion and use in training programs. Contrary to 2D ultrasound, laparoscopy or hysteroscopy where one is restricted to the still images or videos taken at the moment of the examination, volume manipulation during off-line analysis allows for an infinite number of additional sections and information.

How to Obtain the Reference 3D Image for the Evaluation of Uterine Morphology

After having performed a standard 2D evaluation, a 3D volume of the uterus is to be made (Fig. 7.9). The ultrasound probe is hold fixed on a 2D midsagittal or transverse image of the uterus. Especially in case of a wide uterine fundus or an abnormal uterine axis, it may be preferable to start from a transverse image of the uterine fundus (Fig. 7.10). The volume box outline (region of interest) appears on the screen when the 3D button has been activated and the size of the box as well as the sweep angle (usually between 90° and 120°) have to be adjusted so that the volume will include the uterus in full, including the fundal outline. The time of acquisition can be adapted too. A slower acquisition takes more time but results in an better spatial resolution. To evaluate the cervix, one can opt for a separate volume. The quality of the 3D images will be better if this volume is obtained after having enlarged the 2D image so that the region of interest box includes the cervix only (Fig. 7.11). The ultrasound probe is to be hold motionlessly during actual volume capture. It is instructive to pay attention to the sequence of consecutive 2D images of the A plane appearing on the screen during volume acquisition as this gives a first impression of the content of the resulting volume. Once the volume has been obtained, it can be manipulated at once or stored for off-line analysis later and/or elsewhere. Colour Doppler information can be stored during volume acquisition too.

The volume can be studied in different ways, depending on the 3D software available. The "sectional planes" mode depicts three orthogonal planes (A, B, C). If a longitudinal section of the uterus is shown in the A plane and a transverse section of the uterus in the B plane, a coronal uterine cross section is seen in the C plane. If the reference line is on the endometrium in A and B, a mid-coronal image of the uterine cavity is depicted in the C plane. The rendering mode produces a "thick sliced" image and the thickness of it can be adapted. Software may allow adjusting the section plane by curving or tracing the reference line so that it remains central on the endometrium and the cervical canal (Figs. 7.12 and 7.13). The reference image for evaluating

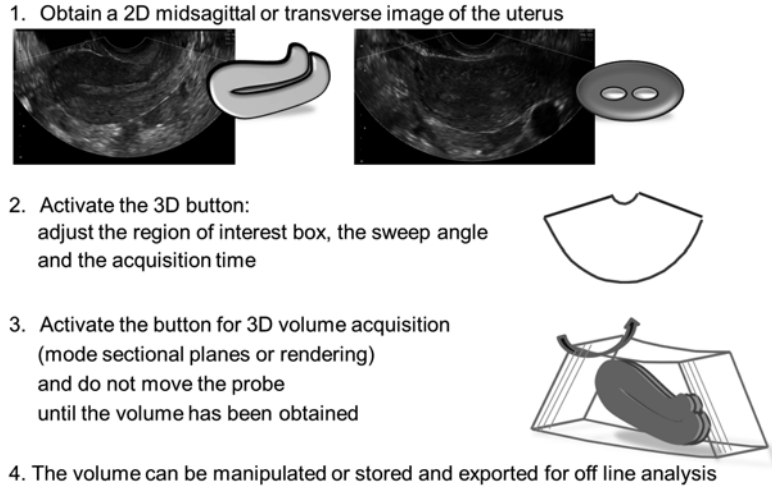


Fig. 7.9 How to obtain a 3D volume of the uterus

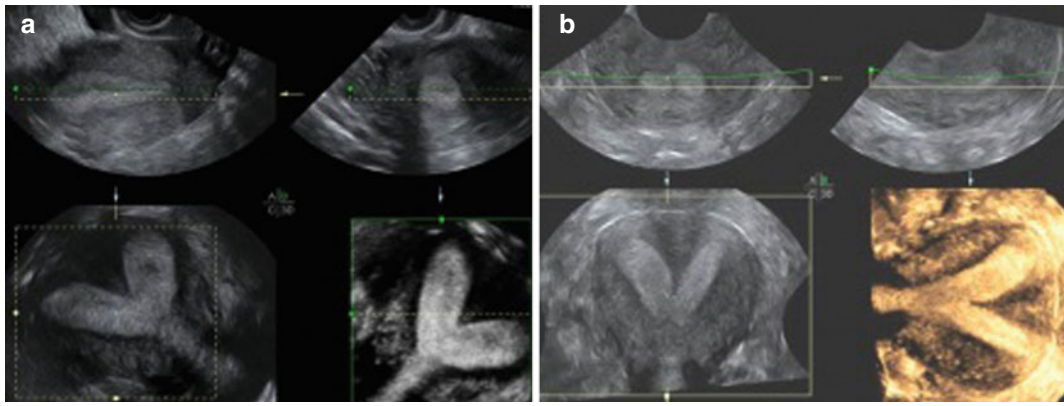


Fig. 7.10 Volume acquisition of ESHRE/ESGE U2a partial septate uterus. (**a**) Starting from a midsagittal image of the uterus. (**b**) Starting from a transverse image of the uterus

uterine morphology in the context of a congenital anomaly is obtained if the image is not only on the central part of endometrium and cervical canal but also mid-coronal through the fundal myometrium. It is wise to manipulate the volume in the sectional planes mode as to ascertain the reference line through the fundal myometrium is perpendicular to the long axis of the uterine cavity and to pay attention to the exact location of the first part of the intramural segment of the Fallopian tube. A rendered image presented without knowledge of the section plane may lead to an inaccurate or erroneous diagnosis. (Fig. 7.14). The fundal outline and fundal indentation may be difficult to assess on a rendered image if the rendering has been done on a thick slice. It may be more informative to rely in this case on a thin mid- coronal image and thus on the C plane of the sectional planes mode.

A volume box that does not include the entire uterus may be misleading too. This stresses the importance of a proper 2D ultrasound evaluation preceding 3D volume acquisition so that the region of interest box and acquisition angle are appropriate and the 3D volume includes the entire uterus. This is even more vital if the volume is intended to be analysed off-line. Information that is not included in the volume

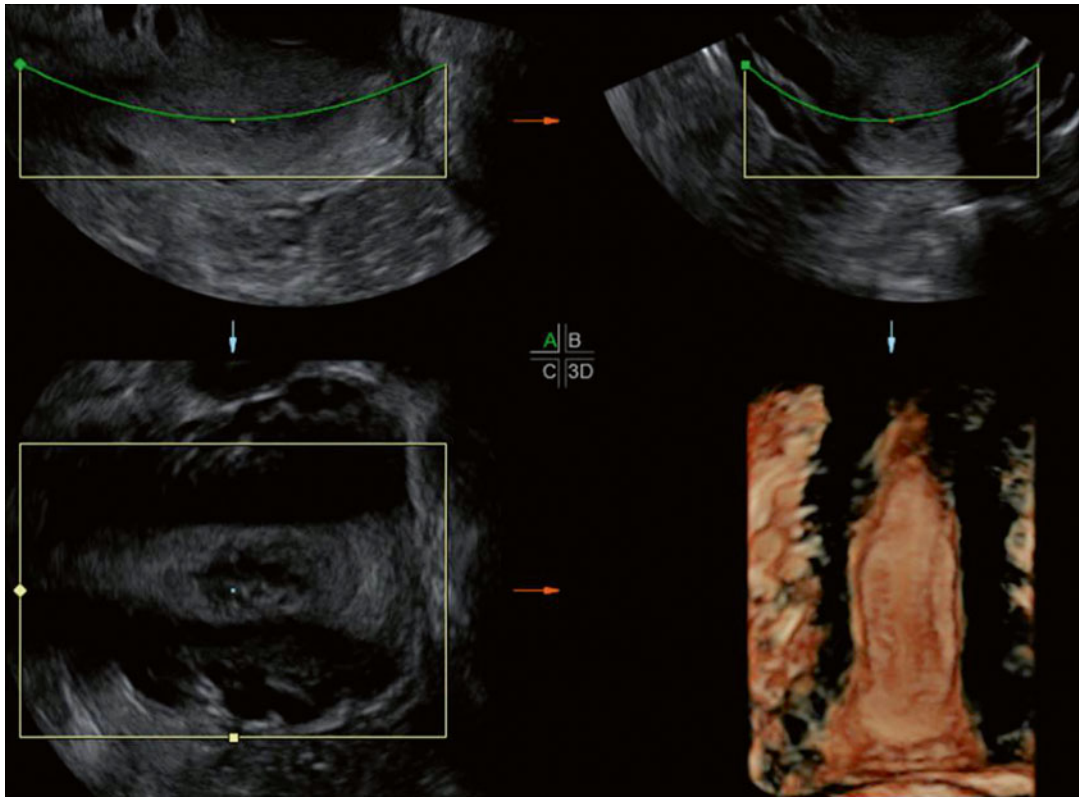


Fig. 7.11 Volume acquisition of the cervix: sectional planes and coronal rendered image of the cervical canal

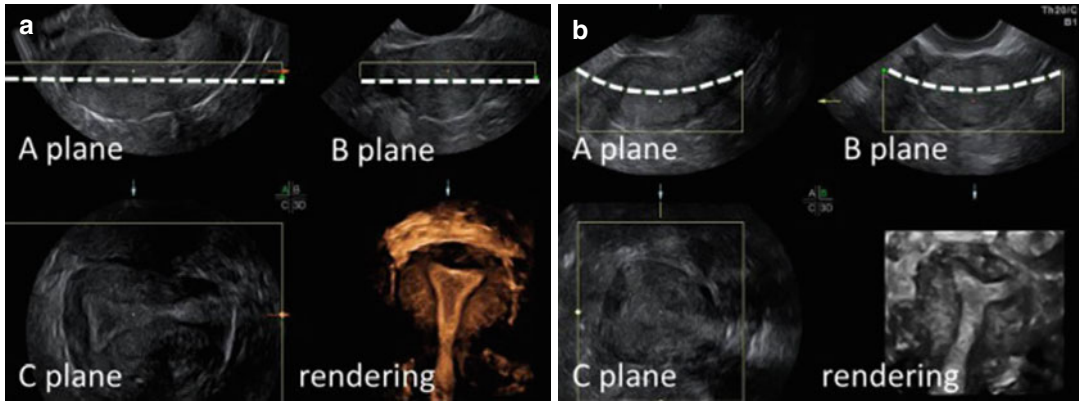


Fig. 7.12 Uterine morphology is assessed on a sectional or rendered image of the mid-coronal plane. The *dotted line* indicates where the volume is "cut" and this image is given in the C plane. The size of the box can be adjusted and its thickness represents the thickness of the slice of the rendered image. (**a**) Adjust the *dotted line* so that it is on the endometrium in the A and B plane. (**b**) If necessary, the *dotted line* can be curved to follow the endometrium

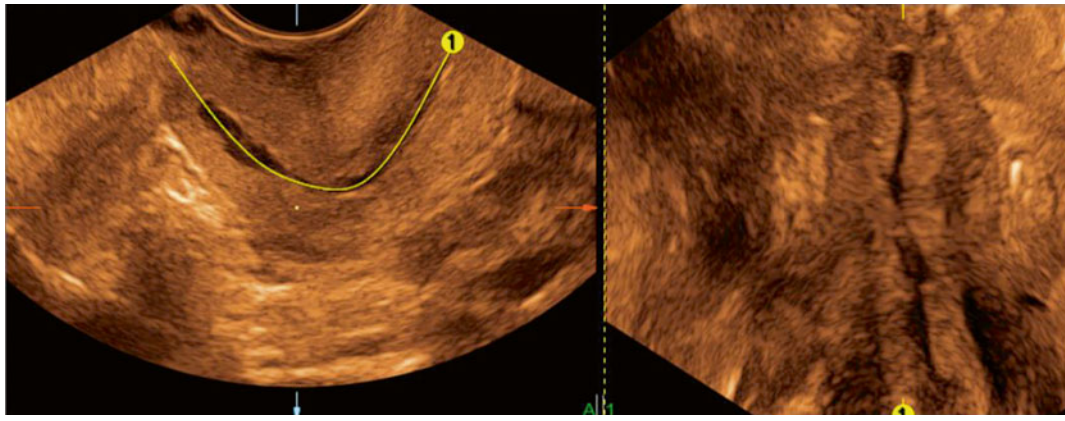


Fig. 7.13 Software may allow tracing the line on the endometrium and cervical canal to obtain the reference image. ESHRE/ESGE Class U1b dysmorphic uterus, infantilis

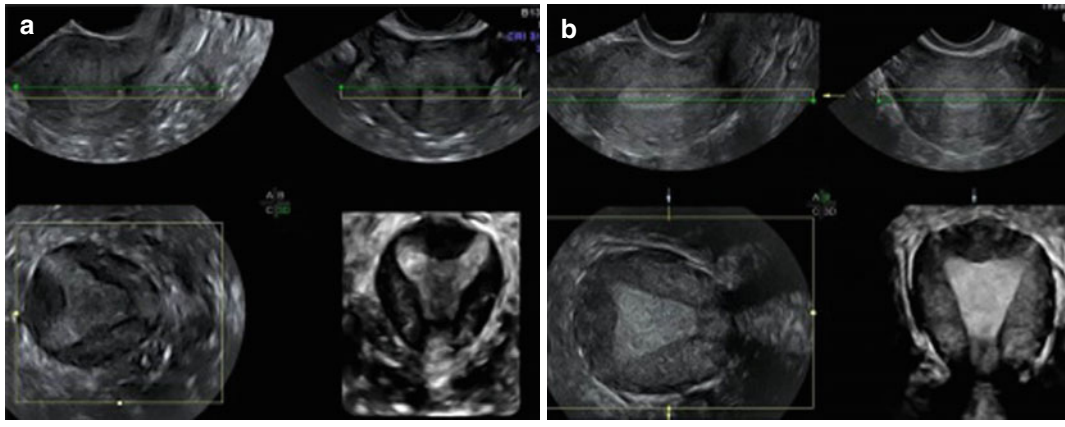


Fig. 7.14 An inaccurate section may result in an erroneous diagnosis. (**a**) The image plane in A is not perpendicular to the long axis of the fundal myometrium. The C plane and the rendered image show an ESHRE/ESGE U2a subseptate uterus but are misleading. (**b**) The image plane in A has been corrected. The images in the C plane and the rendered image are now true coronal images. ESHRE/ESGE U0 C0, normal uterus and cervix

cannot be extracted from it. At best, the patient is to be called in again. Worse, misinterpretation may result in a wrong diagnosis such as a hemiuterus (ESHRE/ESGE class U4) instead of a uterus didelphys (ESHRE/ESGE class U3bC2) (Fig. 7.15). Although not reported in the literature, it is possible that a fundal myometrial contraction may temporarily increase the thickness and the outline of the fundal myometrium and may cause a temporary and usually mild indentation of the uterine cavity. In case of doubt, a repeat scan may be useful.

Tomographic Ultrasound Imaging (TUI) is the representation by a series of parallel slices through the volume and the distance between the slices as well as their number can be configured (Fig. 7.16). This is one example that all modalities of volume ultrasound should be considered depending on the specific information one is looking for.

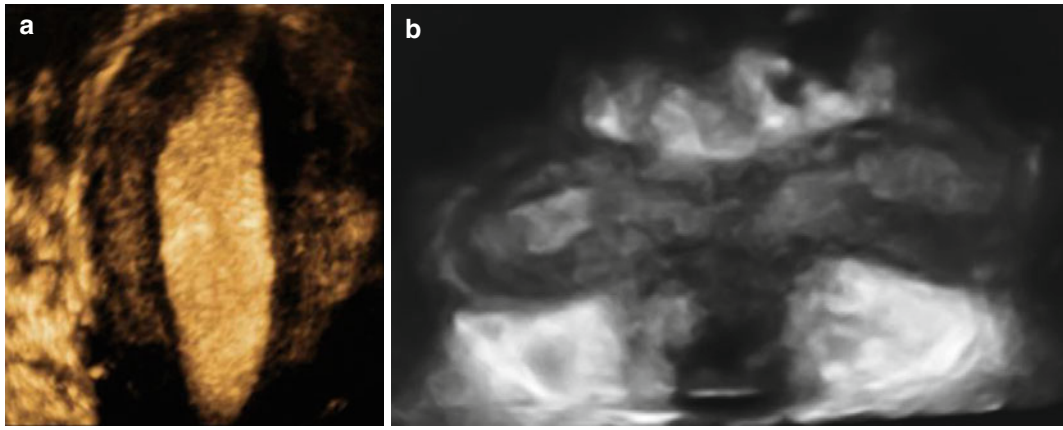


Fig. 7.15 The volume should include the entire uterus. (**a**) An acquisition angle that is too narrow results in a 3D image of only half of the uterus and could lead to an erroneous diagnosis of ESHRE/ESGE U4, hemi uterus. (**b**) Enlarging the angle of acquisition allows for a 3D image of the entire uterus. ESHRE/ESGE U3b C2, complete bicorporeal uterus with double cervix

The ESHRE/ESGE Classification

The ESHRE/ESGE expert consensus classification system of female genital anomalies published in 2013 proposes main and subclasses for uterine anomalies, and co-existent subclasses for cervical and for vaginal anomalies (Figs. 7.17, 7.18 and 7.19). The ESHRE/ESGE consensus differs markedly from other classification systems in that to fit an anomaly in class U1, U2 or U3 the thickness of the fundal uterine wall is to be assessed (Fig. 7.20). Only 3D ultrasound or MRI are diagnostic modalities capable of providing this information.

Future Research

A major drawback of the existing classification systems for congenital female genital anomalies is that morphological changes are a continuum and by fitting this continuum into discrete categories, valuable information gets lost inevitably (Fig. 7.21). The literature on congenital anomalies is extensive indeed, it is confusing too because lack of a detailed description of the so called minor uterine anomalies results in overlap in categories and thus difficult to interpret results on clinical relevance and treatment outcome. As put forward in 2004 already [9], 3D ultrasound has opened new perspectives (Fig.7.22). On a standardized coronal image plane – obtained with 2D, 3D or MRI- standardized measurements are to be performed [7]. Vascular parameters of the intermediate tissue in case of a split in the cavity may have to be considered too. A uniform and objective description of altered uterine morphology is to be related to clinical relevance, irrespective of the existing classification systems. Clinical insignificant variants of uterine morphology can get classified as such and their owners be reassured. If solid data indicate that the morphological uterine alteration is likely to cause a clinical problem, it is a congenital uterine anomaly. In this group, further studies may have to be conducted to come to categories based on the likely clinical problem and/or on the treatment modalities.

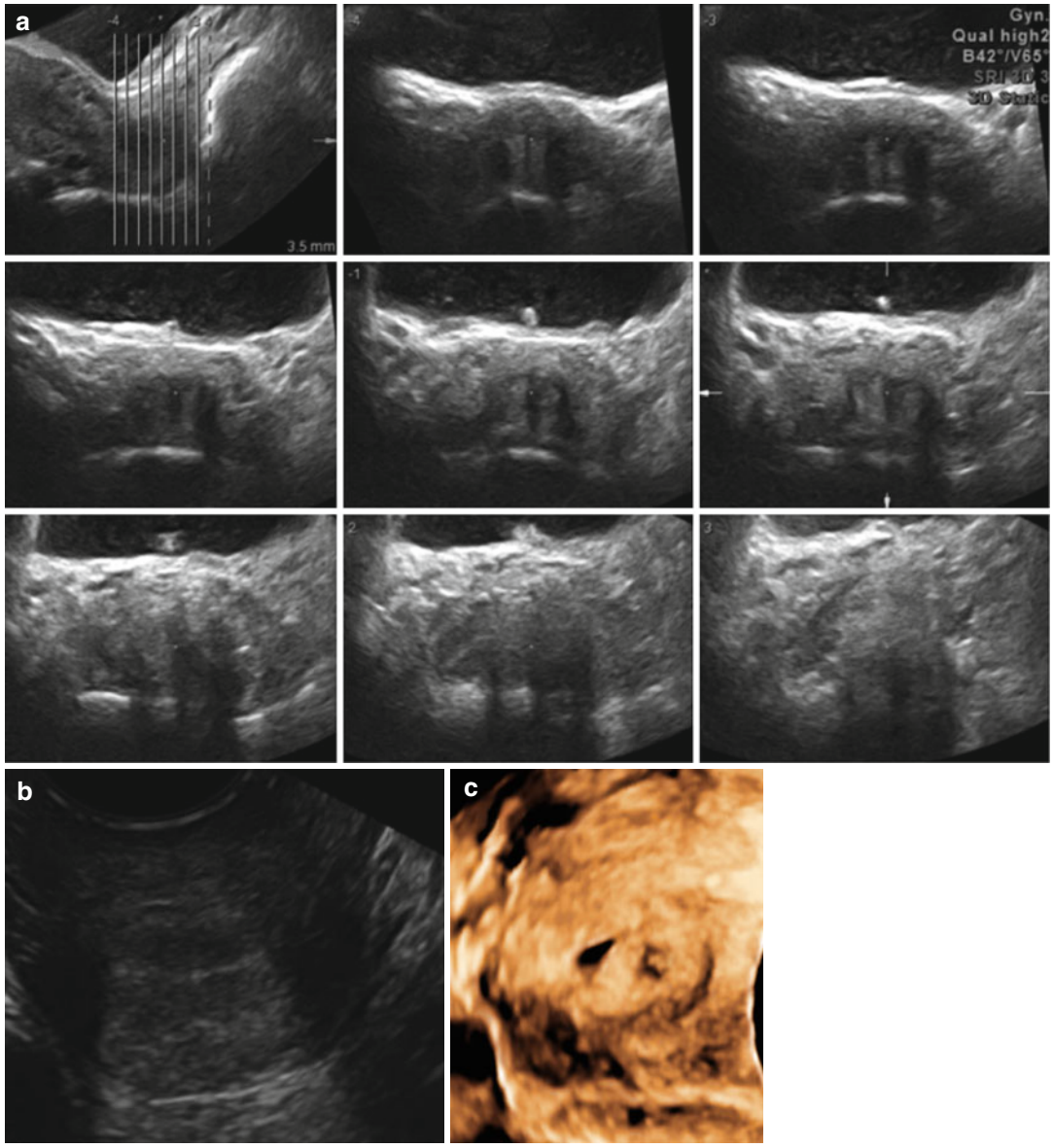


Fig. 7.16 Transverse image of the cervix: (**a**) Tomographic Ultrasound Imaging (TUI) representation of the 3D volume: ESHRE/ESGE C1, septate cervix. (**b**) Transverse 2D section: ESHRE/ESGE C0, normal cervix. (**c**) Transverse rendered 3D image: ESHRE/ESGE C1, septate cervix

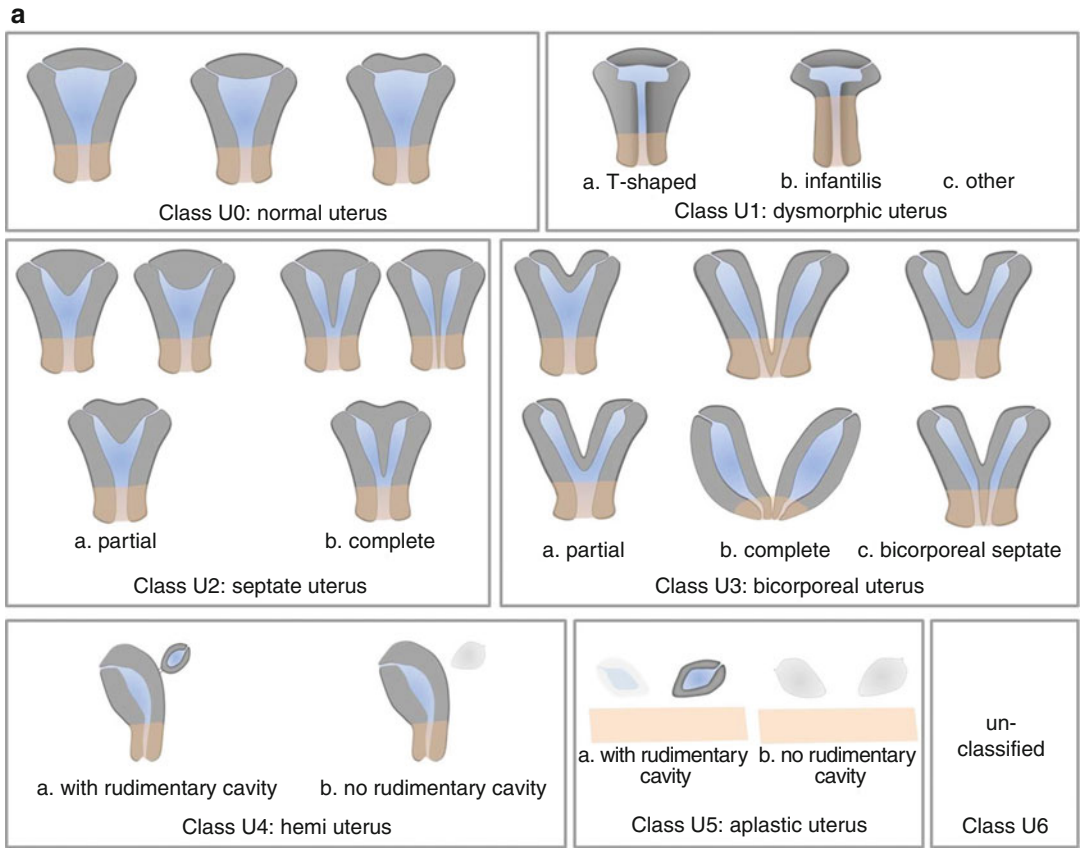


Fig. 7.17 Overview of the Uterine anomalies (ESHRE/ESGE 2013 consensus classification): (**a**) pictograms; (**b**) ultrasound images

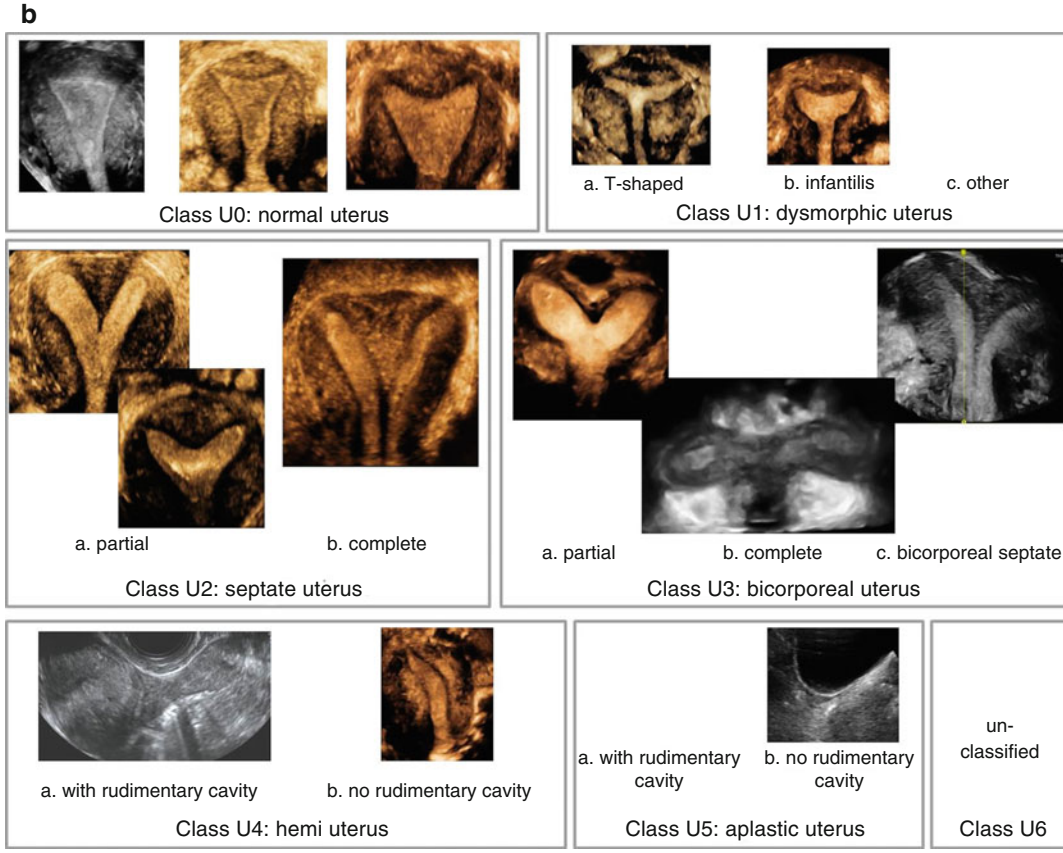


Fig. 7.17 (continued)

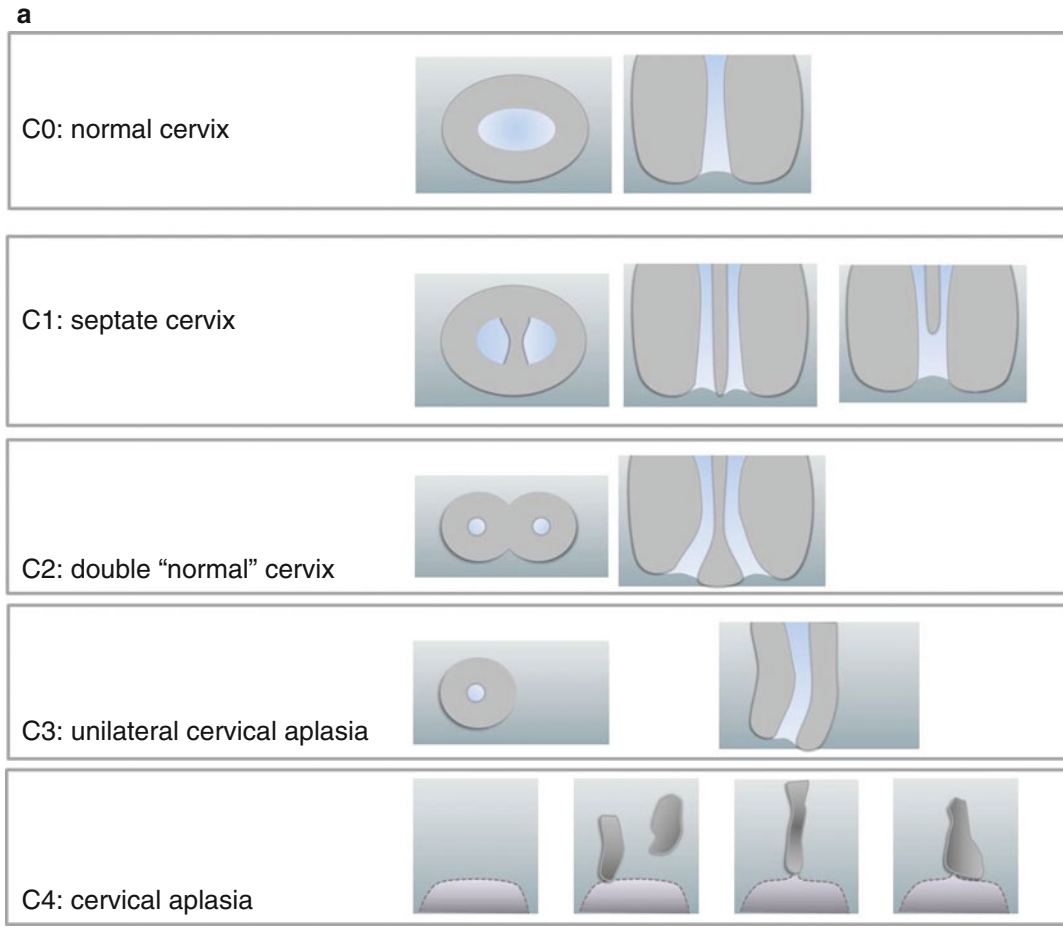
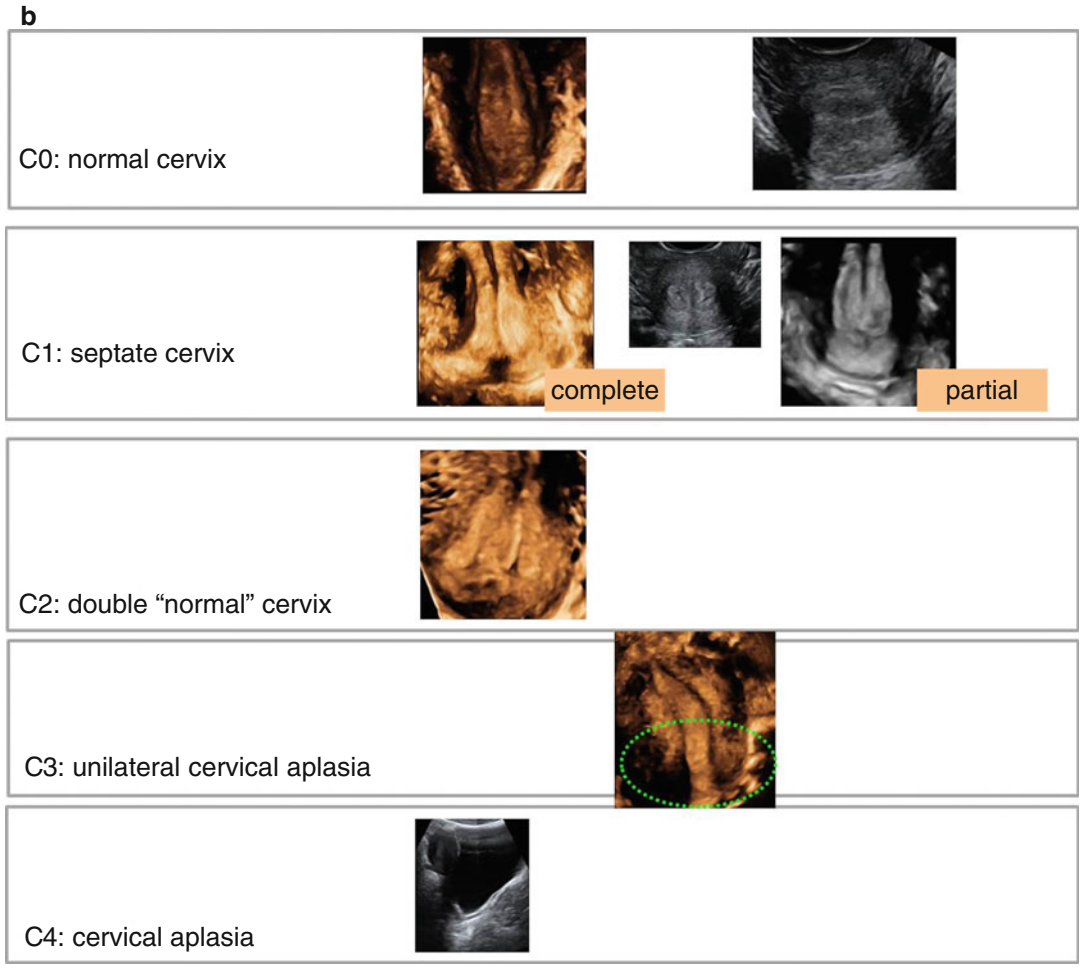


Fig. 7.18 Overview of the Cervical anomalies (ESHRE/ESGE 2013 consensus classification): (**a**) pictograms; (**b**) ultrasound images



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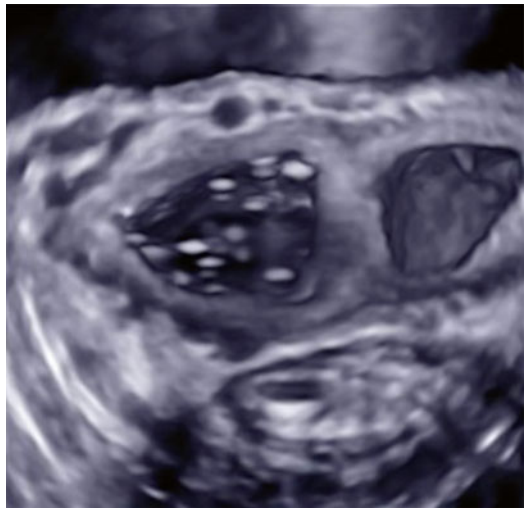

Fig. 7.19 Transverse 3D rendered image of the vagina after instilling ultrasound gel in both hemivagina. ESHRE/ESGE V1: longitudinal non obstructing vaginal septum

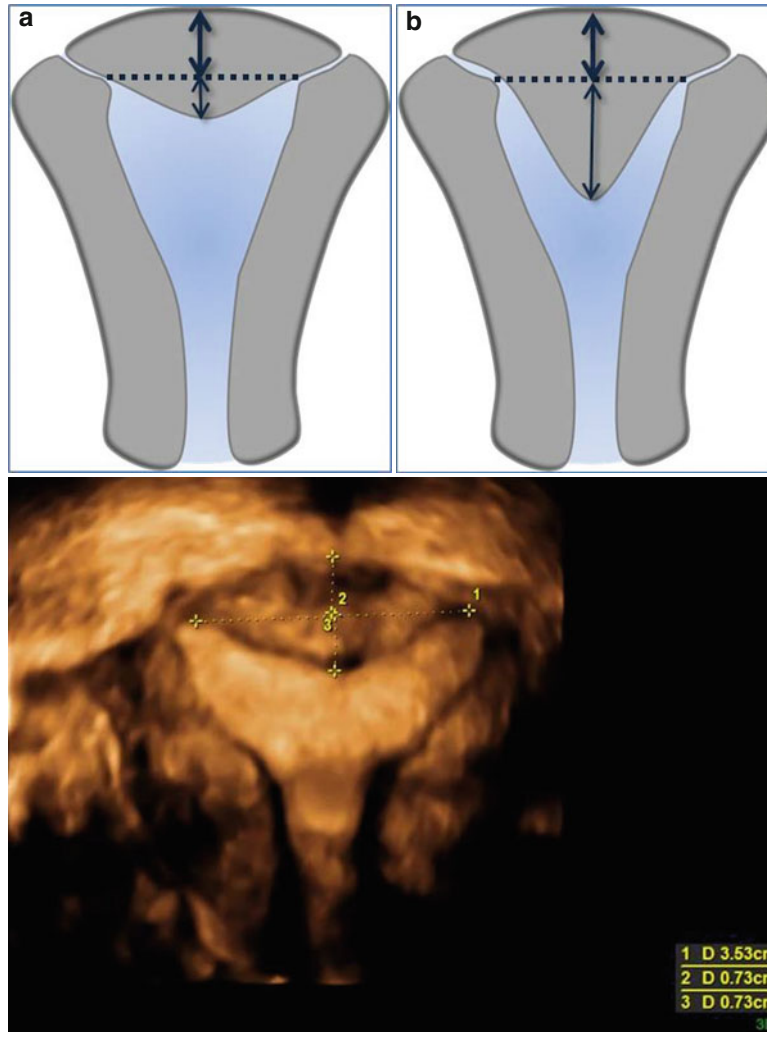

Fig. 7.20 Assessment of the fundal myometrial thickness. (**a**) <50 % of the wall thickness: ESHRE/ESGE U0 normal or U1c dysmorphic uterus. (**b**) >50 % of the wall thickness: ESHRE/ESGE U2 septate uterus

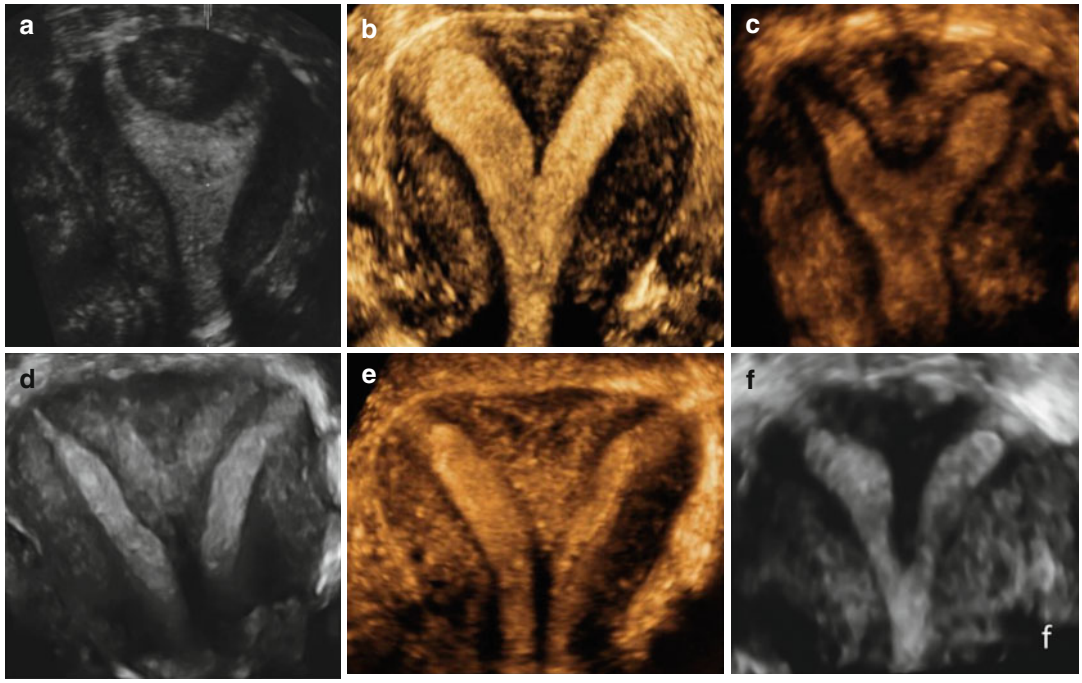

Fig. 7.21 Spectrum of morphology within the same class. (**a**–**c**) ESHRE/ESGE U2a. (**d**–**f**) ESHRE/ESGE U2b. (**d**) broad septum with zonal anatomy. (**e**) intermediate thickness of septum with unclear zonal anatomy. (**f**) narrow septum, no zonal anatomy

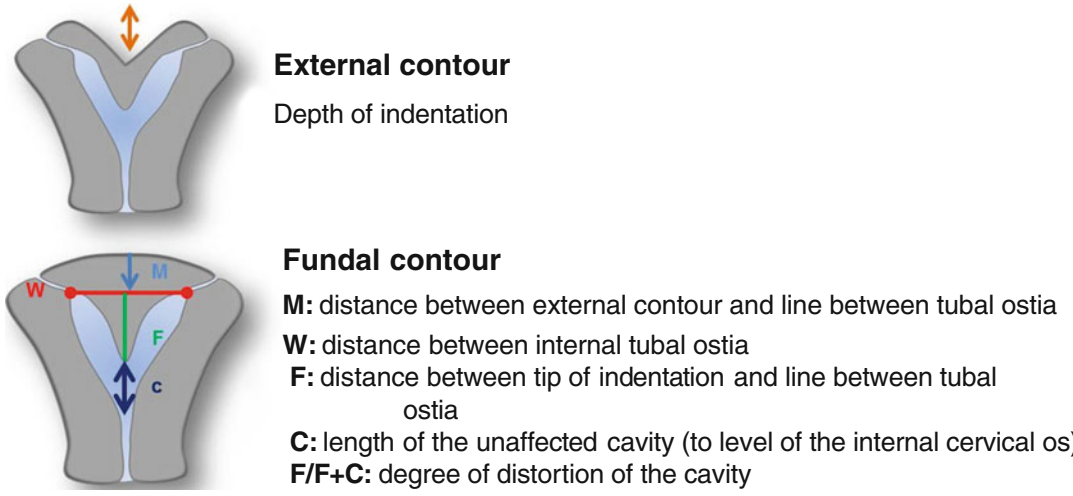

Fig. 7.22 Measurements on a 3D midcoronal image allow for detailed assessment of the uterine morphology (Adapted from Salim and Jurkovic [9])

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Magnetic Resonance Imaging for the Diagnosis of Female Genital Anomalies

8

Leonardo P. Marcal and Maria Angela Santos Nothaft

Introduction

Anomalies of the female genital tract are rare congenital conditions that result from failure of formation, fusion or resorption of the mullerian ducts. The prevalence of these anomalies varies greatly, ranging from 0.4 % in the general population to 8–10 % in women undergoing infertility investigation [1–3]. The diagnosis of female genital anomalies is important clinically due to its high association with infertility, endometriosis, and renal anomalies. Magnetic Resonance Imaging (MRI) has been widely accepted as the imaging modality of choice for the evaluation of female genital anomalies, since it is capable of accurately demonstrating the anatomy of the female genital tract. The purpose of this book chapter is to demonstrate the value of MRI for the diagnosis of female genital anomalies.

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Embryology

The Mullerian (paramesonephric) ducts develop bidirectionally, in the absence of Mullerian-inhibiting factor, to form the female genital tract. The fallopian tubes, uterus, cervix, and proximal two thirds of the vagina are formed by the Mullerian ducts while the urethra and lower third of the vagina are formed by the urogenital sinus [4–6]. The Mullerian ducts, initially separated by a septum, fuse at their inferior margin to form the single lumen uterovaginal canal. Congenital anomalies of the female genital tract may result from arrest or failure of formation (no development or underdevelopment) of the paired Mullerian ducts, failure of fusion, or failure of resorption of the uterovaginal septum. Interruptions in this three-phase process of the duct formation, fusion and septal resorption is used to explain the differences between the female genital anomalies [4–6].

MR Imaging Technique

MRI is remarkably capable of demonstrating the female genital tract anatomy, providing high resolution images of the uterine zonal anatomy, and accurately demonstrating the outer fundal contour. T2-weighted images are the mainstay of MR imaging of the female pelvis, due to its excellent soft tissue contrast, and are able to reliably demonstrate the cervical and uterine

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anatomy, clearly depicting the different signal intensities of the endometrium, myometrium, junctional zone, fibrous stroma of the cervix, cervical mucosa/submucosa, and endocervical canal mucus [3, 7]. As a general rule, the protocol should include a fast gradient – echo or single-shot fast spin echo (SSFSE) localizer to determine the uterine lie. At the same time, it also provides an overview assessment for associated renal anomalies that may be present. Multiplanar Sagittal, axial and coronal Fast-Recovery Fast Spin-Echo (FRFSE) T2 images are prescribed along the long axis of the uterus to characterize the external uterine contour, which is important to differentiate certain Mullerian anomalies. An axial or sagittal spoiled gradient-echo (SPGR) T1-weighted image is useful to demonstrate retained blood products within obstructed uterus, rudimentary uterine remnants or hemi-vagina. An axial dual-echo T1-weighted image is obtained for diagnosis of blood products or fat within incidentally found adnexal lesions. Multiphasic contrast-enhanced volume-interpolated gradient echo with fat suppression sequence may be obtained in the sagittal or axial plane for further characterization of incidentally found pathology.

MRI of Female Genital Anomalies

The strength of MRI for the diagnosis of female genital anomalies lies in its ability to clearly demonstrate the anatomy of the female genital tract. The AFS classification system of Female genital anomalies, initially proposed by Buttram and Gibbons in 1979 and revised by the American Society of Reproductive Medicine in 1988, has been widely accepted worldwide [8, 9]. This system has many limitations, including the lack of classification for vaginal anomalies and difficulty categorizing anomalies that encompass features of different classes [3, 8]. The European society of human Reproduction and Embryology (ESHRE) and the European Society for Gynecological Surgery (ESGS) have developed a new updated classification system of female genital anomalies, which is based on the anatomy of the female genital tract [10]. This updated version of the ESHRE/ESGE classification will be used in this chapter. A comprehensive review of this classification is beyond the scope of this chapter. In short, there are seven distinct classes of anomalies according to this classification system, depending on the severity of anatomic variation and of distortion of the uterine body [10]. Class U0 encompasses all cases with a normal uterine corpus. Class U1 is dysmorphic uterus (T-shaped, infantilis and others). Class U2 or septate uterus, which may be partial or complete. Class U3 or bicorporeal uterus, defined as uteri with an abnormal fundal outline, characterized by a fundal indentation greater than 50 % of the uterine wall thickness. Class U4 or hemi-uterus encompasses all cases of unilaterally formed uterus. Class U5 or aplastic uterus includes all cases of uterine aplasia. Class U6 is reserved for all unclassified malformations. Coexistent cervical and vaginal anomalies are classified in independent supplementary subclasses [10]. C0 is normal cervix, C1septate cervix, C2 duplicated cervix, C3 unilateral cervical aplasia, and C4 cervical aplasia. Vaginal anomalies subclasses include V0 (normal vagina), V1 (longitudinal non-obstructing vaginal septum), V2 (longitudinal obstructing vaginal septum), V3 (transverse vaginal septum / imperforate hymen) and V4 (vaginal aplasia) [10].

Aplasia (ESHRE/ESGE U5)

Aplasia is the most severe form of female genital anomalies. It ranges from complete aplasia to varying degrees of hypoplasia of the uterus, cervix, and upper two thirds of the vagina. The incidence is approximately 1:5,000 cases and associated abnormalities of the urinary tract and/or spine are present in up to 30 % of these patients [10, 11].

The Mayer-Rokitansky Kuster-Hause syndrome occurs when there is complete failure of Müllerian development, resulting in complete agenesis of the uterus, cervix, fallopian tubes, and proximal two thirds of the vagina (Fig. 8.1). Partial agenesis is more common than complete agenesis, and in which cases Müllerian remnants may be present, such as a rudimentary uterus (Figs. 8.2 and 8.3). Sometimes a rudimentary uterus will recannalize and develop a functional endometrium. In such instances, the normal zonal anatomy

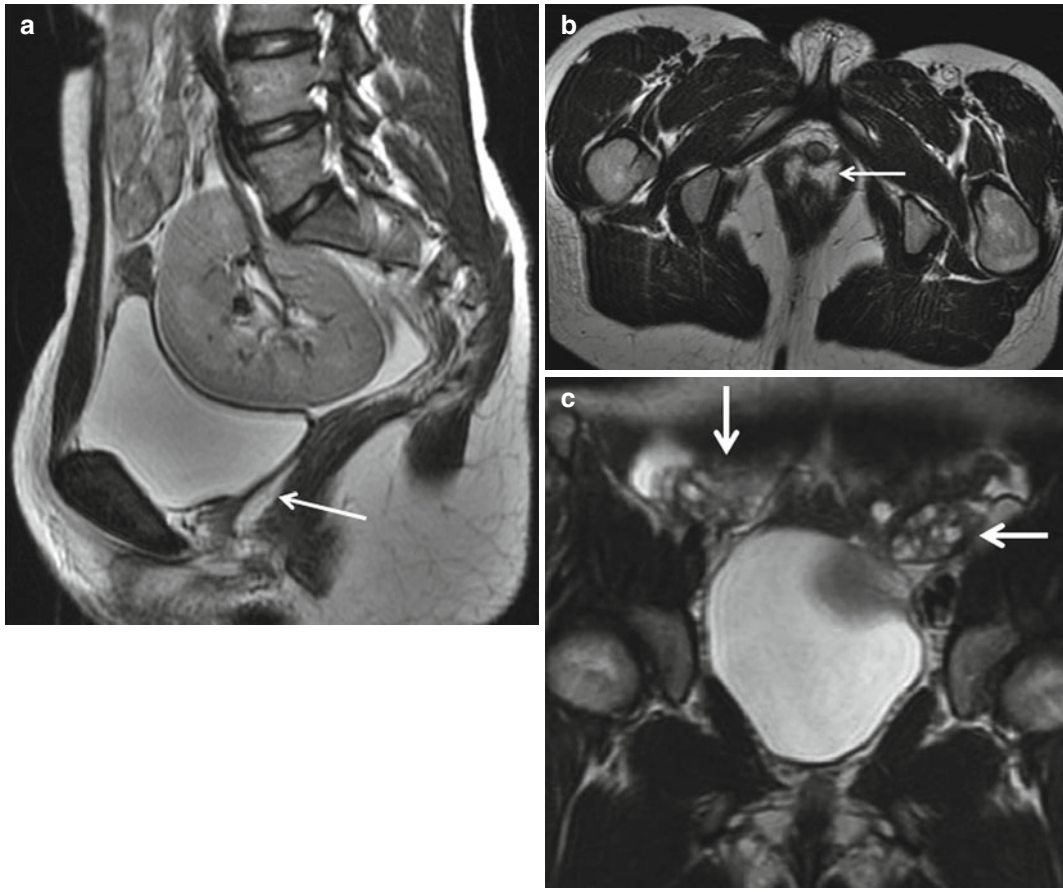

Fig. 8.1 (*ESHRE/ESGE U5b/C4/V4*) Complete aplasia of the uterus and upper two-thirds of the vagina. (**a**) Sagittal (**b**) axial T2WI images show complete aplasia of the uterine corpus, cervix and upper two thirds of the vagina, with fatty tissue present in the expected location of these structures (*arrows* in **a** and **b**). The complete failure of Mullerian development characterizes the Mayer-Rokitansky Kuster-Hause syndrome. Note presence of an ectopic pelvic kidney. Associated renal anomalies are common and MRI can provide a quick overview of the retroperitoneum and renal fossa in a single examination. The normal ovaries are visualized in a coronal T2W image (*arrow* in **c**)

of the uterus is preserved (Fig. 8.4). Rudimentary uteri without a functioning endometrial canal usually lose the usual zonal anatomy [11]. Ovarian development is normal, but these are usually ectopic [12]. The diagnosis of complete agenesis is usually done at puberty with primary amenorrhea. If there is a functioning uterine remnant, patients may present with cyclic abdominal pain [13]. MRI is capable of differentiating between uterine agenesis and hypoplasia. This differentiation is clinically important, since the presence of functioning uterine remnants puts these patients at increased risk of developing endometriosis [13, 14].

Hemi-uterus (ESHRE/ESGE U4)

This type of anomaly occurs in about 10 % of cases [3, 13], and encompasses all types of unilaterally formed uterus (formly "unicornuate" uterus) [10]. There is an asymmetric failure of development of one of the Müllerian ducts, with the formation of an elongated uterus uterine horn, generally shifted to one side of the pelvis, which communicates with a normal vaginal canal. MR imaging typically shows a "banana"-shaped uterus in one side of the pelvis, with or without an associated rudimentary

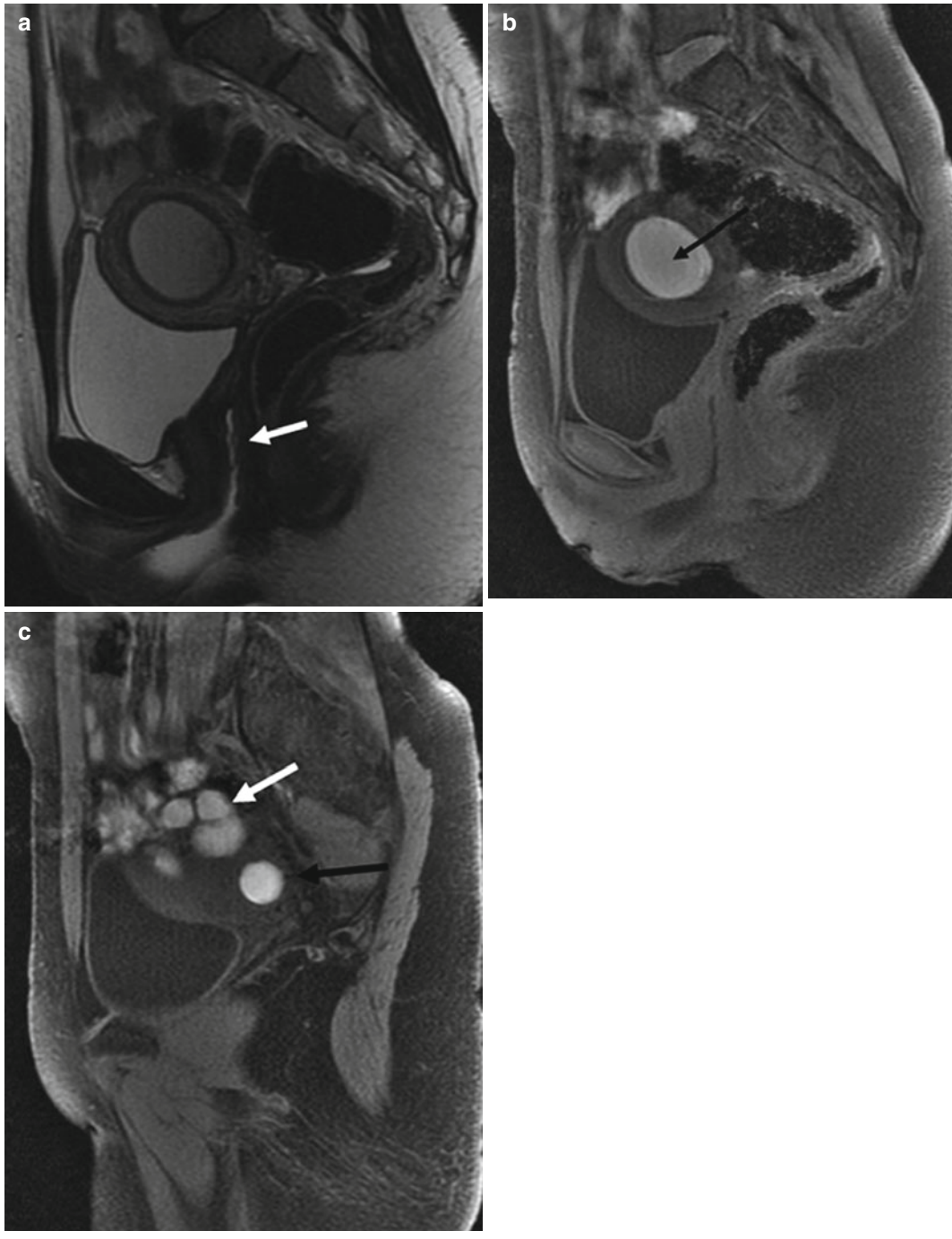

Fig. 8.2 (*ESHRE/ESGE U5a/C4/V4*) Partial aplasia of the uterus and vagina. (**a**) Sagittal T2 weighted image shows aplasia of the lower uterine segment and cervix and upper third of the vagina, with an isolated uterine body and fundus with functional endometrial cavity. Note vaginal gel in the lower two thirds of the vagina (*white arrow*). On sagittal images, the urethra is the anatomic landmark used utilized to separate the upper (above the urethra) from the lower vagina. (**b**, **c**) Sagittal T1 weighted images with fat suppression show hematometra (*black arrow* in **b**), hematosalphynx (*white arrow* in **c**) and endometrioma (*black arrow* in **c**)

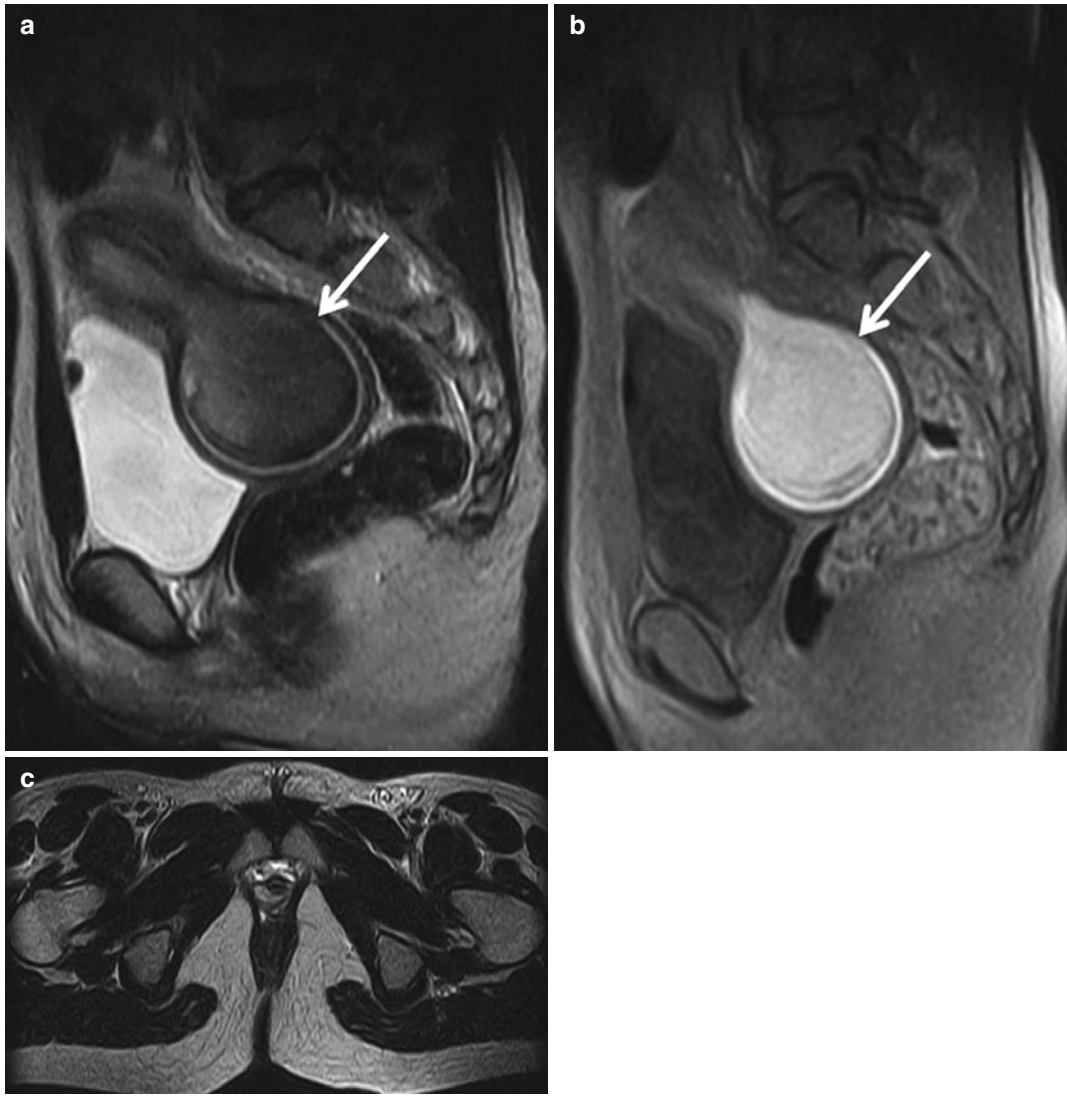

Fig. 8.3 (*ESHRE/ESGE* sub-class V4) Aplasia of the upper two thirds of the vagina. (**a**) Sagittal T2WI and (**b**) Sagittal T1WI with fat suppression show large hematometra, with significant distention of the endometrial cavity and cervical canal with hemorrhagic material (*arrows*). (**c**) Axial T1W1 shows absence of the vagina between the urethra and rectum

horn (Fig. 8.5) [7, 13]. In about 65 % of cases, there is an associated rudimentary horn which may contain functional endometrial tissue or not. The cavity of the rudimentary horn can communicate with the contralateral endometrial cavity in about 10 % of cases [3]. The diagnosis is usually made incidentally during the investigation of infertility. If a rudimentary functioning, non-communicating horn is present, there is retrograde menstrual flow and the diagnosis usually occurs at menarche with the clinical picture of dysmenorrhea and hematometrium [13, 14]. If functional endometrium is present within a non-communicating rudimentary horn, MR will show a distented uterine remnant filled with hemorrhagic material consistent with hematometra (Fig. 8.6). These patients have a greater risk of developing endometriosis, ectopic

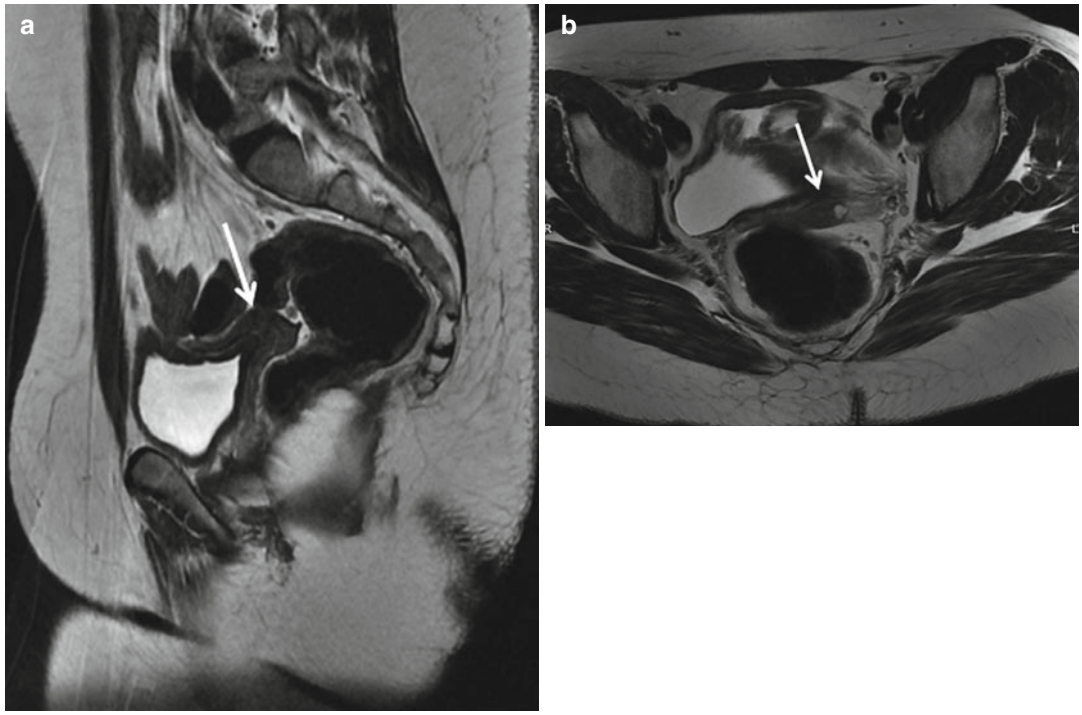

Fig. 8.4 (*ESHRE/ESGE U5*) Uterine hypoplasia. (**a**) Sagittal and (**b**) axial T2WI images show a small rudimentary uterus and cervix, with preservation of the zonal anatomy. The endocervical and endometrial canal are depicted as thin T2-hyperintense (*arrows*) line within the rudimentary uterus

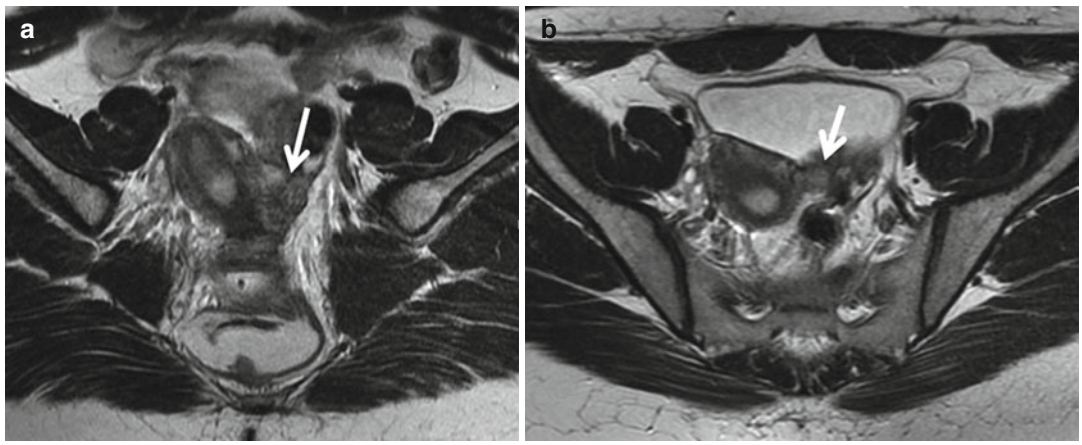

Fig. 8.5 (*ESHRE/ESGE U4b*) Hemi-uterus with a non-functional rudimentary horn. (**a**) Sagittal and (**b**) axial T2WI images show a hemi-uterus displaying normal zonal anatomy. A small rudimentary non-cavitary horn is present on right (*arrow*)

pregnancies, and obstetric complications [13, 14]. In about 40 % of the cases, associated renal anomalies occur, the most common of which is renal agenesis [14], ipsilateral to the rudimentary horn [11].

Complete Bicorporeal Uterus (ESHRE/ESGE U3b)

In this anomaly there is complete failure of fusion of the Mullerian ducts, with formation of

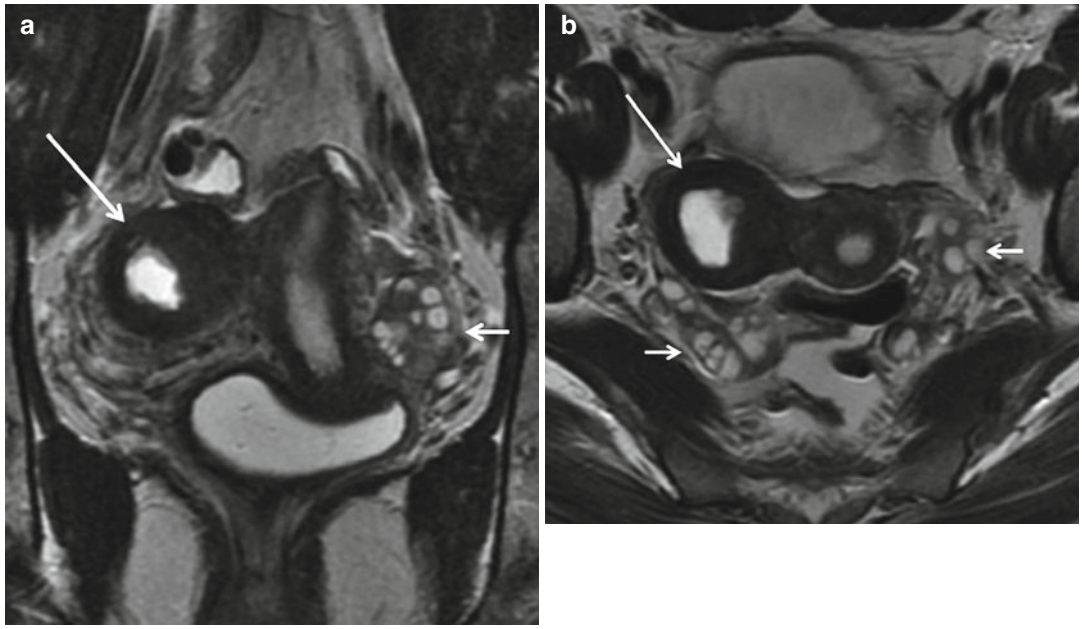

Fig. 8.6 (*ESHRE/ESGE U*4a) Hemi-uterus with an obstructed cavitary rudimentary horn. (**a**) Coronal T2WI and (**b**) axial T2WI show a "banana"-shaped uterus to the left of midline consistent with a hemi-uterus (formerly "unicornuate" uterus). A cavitary rudimentary horn is seen on right (*long arrows*), which is non-communicating resulting in hematometra. Normal ovaries are present (*short arrows*)

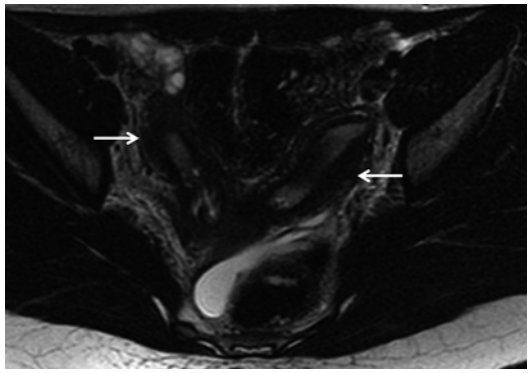

Fig. 8.7 (*ESHRE/ESGE U*3b/C2) Complete Bicorporeal uterus (Formerly "didelphys" uterus). Axial T2WI shows two completely separate uteri and cervices in each side of the pelvis (*arrows*), displaying normal zonal anatomy

two separate uteri with distinct endometrial cavities and cervices, which characterizes the complete bicorporeal uterus (ESHRE/ESGE U3b/C2), the formerly "Didelphys uterus" [10]. In 75 % of cases, there is a complete or partial longitudinal vaginal septum associated. The presence of vaginal septum may lead to the development of hematometrocolpos, increasing the risk of endometriosis [13, 14]. In patients with transverse vaginal septum and obstruction of one hemivagina, the association with ipsilateral renal agenesis is very common [13, 15]. When there is no vaginal obstruction, the patient is usually asymptomatic. If there is obstruction, the diagnosis is often made at menarche, with cyclic pelvic pain and enlarging abdominal girth. On speculum examination, a blocked hemivagina can be identified. MRI shows two separate uteri with normal endometrial-myometrial interface and preserved zonal anatomy (Fig. 8.7). The diagnosis of longitudinal vaginal septa is easily made with the use of vaginal gel or when there is an obstructed hemivagina distended by hematocolpos (Figs. 8.8 and 8.9).

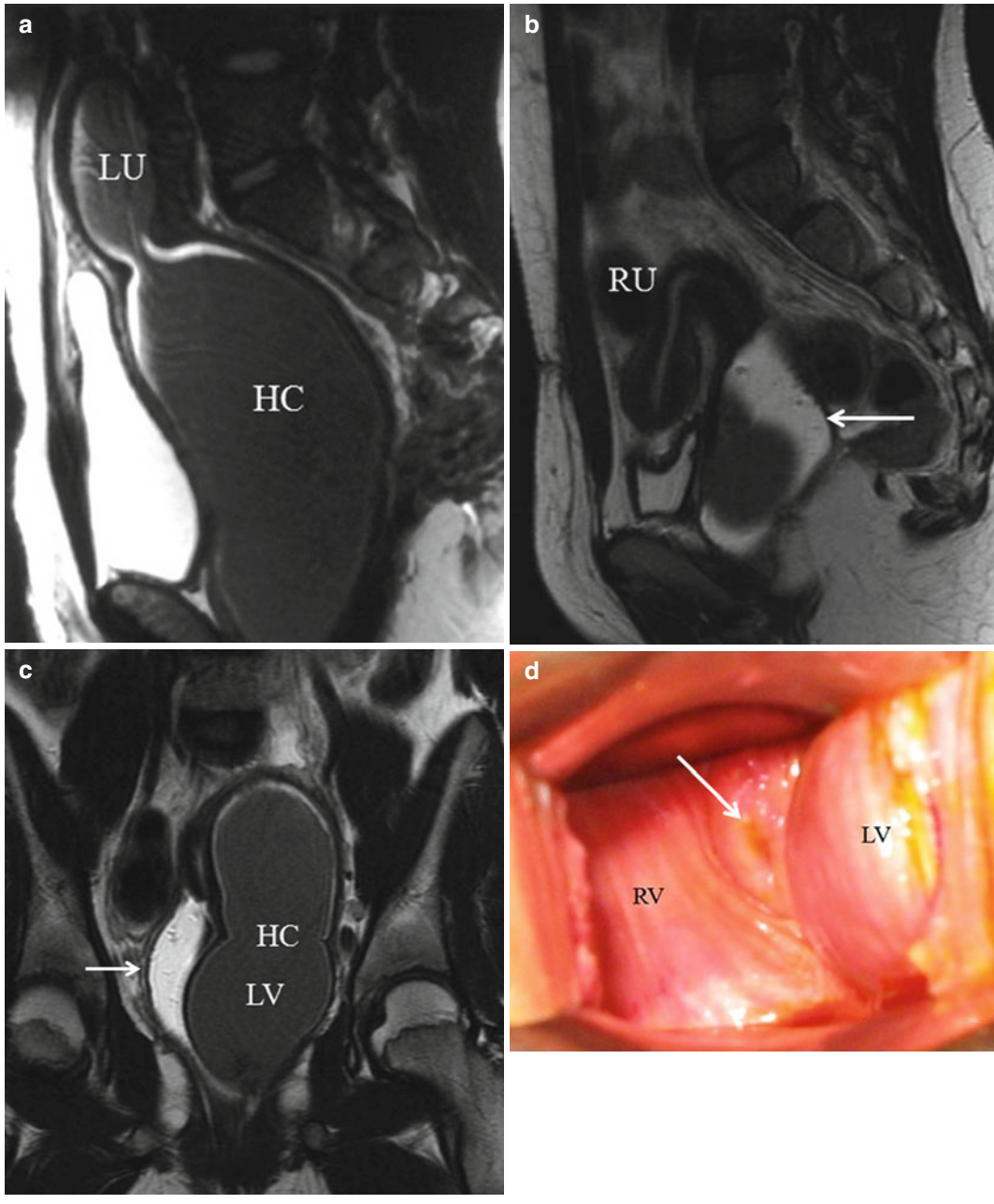

Fig.8.8 (*ESHRE/ESGE U*3b/C2/V2) Complete Bicorporeal uterus (formerly "dildephys") with obstructing longitudinal vaginal septum. (**a**) Sagittal T2WI to the left of midline shows large hematocolpus (*HC*) and hematometra on the left (*LU* left uterus). (**b**) Sagittal T2WI to the right of midline shows a separate right uterus (*RU*) with normal zonal anatomy. The right hemivagina is distended with vaginal gel and is hyperintese (*white*) on T2Weighted images (*arrow*). (**c**) Coronal T2WI shows the obstructed left-hemivagina (*LV*) with hematocolpus (*HC*) and hematometra (*LU* left uterus). The normal right hemi-vagina distended with gel (*arrow*). (**d**) Direct examination shows normal right hemivagina (*RV*) and right cervical os (*arrow*). The obstructed left hemivagina (*LV*) is seen on the left (*HC*)

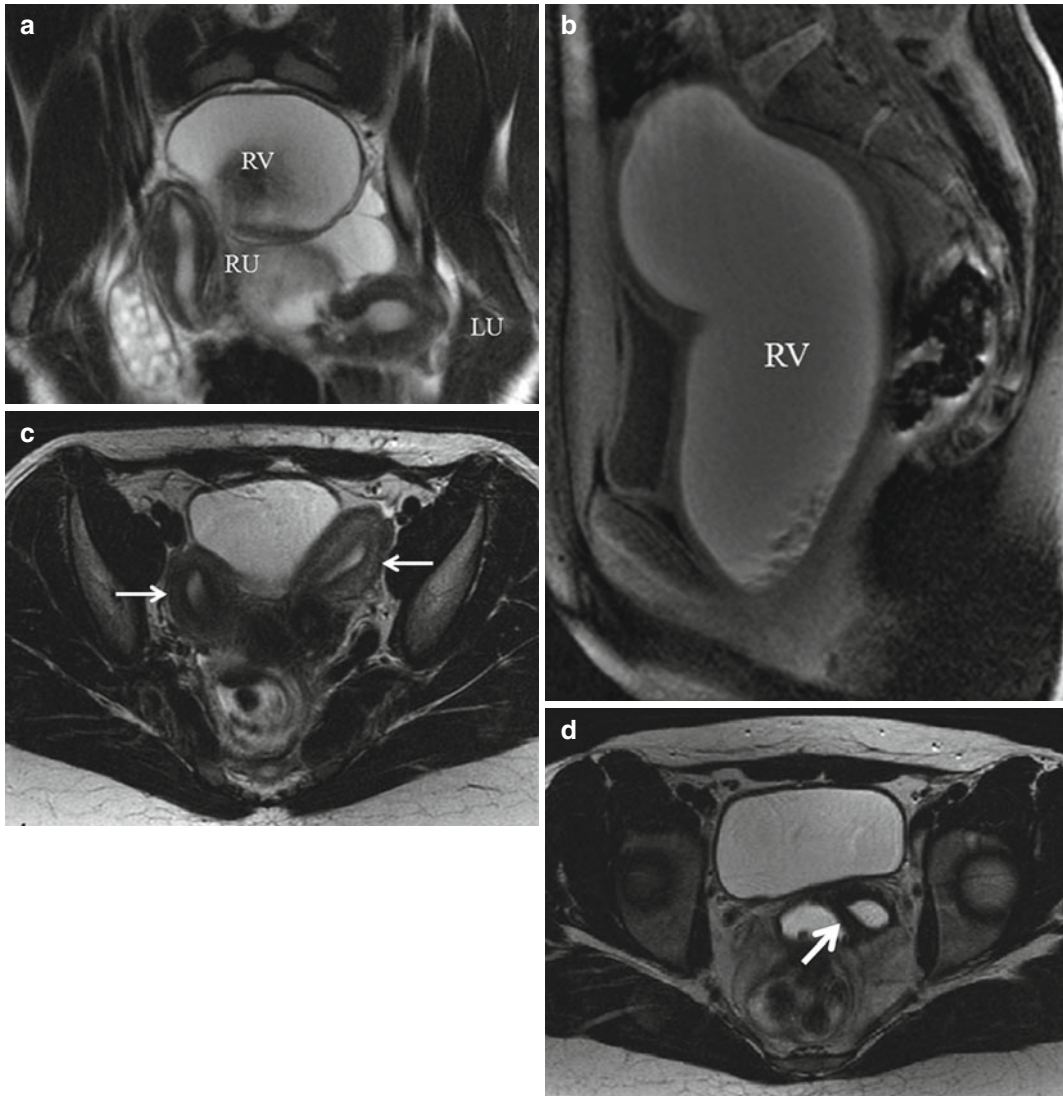

Fig. 8.9 (*ESHRE/ESGE U*3b/C2/V2) Bicorporeal uterus (didelphys) with obstructed right hemi-vagina. (**a**) Coronal T2WI two divergent completely separate uteri and cervices, consistent with complete bicorporeal uterus (didelpys) (*RU* right uterus and *LU* left uterus). There is an obstructing longitudinal vaginal septum, and the right hemi-vagina is obstructed and disdented with hemorrhagic material (*RV* right vagina). (**b**) Sagittal T1WI with fat suppression shows the extensive right hematocolpus (*RV* right vagina). (**c**, **d**) Axial T2WI images following surgery show two normal separate uteri (*arrows* in **c**) and two separate hemi-vaginas distended with gel, separated by a longitudinal septum (*arrow* in **d**)

Bicorporeal Uterus (ESHRE/ESGE U3)

In this anomaly, there is incomplete fusion of the Mullerian ducts, forming two symmetrical horns, which merge caudally usually in the isthmus, forming a bicorporeal uterus with normal cervix (ESHRE/ESGE U3), the formerly "Bicornuate" uterus. The bicorporeal uterus may be partial (class U3a) or complete (class U3b), depending on the degree of separation of the uterine corpus by the external fundal indentation [10]. It occurs in approximately 10 % of cases [12, 13]. Both uterine horns are divergent (intercornual distance greater than 4.0 cm) and there is a deep cleft

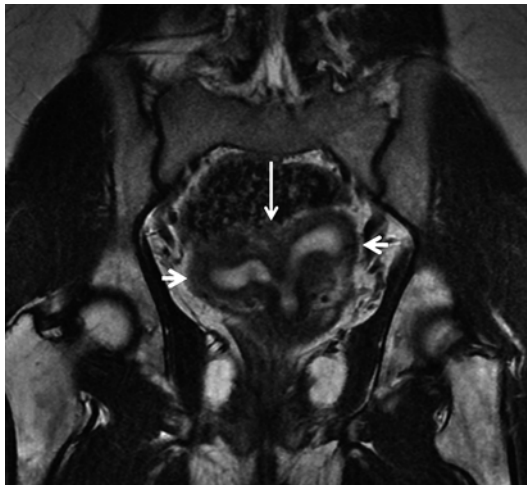

Fig. 8.10 (*ESHRE/ESGE U*3b/C0) Bicorporeal uterus (Formerly bicornuate). Coronal T2WI shows duplication of the uterine horns (*short arrows*). There is fusion of caudal uterine body and cervix (Note significant divergence of the right and left uterine horns, separated by a deep midline cleft, exceeding 50 % of the uterine wall thickness (*long arrow*))

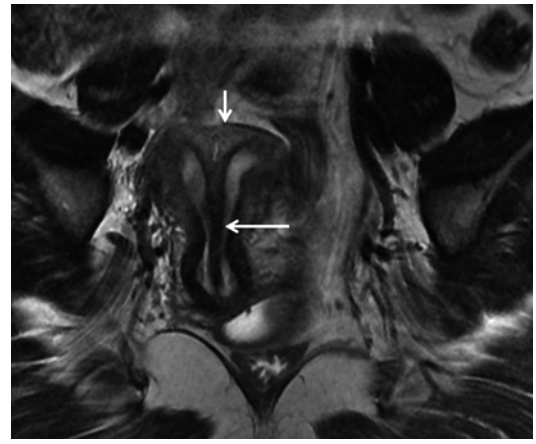

Fig. 8.11 (*ESHRE/ESGE U*2b) Septate uterus. Axial T2WI shows a complete septum, extending from the fundus to the cervical region (*arrows*). Note that the upper segment of the septum in the fundus and body of the uterus is muscular (*long arrow*), displaying intermediate T2 signal identical to the myometrium. The lower segment of the septum is fibrous, displaying low T2 signal intensity typically seen with fibrotic tissue (*short arrow*). MR clearly shows the convex outer uterine contour, which is important to differentiate it from bicorporeal uterus (formerly "bicornuate"). The excellent soft tissue contrast of MR provides information not only about the presence and extent of the septum, but is also capable of demonstrating its composition, as illustrated in this case

between the horns (exceeding 50 % of the uterine wall thickness) (10). Patients are usually asymptomatic; however, there is a high rate of associated obstetric complications [3, 12]. MR demonstrates noninvasively the outer contour of the uterine fundus, with two divergent uterine horns, and a large fundal indentation (exceeding 50 % of the uterine wall thickness) between them (Fig. 8.10). The zonal anatomy is preserved in both horns. Associated pathologies such as leiomyoma and adenomyosis are also easily identified. In a bicornuate-bicoli uterus there is some communication between the horns, unlike didelphic uterus where the uteri are completely separate.

Septate Uterus (ESHRE/ESGE U2)

This anomaly results from partial or complete failure of resorption of the utero-vaginal septum, and is the most common anomaly of the female genital tract [3, 13, 14]. The septum, arising in the midline along the fundal region, may be formed predominantly by muscular, fibrous or a combination of both components. It can be partial (ESHRE/ESGE U2a) or complete (ESHRE/ESGE U2b), extending to the external orifice of the cervix or even into the vagina [10]. The outer contour of the fundus can be normal, flat or slightly concave, with no deep indentation or significant divergence of the horns. Septate uterus is the anomaly with the highest association with obstetric complications [3, 13, 16]. MR imaging clearly shows the presence and extent of the septum along the midline, and provides an accurate assessment of its thickness, all of which is relevant information for adequate surgical planning (Figs. 8.11, 8.12 and 8.13) [7, 14]. MR is useful to differentiate between Bicornuate and septate uterus, and this differentiation is clinically relevant, since the latter can be treated by hysteroscopic resection of the septum, decreasing obstetric complications.

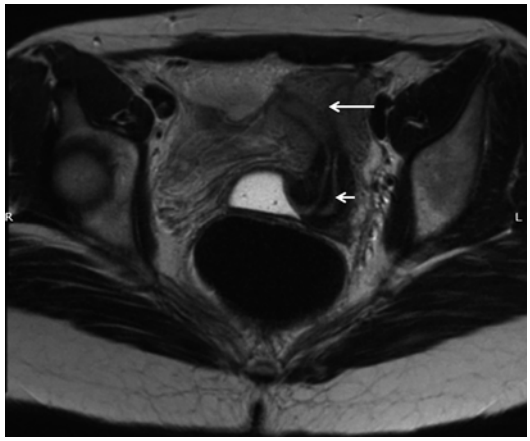

Fig. 8.12 (*ESHRE/ESGE U*3b) **Septate uterus**. Coronal T2WI shows a complete uterine septum, extending from the fundus to the cervix (*long arrow*). Note the slightly convex external fundal contour of the uterus (*short arrow*), without evidence of a cleft. The multiplanar capabilities of MR make it the ideal imaging modality to demonstrate external fundal contour of the uterus, which is key to adequately differentiate between the Mullerian anomalies

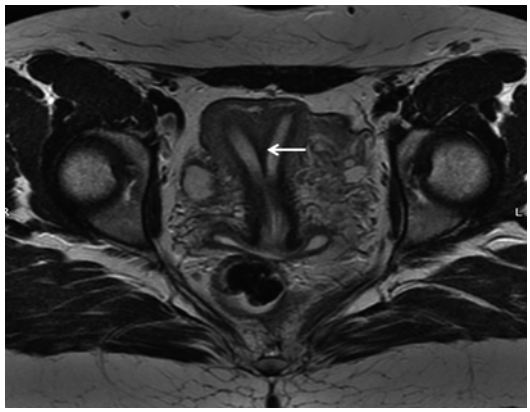

Fig. 8.13 (*ESHRE/ESGE U*3a) Partial septate uterus. Axial T2WI MR shows partial septate uterus. The upper portion of the septum has myometrial composition and does not extend into the cervix (*arrow*). The outer uterine contour is slightly flattened

Dysmorphic Uterus (ESHRE/ESGE U1c)

Considered by some authors as normal variant, this anomaly formerly known as "Arcuate uterus" is characterized by the presence of a small indentation of the external fundal uterine contour, never exceeding 50 % of the uterine wall thickness (Fig. 8.14) [13]. It is debatable whether arcuate uterus truly represents an anomaly or a just a normal variant. It is likely that most cases previously categorized as "arcuate uterus" will fall under either class U1c (minor deformities of the uterine cavity) or simply class U0 (normal uterus) in the new ESHRE/ESGE classification [10]. Most patients with this condition are asymptomatic and have normal obstetric outcome.

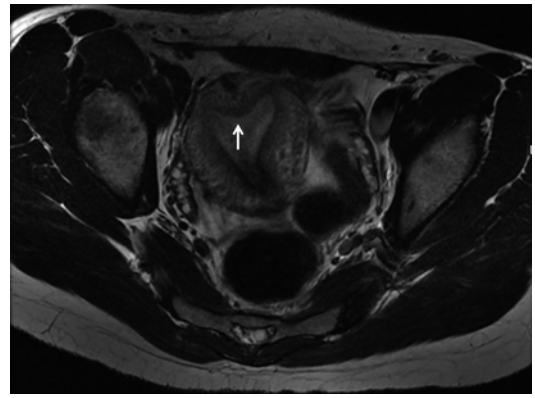

Fig. 8.14 (*ESHRE/ESGE U*1c) Arcuate uterus. Axial T2WI shows a small projection of the myometrium into the endometrial cavity in the uterine fundus (*arrow*). The uterus is normal is size and the outer fundal contour is convex

Dysmorphic Uterus (ESHRE/ESGE U1a)

Class U1 or "T"-shaped uterus encompasses all cases with a markedly narrow uterine cavity. Exposure to Diethylstilbestrol (DES), a synthetic estrogen widely used in the 1970s for the treatment of premature labor, has been associated with the development of T-shaped uterus, clear cell carcinoma of the vagina, and vaginal deformities. Since the use of this drug has been suspended for more than three decades, this anomaly is now hardly ever encountered in clinical practice [14].

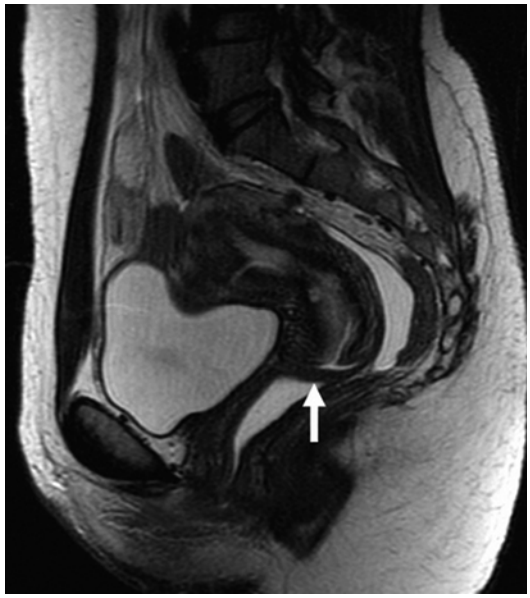

Fig. 8.15 (*ESHRE/ESGE sub-classV3*) Transverse vaginal septum. Sagittal T2WI shows the presence of a transverse vaginal septum in the upper vagina (*arrow*). Distention of the vagina with gel is essential for the adequate diagnosis of vaginal septations, which can be easily overlooked without proper vaginal distention

Vaginal Anomalies

Transverse Septum (Sub-class V3)

This anomaly results from lack of resorption of tissue originating from the urogenital sinus and the caudally fused mullerian ducts [4]. The incidence varies from 1:2,100 to 1:72,000 [17]. It can occur anywhere in the vagina, being more frequent in the upper third (46 %) [18]. The symptoms will vary according to the degree of obstruction. If the obstruction is complete, the diagnosis is usually made at menarche with primary amenorrhea, abdominal pain and abdominal mass. When the obstruction is partial, the diagnosis may be delayed, and the patient may present with dispaurenia and dysmenorrhea. MRI typically shows a transverse septum in the upper vagina (Fig. 8.15). Vaginal distention is very helpful for an accurate MRI diagnosis, which can be achieved with instillation of endovaginal ultrasound gel prior to exam, in sexually active patients.

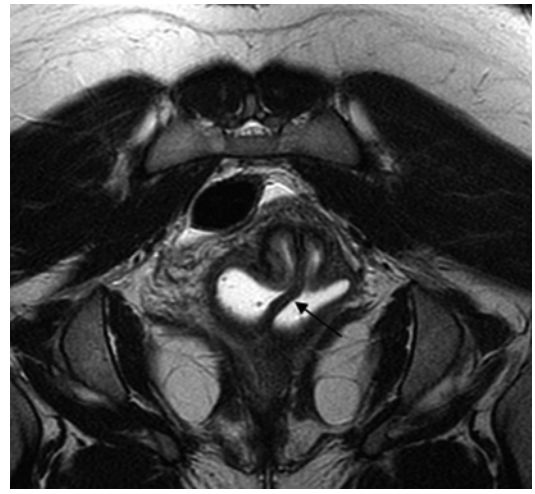

Fig. 8.16 (*ESHRE/ESGE subclass V1*) Longitudinal vaginal septum. Axial T2WI shows the presence of a high non-obstructing longitudinal vaginal septum, extending from the cervical region to the upper vagina (*arrow*)

Longitudinal Septum (Sub-class V1 or V2)

The origin of the longitudinal vaginal septa is not entirely understood. Most authors believe it may arise either from failure of fusion of the Mullerian ducts (in which case it is seen with uterus didelphys) or lack of resorption of the vaginal septum [18–20]. The septum can be complete (from the cervix to the vaginal introitus), high partial (when it originates in the cervix and extends to any level above the vaginal introitus), or low partial (from the hymen to any level in the vagina, without reaching the cervix) [19, 20]. The isolated longitudinal vaginal septum is not associated with infertility or obstetric complications, being often asymptomatic [13, 19, 20]. MRI shows the presence of a longitudinal septum separating two hemivaginas, which may be obstructed (sub-class V1) or not (sub-class V2) (Fig. 8.16). The multiplanar capabilities of MRI are very useful for the diagnosis and evaluation of the extent of the septum. Whenever feasible, vaginal distention with ultrasound gel should be obtained to aid the diagnosis.

Conclusion

MRI is the best imaging tool for the evaluation of female genital anomalies, and is capable of reliably demonstrating the key imaging features for the correct diagnosis of Mullerian anomalies. In addition, MRI can provide essential information for proper surgical management and treatment planning of these anomalies, and in a single examination, a comprehensive evaluation of incidental pelvic pathology and associated renal anomalies that may be present, obviating the need for further diagnostic tests.

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Diagnosis of Uterine Congenital Anomalies: Endoscopy

9

Stephan Gordts

Introduction

The prevalence of congenital uterine anomalies is estimated to be 6 % in the general population of reproductive age [1]. The most common anomalies are the arcuate and septate uterus [2]. This incidence is comparable to the reported incidence of 7 % in the infertile population. In contrast, the estimated incidence is between 13 and 17 % in patients with a history of repeated miscarriages.

Due to the inconsistency of current diagnostic tools in identifying congenital uterine anomalies and the lack of an adequate classification system, the impact of these anomalies on fertility remains a matter of debate. Moreover, the results of operative corrections are difficult to evaluate. Furthermore, most women with septate uteri have normal reproductive performance; only 20–25 % may experience reproductive failure [3, 4]. On the other hand, evidence from patients with otherwise unexplained infertility and from ART cycle studies has shown that correcting congenital uterine pathologies can ameliorate fertility and reproductive outcome [5–8].

In contrast with most of the acquired intrauterine pathologies, like polyps and submucosal myoma, the diagnosis of congenital uterine anomalies requires an evaluation of the uterine cavity and an assessment of the uterine muscular wall involvement.

Hysterosalpingography (HSG) is a widely accepted, commonly used diagnostic tool for detecting abnormalities of the uterus. Currently, it is widely available, and it is frequently included in the typical arsenal for explorations of fertility. HSG and Hysteroscopy are useful for detecting divisions of the uterine cavity, but they do not allow visualisation of the outer uterine contour. This may give rise to confusion in the differential diagnosis between a septate and bicorporeal uterus. With the introduction of more sophisticated, indirect methods of evaluation, it is questionable whether the approaches previously considered 'gold standards' continue to merit that title.

Hysteroscopy

Hysteroscopy is considered the gold standard in evaluations of the uterine cavity. However, the widespread use of hysteroscopy is disappointing, and some gynaecologists continue to consider it an invasive technique that requires general anaesthesia. With the introduction of new-generation, small hysteroscopes, diagnostic hysteroscopy can be performed as a minimally invasive examination. In a randomised controlled trial for assessing pain scores after SIS or an office hysteroscopy, the majority of women preferred the office hysteroscopy over SIS (46 >< 21 %) [9].

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Technique for the Minimally Invasive Approach

In a prospective, randomised study, which evaluated the visualisation index, it was clearly shown that, by reducing the diameter of the hysteroscope, visualisation was improved compared to the 5-mm hysteroscope. Moreover, the patient's parity and surgeon's experience no longer had an important impact on the success of visualisation [10].

The use of a watery distension medium was reported to be superior to the use of CO_2. It caused less discomfort for the patient and had the positive effect of flushing blood, mucus, and small particles out of the visual field [11, 12].

It is also important to limit intra-uterine pressure during the examination. Ideally, this pressure should be maintained below the mean arterial pressure [13].

The diagnostic hysteroscopy is performed with the patient in a normal, gynaecological decubitus position. With the use of a small 2–2.9 mm hysteroscope, there is no need for general sedation or local anaesthesia. After insertion of the hysteroscope into the vagina, a vagino-cervico-hysteroscopy can be performed without the use of a tenaculum or forceps [14]. Once the ostium externum of the cervix is visualised, the hysteroscope is gently introduced. As a result of the dilatation induced by the watery distension medium, it is possible to determine the direction of the cervical canal. The hysteroscope is gently pushed forward in this direction, until the uterine cavity is reached. By turning the 30° angled endoscope around its longitudinal axis, a complete visualisation of the cavity can be achieved (Fig. 9.1).

Requirements for Minimally Invasive Hysteroscopy

- Ambulatory endoscopic unit
- Small diameter instrumentation with high optical quality
- watery distension medium
- low intra-uterine pressure
- atraumatic technique (vagino-cervico-hysteroscopy)

Hysteroscopy, Laparoscopy, and Indirect Imaging

Although hysteroscopy provides direct visualisation of the uterine cavity, a major drawback is that it is difficult to make exact measurements of intra-uterine pathology, and more specifically, to measure the indentations of the uterine fundus. These measurements are based on subjective estimations performed at the time of examination. It is therefore not surprising that, in a recent report, the international inter-observer agreement was very disappointing for hysteroscopic distinctions between a septate and arcuate uterus (ICC 0.27) [15, 16]. However, a recent study showed that the accuracy in detecting intra-uterine pathology with hysteroscopy was higher than with HSG; the reported agreement between the two procedures was only 33.3 % in the diagnosis of uterine septum/subseptum [17, 18]. Like the HSG, the hysteroscopy does not allow visualisation of the outer uterine contours. For an accurate diagnosis, supplementary examinations with ultrasound and laparoscopy are necessary.

Previously, hysteroscopy and laparoscopy were the gold standard for diagnosing and evaluating congenital uterine malformations [19, 20]. However, endoscopic diagnosis relies on the surgeon's subjective impressions and lacks strict objective criteria and measurements; thus, it does not allow assessments of subtle uterine morphological differences [21]. The AFS classification system, which is used routinely, does not include morphological criteria. With the inability to perform exact measurements, it is not surprising that there is wide variability in estimations of the prevalence of uterine anomalies among different studies, and more specifically, in the diagnoses of septate and arcuate uteri. Without a means for making accurate measurements and standardised procedures for performing these measurements, it will not be possible to determine the true incidence of uterine congenital anomalies and their impact on fertility and reproductive outcome.

The 3-D ultrasound approach offers a promising means for making exact measurements of morphological alterations in congenital uterine pathology (Fig. 9.2). A study by Salim et al. [22] reported very good inter-observer agreement

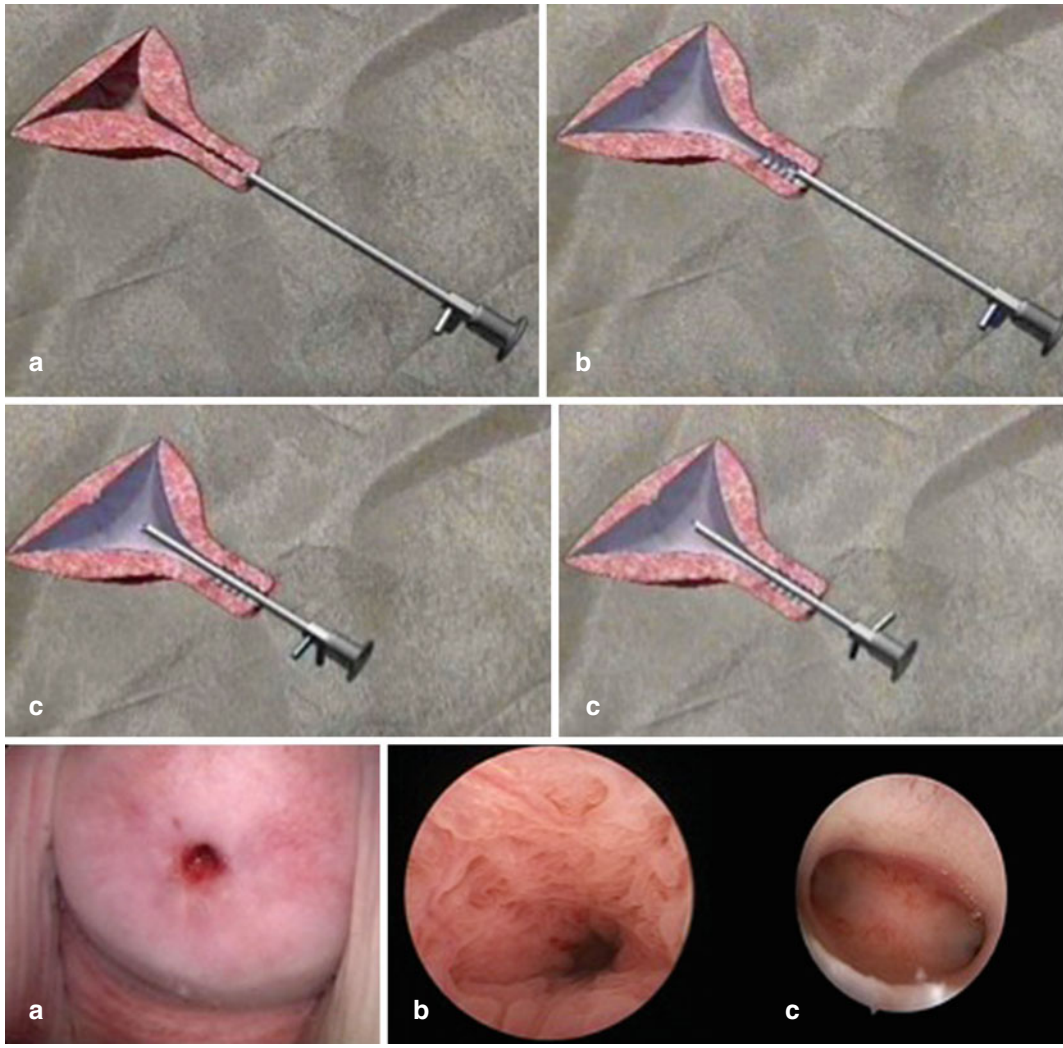

Fig. 9.1 Vagino-cervico- hysteroscopy provides a minimally traumatic performance of diagnostic hysteroscopy. It only requires a hysteroscope and a watery distension medium. Steps: (**a**) hysteroscope locates the cervix with visualisation of ostium externum cervici; atraumatic insertion of the small hysterosope: the distension medium dilates the cervical channel; (**b**) visualisation of the direction of the cervical channel with further insertion into the uterine cavity; after insertion, the hysteroscope is rotated about the axis for visualisation of the uterine cavity (**c**)

with 3-D ultrasound measurements. They demonstrated the feasibility of performing studies to investigate the reproducibility of diagnoses of uterine anomalies. Once exact measurement techniques are standardised, it will be possible to make comparisons among data from different studies.

In a recent publication, Ludwin et al. [23] compared the accuracy of 2-D and 3-D ultrasound to the gold standards of hysteroscopy and laparoscopy. They demonstrated accuracies of 100 % for 3-D SIS, 97.4 % for 3-D, 94 % for 2-D SIS, and 90.6 % for 2-D, when performed by experts. Several other studies have also mentioned high accuracy rates for 3-D ultrasound in the detection of uterine anomalies compared to hysteroscopy and laparoscopy [24–26]; the best results showed 100 % sensitivity, specificity, and accuracy.

There is growing evidence that 3-D ultrasound may replace hysteroscopy and laparoscopy as the gold standard for the diagnosis and classification of aberrant uterine morphology; particularly for

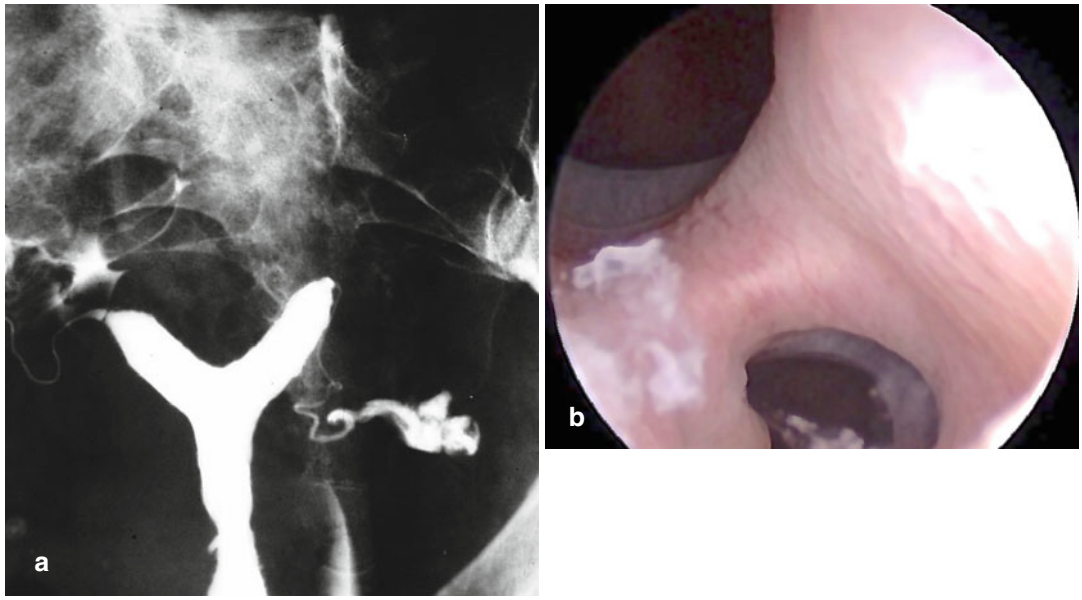

Fig. 9.2 Like the HSG, (**a**) hysteroscopy (**b**) shows a clear division in the uterine cavity. A 3D ultrasound examination is required to make a final differential diagnosis between a partial septate uterus (U2a) or a partial bicorporeal uterus with (U3c) or without a partial septum (U3a)

non-complex uterine anomalies, like classes U1, U2, and U3, according to the new classification system of Grimbizis et al. [27, 28]. Although hysteroscopy is currently considered a minimally invasive procedure, it requires training, and the risk of complications remains relevant [29].

In the diagnosis of more complex anomalies, hysteroscopy and laparoscopy continue to play important roles. In adolescents with severe dysmenorrhoea, a complete exploration should be performed, starting with a careful examination of the vagina. A visualisation of the cervix should be performed by direct visual inspection or by vaginoscopy, and it is necessary to exclude cervicovaginal aplasia. Additional information can be gained with indirect visualisation methods, like 3-D ultrasound and magnetic resonance imaging (MRI). Indirect imaging should be conducted for identifying the presence, localisation, and size of haematometra, haematocolpos or pyocolpos. MRI is typically reserved for complex or indeterminate cases, it is non-invasive and allows excellent soft tissue visualisation [30]. Non-descended ovaries are well known to occur in case of uterine anomalies [31]; due to difficulties in visualising the key regions, this condition can be missed with laparoscopy. MRI can be useful for locating these ovaries. Some authors advise performing ovarian stimulation with clomiphene to improve and facilitate visualisation of these ovaries during MRI [32].

Laparoscopy can provide the means for exact descriptions of aberrant uterine anatomy, it can detect the partial presence or absence of tubes and ovaries, and it can determine normal or abnormal positioning. Laparoscopy is also necessary for a differential diagnosis of uterine malformations, like a non-communicating rudimentary horn or juvenile cystic adenomyoma [33].

Many patients experience problems with infertility or recurrent pregnancy losses; thus, concomitant pathology that might interfere with fertility must be excluded. Among cases of congenital uterine anomalies, endometriosis occurred in 20–30 % of patients [8, 34–37]. Among cases with obstructive pathology,

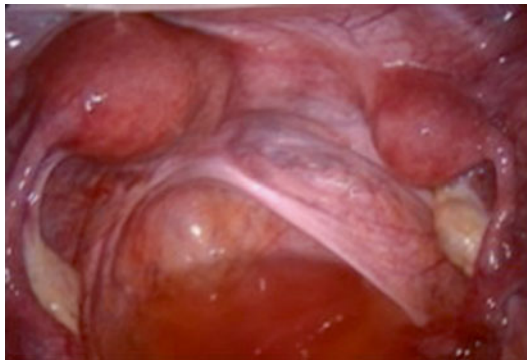

Fig. 9.3 Laparoscopic visualisation of a hemi uterus (*left*) with a rudimentary horn (*right*). With additional ultrasound, a differential diagnosis would be possible between Class 4a (with rudimentary cavity) and Class 4b (without rudimentary cavity) morphology

endometriosis occurred in 77 % of patients [38]. Laparoscopy offers the potential for both diagnosing and surgically treating pathology, when indicated.

Laparoscopy provides direct visualisation of the pelvis and facilitates the identification of congenital uterine anomalies. However, it requires the aid of indirect imaging techniques to determine whether a rudimentary cavity is present in cases with a rudimentary horn (Fig. 9.3).

The benefit of direct endoscopic visualisation of the pelvis and uterine cavity be balanced against the risk of related complications. Laparoscopy is not an innocuous procedure with up to 50 % of complications related to laparoscopic entry [39].

Conclusion

Hysteroscopy and laparoscopy continue to be considered the gold standard for the identification of congenital uterine anomalies; both techniques are inconvenient, because they cannot provide information on the composition of the soft tissues, like the uterine muscular wall, or the presence of a rudimentary cavity. The currently available data provide strong evidence that the non-invasive 3-D ultrasound /3-D SIS technique is very accurate for diagnosing non-complex uterine anomalies (classes U1, U2, U3). For that purpose, the latter technique can be considered the preferred method, and it may become a mandatory procedure. The visualisation of the contours of uterine soft tissue is an added value; it allows the differential diagnosis between U2 and U3 abnormalities. In more complex cases, the full arsenal of diagnostic tools should be used, including a clinical examination, 3-D ultrasound, MRI, hysteroscopy, and laparoscopy. Direct visualisation with hysteroscopy and laparoscopy will provide information on the presence of concomitant pathology that can impair fertility. Performance of a full exploration will enable the physician to provide the patient with exact information and obtain fully informed consent before attempting a surgical correction.

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Current Work-Up for Screening and Diagnosing Female Genital Malformations

10

Attilio Di Spiezio Sardo, Marialuigia Spinelli, and Carmine Nappi

Introduction: Definition and Epidemiology

The diagnostic work-up for female genital tract anomalies continues to represent a great challenge for the gynaecologist due to the presence of various techniques available for the diagnosis that differ in their invasiveness, availability, needs for training and, more importantly, diagnostic accuracy. It seems that, despite advances in ultrasound and new pelvic imaging techniques, late diagnosis of female genital tract anomalies remains frequent, accounting for 10 % of the causes of primary infertility [1].

Furthermore the current dispute for diagnosing female genital tract anomalies embeds its roots in the terminologic issue, from which it derive concerns for definition and, consequently, classification of such anomalies [1, 2].

A key topic in the "*terminology*" used for the description of female genital tract anomalies is the misleading use of the various terms for their definition: "uterine anomalies", "congenital malformations of the female genital tract" and "Mullerian anomalies" often used as synonymous, although they, actually, are referring to different concepts. The expression "congenital anomalies of female genital tract" includes those malformations that affect the development and morphology of the Fallopian tubes, uterus, vagina and vulva, with or without associated ovarian, urinary, skeletal or other organ malformations. On the other hand, "Mullerian anomalies" include those malformations that affect the embryological development of paramesonephric ducts, also called Mullerian ducts, thus being only part of the female genital anomalies. Furthermore, only a subcategory of Mullerian anomalies is represented by "uterine anomalies". However, as most of the "female genital tract malformations" affect the uterus, they are often reported as "uterine" or "Mullerian" (paramesonephric) malformations explaining the existing confusion in the terminology [1–5].

The true incidence of congenital anomalies of female genital tract in the general population and among women with poor reproductive outcome is not known accurately. Although incidences of 0.16–10 % have been reported, recent reviews of all published studies [6–8] suggests an incidence of ~5.5–6 % in the general population, 8 % in infertile women, 16 % in women with recurrent pregnancy loss and poor reproductive outcomes and 24.5 % in those with miscarriage and infertility. Overall, the prevalence of major congenital anomalies appears to be at least ~ three-fold higher in women with poor reproductive outcome compared with general population [8].

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Diagnostic Work-Up for Female Genital Tract Anomalies: Opened Issues

Currently, despite technical and technological advances of the diagnostic imaging techniques in gynecology, the work-up for screening and diagnosing female genital tract anomalies is still long lasting and twisted. Several reasons have been claimed to explain such an issue.

First, *non-specific symptomatology can be associated with such anomalies* [9, 10], since it may vary from being asymptomatic to various forms of impaired reproductive outcome and, in more complex forms to obstructive phenomena. Indeed, most of female genital tract anomalies are not easy to be detected, as most of them remain unrecognized until the radiologic exploration for infertility or for a history of recurrent miscarriage. Moreover, clinical symptoms leading to the diagnosis could vary depending on the type of the anomaly. Therefore, the course of patients before appropriate diagnosis could be long and difficult because of these inconsistent and wide-ranged symptoms. According to Mazouni et al. [1], the circumstances leading to the diagnosis were infertility (33.6 %), repeat miscarriage (18.2 %), ultrasonography during pregnancy (12.7 %), pregnancy complications during third trimester (11 %), abnormal findings during gynaecological examination (8.2 %) and, other miscellaneous causes (16.3 %). Furthermore, some forms of uterine anomalies are diagnosed in childhood and adolescence [10]. Indeed, obstructive forms of female genital tract malformations are, usually, detected during adolescence, when young girls experience dysmenorrhea, pelvic pain, or difficulty in inserting tampons.

Secondly, *the diagnosis in most cases is late*, *generally in the third decade of life*, *and multiple diagnostic examinations are often scheduled before formulating final diagnosis*. Mazouni et al. [1] analysed the diagnostic work-up of 110 women with a "suspicious" of congenital uterine anomalies. Radiologic diagnosis required two complementary imaging techniques in 62 % of patients and more than two in 28 %. The correct diagnosis was established in only 40 % of cases before hospitalization. Most of the anomalies were initially diagnosed at hysterosalpingography and ultrasonography. The mean time between the first imaging examination and the diagnosis in a specialized department was 6.7 months. The authors concluded that the diagnosis of female genital tract anomalies in adults is often made at the time of conception and/or obstetric complications. They revealed that there is a tendency toward the use of multiple imaging techniques and this delayed the diagnosis.

Thirdly, *a consensus is difficult to be reached in that experts are still strongly "anchored" on their own beliefs*, comforted by scientific evidence all equally acceptable. Another problem seem to be the lack of communication among experts, and moreover, the difficulty for each of them to read other's reports. Overall, it would be desirable that the training of general practitioners and sonographers be improved, in order to, (1) increase the diagnostic accuracy of the currently available imaging diagnostic techniques and, (2) enhance the use of a standardized diagnostic codes, in order to improve communication among different specialists.

Is There a Place for Screening in the Diagnosis of Female Genital Anomalies?

In order to critically analyze the currently existing open issues in the diagnostic work-up of female genital tract anomalies, it is important to start describing the differences between screening and diagnostic tests. Thus, as screening test (the term screening comes from the verb "to screen", that is like "to scour", "to sieve") is defined any method used to detect early disease or risk factors for a disease in a large numbers of apparently healthy individuals, without signs or symptoms. On the contrary diagnostic tests determine the presence or the absence of a disease when a subject has signs or symptoms of that disease. Screening tests are not designed to be diagnostic. In other words, we cannot know what we are looking for, if we don't understand which are our expectations.

Screening can be: (1) universal, involving screening of all individuals in a certain category, or (2) case finding, involving screening a smaller group of people based on the presence of risk factors. On the other hand, diagnostic tests are performed after a positive screening test to establish a definitive diagnosis.

The main principles of screening process are the following: (1) the condition should be an important health problem, (2) there should be a treatment for the condition, (3) facilities for diagnosis and treatment should be available, (4) there should be a latent stage of the disease, (5) there should be a test or examination for the condition, (6) the test should be acceptable from the population, (7) the natural history of the disease should be adequately understood, (8) there should be an agreed policy on whom to treat, (9) the total cost of finding a case should be economically balanced in relation to medical expenditure as a whole and, finally, (10) case-finding should be a continuous process, not just a "once and for all" project.

However, a screening program has also some important limitations: (1) screening can involve cost and use of medical resources on a majority of people who do not need treatment, (2) adverse effects of screening procedure (e.g. stress and anxiety, discomfort, radiation exposure, chemical exposure), (3) stress and anxiety caused by a false positive screening result, (4) unnecessary investigation and treatment of false positive results, (5) stress and anxiety caused by prolonging knowledge of an illness without any improvement in outcome and, (6) a false sense of security caused by false negatives, which may delay final diagnosis.

Hence, *the first challenge for female genital tract anomalies is the attempt to specifically apply the principles of a possible screening process to such anomalies*. A screening program for female genital tract anomalies would be desirable because many of them, if early diagnosed (i.e. before these women have reproductive desire) could prevent many disease-associated obstetrical and gynecological complications. The primary purpose of screening of female genital tract anomalies should be to detect them early or detect "risk factors" for such condition in individuals without signs or symptoms.

However, despite the facts that female genital tract anomalies have, as already reported, an estimated prevalence of 4–7 % in the general population [8], and their occurrence could be associated with many reproductive problems [11], the following are the main limitation for the widespread of a screening program for them:

1. Costs: involving all women of reproductive age is not convenient. The test is too expensive considering his infrequence
2. Established risk factors: except for a few selected cases, there are not certain risk factors and,
3. Some principles of screening cannot be satisfied: for example, not all the female genital tract anomalies are surgically correctable, in many clinical contests there is a lack of facilities for diagnosis and treatment; for female genital tract anomalies a latent stage of the disease is missing; there is a lack of an agreed policy on whom to treat. Finally, the total cost of finding a case in some cases is not economically balanced in relation to medical expenditure as a whole.

However, analyzing the data critically, we could realize that there is a paradox: indeed, considering the overall population, the screening may result too expensive, useless and statistically ineffective; however, on the contrary, considering the single individuals, a screening program is clinically useful and effective, mostly when it is confirmed successively by a proper diagnostic test.

Therefore, in order to overcome the "*screening paradox*", we should "minimize" the screening program, trying to adapt it to the specific issues raised by the complex diagnostic work-up of female genital tract anomalies. In other words, it would be desirable to select those individuals who may have a benefit from the screening, in order to obtain an early diagnosis, avoiding the use of multiple imaging techniques and, ultimately, a delayed treatment. Furthermore, in the light of these considerations, second-line examinations (which are expensive, or invasive, or requiring complex procedures and/or expert

operators) should be scheduled only in those patients selected by a proper screening program.

From Screening to Diagnosis: The Need for Classification

For moving from screening to diagnosis a proper diagnostic route is needed. Every diagnostic process is a process of knowledge. And as the Masters of ancient Greece teach us, the process of knowledge can be dual: deductive or inductive. The philosophical definition of inductive reasoning consists of a progression from particular/individual instances to broader generalizations. Thus, the premises of an inductive logical argument indicate some degree of support (inductive probability) for the conclusion but do not entail it; that is, they suggest truth but do not ensure it.

It seems reasonable for us, the diagnostic route of female genital tract anomalies to follow the inductive reasoning: in other words, a woman suspected to have a female genital malformation (inductive probability) should be investigated by specific second-line examinations which should provide more details of the anomaly; successively, the final diagnosis should be obtained integrating all data provided by the second-line diagnostic tests.

But, what is specifically required for an "ideal" diagnostic test for such anomalies? First, to identify the presence of the anomaly; secondly, to differentiate among the various subtypes; and, finally, to select which abnormalities are amenable to treatment. However, for satisfying the second as well as the third request, a proper classification system is required.

Until few years ago, a clear categorization that might allow effective differential diagnosing and, consequently, planning an effective therapeutic strategy did not exist. Over time, at least three systems have been proposed for the classification of female genital tract anomalies, although historically attempts for their categorization started quite earlier: the American Fertility Society's (AFS) [4] currently American Society of Reproductive Medicine system, the embryological-clinical classification system [2] of genito-urinary malformations and the Vagina, Cervix, Uterus, Adnexae and associated Malformations system based on the tumor nodes metastases (TNM) principle in oncology [12]. Although each proposal did not receive the same acceptance, with that of the AFS classification system to be higher than the others, all of them seem to be associated with serious limitations in terms of effective categorization of the anomalies, clinical usefulness, simplicity and friendliness. It is noteworthy to mention that these limitations also gave place to further subdivisions for certain categories of anomalies [13, 14]. A systematic re-evaluation of the current proposals, within a project of the European Academy for Gynecological Surgery (EAGS), has been already published underlying the need for a new and updated clinical classification system [15, 16].

An "ideal" classification system should be clear and accurate for diagnosis and differential diagnosis, comprehensive, incorporating all possible variations, correlated with the clinical presentation and the prognosis of the patients, correlated with the treatment of the patients. In other words, it should be as simple as possible, aimed at avoiding both an over-treatment and an under-treatment. Recently, a working group under the name CONUTA (CONgenital UTerine Anomalies) composed by experts of the European Society of Human Reproduction and Embryology (ESHRE) and the European Society for Gynaecological Endoscopy (ESGE), have developed a new updated classification system, primarily based on the anatomy of the female genital tract [17].

Indeed, according to this new ESHRE/ESGE classification system, anomalies are classified into the following main classes, expressing uterine anatomical deviations deriving from the same embryological origin: U0, normal uterus; U1, dysmorphic uterus; U2, septate uterus; U3, bicorporeal uterus; U4, hemi-uterus; U5, aplastic uterus; U6, for still unclassified cases. Main classes have been divided into sub-classes expressing anatomical varieties with clinical significance. Cervical and vaginal anomalies are classified independently into sub-classes having clinical significance (See Chap. 4). This new classification system seems to surmount the

limits of the previous proposals, satisfying the expectations and the needs of the scientific community; nonetheless, its clinical effectiveness still needs to be proved in routine practice.

In the near future the ESHRE/ESGE classification system of female genital anomalies could be used as a starting point for the development of guidelines for their diagnosis and treatment.

Diagnostic Accuracy of the Different Methods

Hysteroscopy allows direct visualization of the intrauterine cavity and tubal ostia. It is, therefore, very accurate in identifying congenital uterine anomalies and is often used to establish a definitive diagnosis after an abnormal HysteroSalpigoGraphy (HSG) finding (See Chap. 5). However, it does not allow the evaluation of the external contour of the uterus and is, therefore, often inadequate in differentiating between different anomaly subtypes. Consequently, for the correct differentiation between the different subtypes, further investigation is required. The diagnostic accuracy of hysteroscopy, compared with other examinations, is reported in Table 10.1.

Traditionally, diagnostic laparoscopy is considered the best complementary examination to hysteroscopy, and the *combination hysteroscopy/laparoscopy is accepted as the* "gold standard" *in evaluating congenital uterine anomalies*. Hysteroscopy with laparoscopy offers the added advantage of concurrent treatment, as in the case of a uterine septum resection.

However, laparoscopy is an invasive and expensive one, therefore the scientific efforts have recently focused at allowing the differential diagnosis of the various anomaly subtypes without it. Furthermore, with the new ESHRE/ESGE classification and the need to measure fundal, septal and lateral uterine wall thicknesses, it could be hypothesized that the actual gold standard test may be replaced by another imaging modality in the future. Indeed the laparoscopic approach does not always allow accurate and objective uterine measurements. Furthermore, another theoretical limit of any endoscopic imaging technique, including either hysteroscopy alone or the current hysteroscopic and laparoscopic "gold standard" approach, is that they are based only on the subjectively impression of the clinician who performs the examination and do not always allow accurate and objective uterine measurements.

Table 10.1 Classification of investigation according to diagnostic accuracy

Class Ia
Investigations capable of accurately identifying congenital uterine anomalies and classifying them into appropriate subtypes (accuracy >90 %):
Hysteroscopy and laparoscopy
SHG
3D US
Class Ib
Investigations capable of accurately identifying congenital uterine anomalies without being able to classify them into appropriate subtypes (accuracy >90 %):
Hysteroscopy alone
Class II
Investigations capable of identifying congenital uterine anomalies (accuracy <90 %):
HSG
2D US
Class III
Investigations of which the accuracy in diagnosing congenital uterine anomalies is uncertain:
MRI
Physical examination during pregnancy or delivery

Modified from Saravelos et al. [18]

Various types of ultrasound examinations are nowadays available for the diagnostic of female genital anomalies [18, 19]. They have the advantages of being non-invasive, easily accessible and well-accepted form the patients. With the use of various ultrasound techniques measurable and objective estimations of uterine wall, uterine cavity and the external uterine contour could be done.

Two dimensional ultrasound is simple, available in almost every outpatient clinic, and can give reliable, reproducible and measurable informations on uterine anatomy, leading to the exact diagnosis as well as the differential diagnosis between the different categories (See Chap. 6). However, it has a lower diagnostic accuracy in

comparison with the other sonographic techniques (Table 10.1) [18–20].

Hystero-contrast-sonography (HyCoSy) by using the contrast medium in the uterine cavity offers the additional advantage of a better internal delineation of the uterine contour, providing additional information of the morphology of the uterine cavity; furthermore, it is an office procedure, with low risk and high patient satisfaction rates (See Chap. 6) [21]. However, some patients experience some degree of pain, which is however reduced compared to HSG or hysteroscopy. The diagnostic accuracy of this method is estimated to be higher, with a sensitivity and specificity of 93 and 99 % respectively [18] (Table 10.1).

Three dimensional Ultrasound is a non invasive and highly reproducible method of investigation, which provides the simultaneous view of the three planes of the uterus, along with the complete volume scan (See Chap. 7) [18, 22]. Due to its highest diagnostic accuracy (Table 10.1) it seems that it could be the new "gold standard" in the diagnosis of female genital malformations especially the uterine ones.

Recently, new data are emerging regarding the integration of hysteroscopic findings with 3D US data. This trend is motivated by safety and non-invasiveness of 3D US and by its high accuracy (class IA). Indeed, 3D US in expert hands enables clear visualization of the uterine fundus and investigation of coexisting adnexal disease [18, 22].

Magnetic resonance imaging (MRI) (See Chap. 8) is a relatively sensitive tool (Table 10.1) and some authors suggest that it could supply invasive procedures such as hysteroscopy and laparoscopy for the diagnosis of a malformed uterus, especially in cases of adolescent patients and/or children in which the diagnosis is performed for other reasons than infertility (ie pelvic pain, menstrual abnormalities etc). The disadvantages of this technique are that it is expensive and not available in many clinical contests [18, 19].

The evidence to date suggests that several investigations have a satisfactory overall accuracy in diagnosing the presence of a female genital tract congenital anomaly. The most accurate investigations in order seems to be: (i) 3D US, (ii) HyCoSy, (iii) MRI, (iv) 2D US and (v) HSG [8].

However, it seems that conclusions as to which investigations are able to correctly subclassify the anomalies could not be considered as completely final. This is due to the fact that, prior to the ESHRE/ESGE classification, in the absence of clear definitions, there was no unanimous agreement how to objectively distinguish between the normal and the arcuate uterus, the arcuate and the septate uterus, the bicornuate and the didelphys uterus and the combined septate bicornuate uterus.

As the concordance between 3D US and combined hysteroscopy and laparoscopy appears to be the high (Table 10.1), and considering the need to obtain accurate measurements of the uterine walls in order to make the appropriate diagnosis (as highlighted in the new ESHRE/ESGE classification), it appears that the new gold standard method of choice should be the 3D US.

A Diagnostic Algorithm for Female Genital Tract Anomalies: Proposals

Looking for a diagnostic algorithm for female genital tract anomalies, it is out of doubt that all the available first- and second- line diagnostic tools used for diagnosing such anomalies present advantages and disadvantages and that, generally, the final diagnosis is possible only by integrating two or more examinations (Fig. 10.1).

However, the current proposal for the investigation does not include the phase of the screening. This is, mainly, due to the fact that the question, which should be the choice in case of a suspicious uterine anomaly, could not be answered.

It seems that a wide variety of diagnostic tests are available for the interpretation of the female genital tract anatomy; their diagnostic properties as well as their diagnostic accuracy was presented previously. It seems that, based on the clinical presentation of the patient, the clinician should start with the gynaecological examination before scheduling the patients for imaging techniques. HSG cannot be considered as a first line diagnostic tool, and should be used under specific conditions only. On the contrary, 2D-US seems to

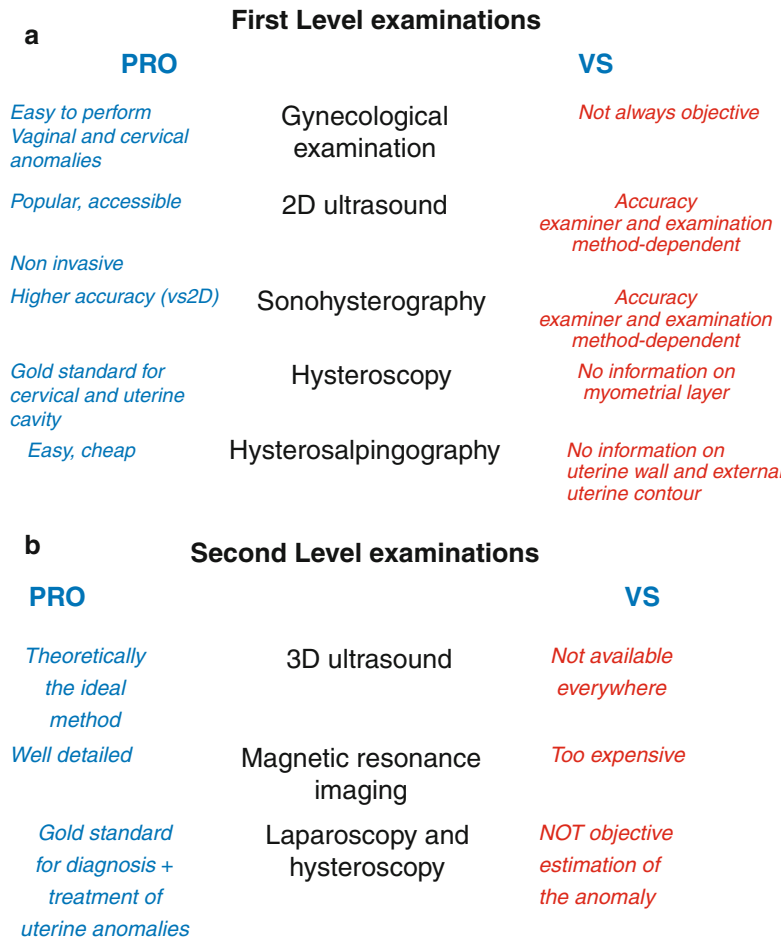

Fig. 10.1 The available first- (**a**) and second- (**b**) line diagnostic tools used for diagnosing female genital tract anomalies with their advantages and disadvantages

be the basic imaging method; in case of suspected female genital anomaly or straightaway in case of high risk population, further detailed information on inner and outer uterine anatomy can be then obtained with the use of 3D-US (Fig. 10.2). HyCoSy and ambulatory mini-hysteroscopy can be used whereas specifically indicated (i.e. evaluation of tubal patency, suspicious of intrauterine pathologies or evaluation of double uterine cavity).

Thus, according with the updated evidence, the finding of a suspicious "double" uterine cavity as well as of a suspicious "dysmorhic" uterus (T-shaped or tubular shaped/infantilis uterus) suggests the indication for a 3D-US. In case of "double" uterine cavity, the sonographer provides us with important data, following the directions provided by Gubbini et al. in this paper published in 2009. This technique makes it possible to obtain a coronal view of the uterus, which usually lies perpendicular to the ultrasound beam. Analysis of uterine architecture is performed in a standardized plane using the interstitial portions of the fallopian tubes as reference points. The distance between the midpoint of the line joining these points (interostial line) and the distal tip of fundus indentation or septum are measured in each patient. In addition, the distance between the midpoint of the interostial line and the fundus external contour was measured. In this way, all "double" uterine anomalies are sub-classified in 12 categories (Fig. 10.3).

In case of "dysmorphic" uterus, analysis of uterine architecture is performed in a standardized plane using the interstitial portions of the fallopian tubes as reference points. The distance

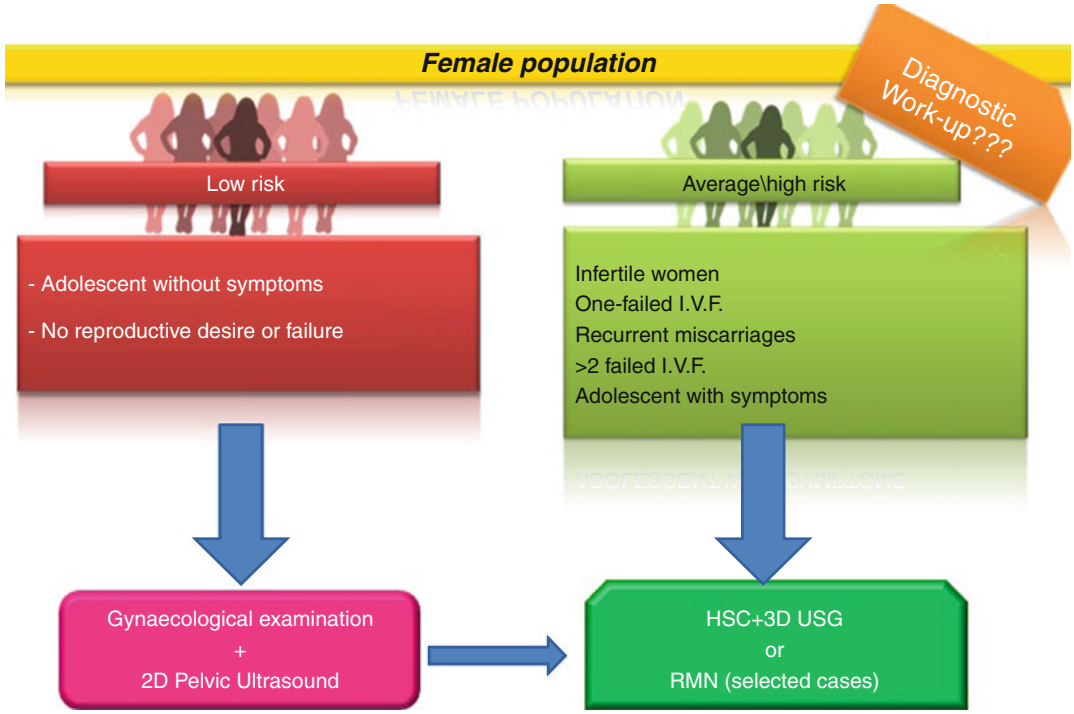

Fig. 10.2 A proposal of diagnostic algorithm for female genital tract anomalies

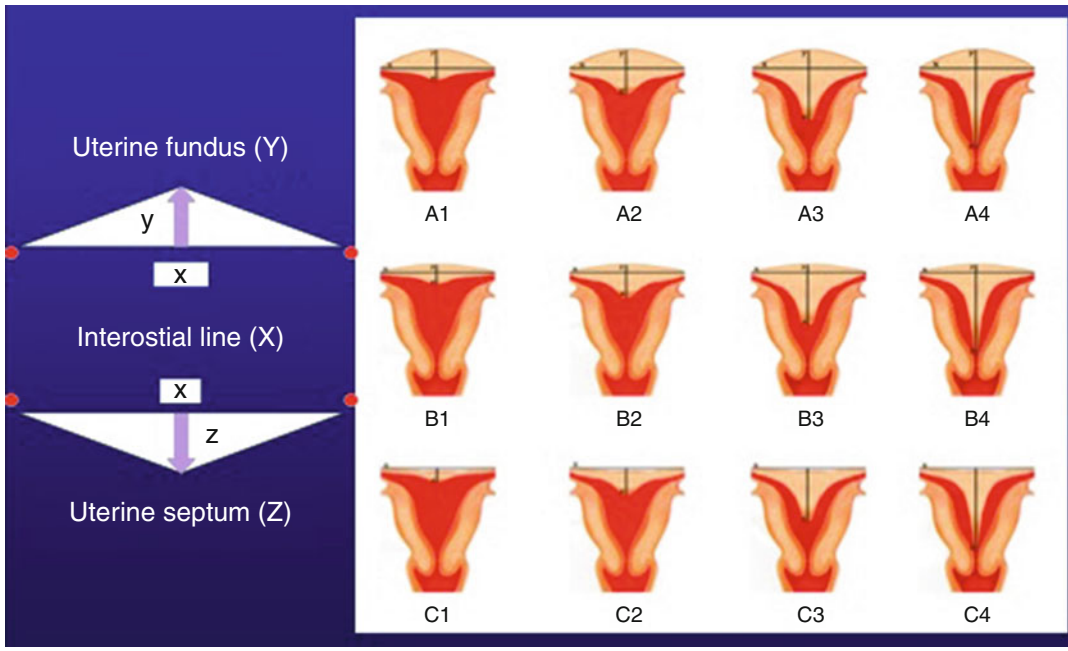

Fig. 10.3 Three subgroups (**A**-**B**-**C**) are identified according to the variable Y: (**A**) Normal uterine fundus; (**B**) Straight uterine fundus; (**C**) Concave uterine fundus. Four subgroups (**1**-**2**-**3**-**4**) are identified according to the Z variable: (**1**) septum ≤ 0,5 cm ; (**2**): septum interests 1/3 of the uterine cavity; (**3**): septum interests 2/3 of the uterine cavity; (**4**): septum interests 3/3 of the uterine cavity. Subclassification system for "double" uterine cavity proposed by Gubbini et al. [13]

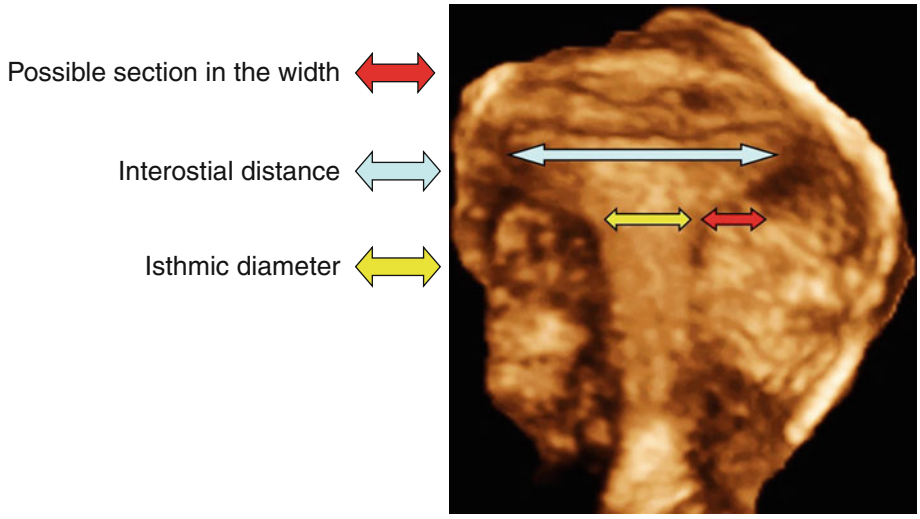

Fig. 10.4 Three-dimensional transvaginal ultrasound imaging referring to the landmarks of the metroplasty for dysmorphic uteri (HOME-DU technique): the distance between tubal ostia (IO, interostial distance); the transversal diameter at the isthmus (I, isthmic diameter), as well as the depth of the healthy myometrium up to the serosa (in whom sections are allowed)

between tubal ostia, the transversal diameter at the isthmus, as well as the thickness of the uterine side walls and the depth of the healthy myometrium up to the serosa are measured (Fig. 10.4).

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Part III

Clinical Implications of the Female Genital Malformations

Prevalence in the General and Selected Populations

11

Sotirios H. Saravelos and Tin-Chiu Li

Introduction

The female genital tract malformations have gained increased interest in the last few years in both the scientific and the public eye. The reason for this is the increasing awareness and incidence of reproductive failure, and the striving of clinicians and patients to improve reproductive outcomes. With more and more comprehensive assessments as part the work-up for any woman with reproductive failure, the female genital tract malformations are becoming more and more evident owing to improved imaging modalities. Important developments in the last couple of decades include non-invasive 3-dimensional ultrasound (3DUS) and magnetic resonance imagining (MRI) but also minimally invasive office hysteroscopy all of which can diagnose the presence of a female genital tract abnormality with accuracy and ease.

However, clinicians have to remain cautious with the large influx of information that will be becoming available, as many will encounter an increasing number of patients being diagnosed with a female genital tract malformation either as part of a targeted work-up or entirely incidentally. There will be several questions that need to be addressed: Which female genital tract anomalies cause reproductive failure and obstetric complications? Which malformations need to be treated? Which patients need to be treated? When should malformations be left alone? To start with, the most prudent of questions in any such context are the questions of epidemiology: How common are these malformations? Are they indeed more common in women with reproductive failure and obstetric complications? Are specific malformations more common in women with reproductive failure and obstetric complications? Answering these questions will help not only with the counselling and treatment of women on an individual basis, but also gauges the magnitude of the problem and allows for planning of services at regional or national level.

In this chapter, the epidemiology of female genital tract malformations will be critically discussed, explaining the difficulties that exist in estimating the prevalence accurately, how the most current estimates have been derived, and where new developments will be taking us in the future.

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Why Is It So Difficult to Estimate the Prevalence?

One of the main issues concerning the subject of female genital tract malformations has been the lack of consistency in the estimates of prevalence. Certainly until the turn of this century it was not clear how prevalent female genital tract malformations were in different populations of women. The reason for this was that most studies were lacking three indispensable key factors that are required for the accurate estimation of the prevalence of these malformations:

1. A clear definition and selection of the populations examined.
2. The use of a clear and consistent classification of the malformations.
3. The use of accurate investigations to make the correct diagnosis of the malformations.

Populations

In terms of the populations examined, an unselected or general population needs to provide the background prevalence of the condition and serve as a comparison for other population groups. However, often even the 'general population' may be subject to selection bias, as historically women may have been screened for female genital tract malformations during pregnancy or labour [1], or due to suspected pathology due to symptoms such as dysfunctional bleeding, or pelvic pain [2]. This in itself may affect the estimated prevalence of a true unselected population, as for example women who are already pregnant may have lower rates of female genital tract malformations, whereas women with pelvic pain or even polycystic ovaries may have higher rates of female genital tract malformations [3, 4].

In terms of selected populations, the most relevant populations examined are those of infertile women and women with recurrent miscarriage. In women with infertility, the definition of infertility, the duration of infertility and whether it primary or secondary may affect the prevalence of malformations. In addition, whether women with unexplained infertility or all women with infertility have been investigated will affect the prevalence; for example in couples where male factor infertility is present, women may be expected to have a similar prevalence of female genital tract malformation compared with women of the general population.

In women with recurrent miscarriage, it is of upmost importance to consider the definition used. Traditionally, the European Society of Human Reproduction and Embryology (ESHRE) has considered three or more miscarriages as the definition of recurrent miscarriage [5], whereas the American Society for Reproductive Medicine (ASRM) has considered two or more miscarriages as part of the definition [6]. Furthermore, the kind of miscarriages included within the definition are important and particularly whether biochemical pregnancy losses are included or not. For example, in the definition of the ASRM, it is explicitly mentioned that only pregnancies with ultrasonographic or histological evidence will be included in the definition. Interestingly, there have been studies that have shown that the prevalence of female genital tract malformations are similar in women with two versus three miscarriages [7, 8]. However, common logic would suggest that women with two early biochemical pregnancy losses secondary to aneuploidy may be less likely to have lost their pregnancies due to a female genital tract malformation compared to women with three of more late miscarriages with normal karyotypes of the conceptus. Along this train of thought it could be argued that correcting malformations for women that have lost pregnancies due to aneuploidy alone may not be entirely justified.

Classifications

In terms of the classifications that have been used to diagnose female genital tract malformations, there have been many changes over the last few decades. This has made the consistency of prevalence estimates very difficult due to the use of different classification systems.

The first classifications for female genital tract malformations originated from the mid-nineteenth century with descriptions from Cruveilher, Foerster and von Rokitansky between 1842 and 1859 [9]. Several publications describing various classifications were subsequently published and

used interchangeably until Buttram and Gibbons proposed a classification based on the degree of failure of the Mullerian ducts to develop normally, and devised groups of anomalies with similar manifestations, treatments and prognoses [10]. This was later revised and modified by the American Fertility Society (currently the ASRM) to provide the most universally accepted and used classification for 25 years [11]. Although recent advances in imaging now permit subtle differences between anomalies to be detected, the AFS classification did not provide clear definitions which would permit clear distinction between certain sub-types [12]. For example, it was difficult to differentiate between a complete bicornuate uterus and a didelphys uterus, between a subseptate uterus and an arcuate uterus, and between an arcuate uterus and a normal uterus. Newer novel classifications such as the VCUAM classification [13] and the Embryological clinical classification for female genitourinary problems [9, 14] unfortunately did not solve this problem, and for this reason the European Society for Gynaecological Endoscopy (ESGE) and the European Society for Human Reproduction and Embryology (ESHRE) combined to form a working group in order to create a new classification system. The final classification was published jointly in 2013 and received wide acceptance of the scientific community experts through formal voting procedures [15, 16]. Perhaps the most important novelty of this new classification is that the entities of arcuate uterus and didelphys uterus have been abolished, and are now incorporated in the subdivisions of the septate and bicorporeal uteri respectively. Furthermore, the new classification system introduced the concept of objective, quantitative measurements to diagnose these anomalies, which is discussed in further details in another chapter of this book.

Unfortunately, despite the current availability of this new classification, the prevalence estimates to date are inadvertently based on studies using the AFS classification. As a result, the main limitation we face is that it is not clear which uterine anomalies of the 'arcuate' type would fall into the 'normal uterus' category and which would fall into the 'subseptate uterus' category of the new ESGE/ESHRE classification.

Investigations

Perhaps the most important factor affecting the estimates of prevalence of the female genital malformations are the different investigations used to diagnose them. These can include, physical/gynaecological examination, hysterosalpingogram, 2D US, 3D US, saline infusion US, MRI, hysteroscopy and laparoscopy. In the past, studies have estimated the prevalence of female genital tract malformations using any of these different modalities. However, the accuracy of each investigation is significantly different. The most important factor to consider is whether the chosen investigation can examine accurately both the internal and external contour of the uterus to make a precise diagnosis. For example, performing HSG or hysteroscopy *alone* may show an indentation of the internal uterine contour but will not be able to assess the external contour to differentiate between a septate or bicorporeal uterus.

As a result, the most accurate investigations according to a systematic review assessing the sensitivity, specificity, positive and negative predictive value of all modalities, are 3D US, saline infusion US, MRI and combined hysteroscopy and laparoscopy (Table 11.1) [17]. Therefore, accurate assessments of prevalence of female

Table 11.1 Accuracy of different investigations in the diagnosis of congenital uterine anomalies

Diagnostic modalities	Cases (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
2D US	350	56	99	96	87	84
HSG	625	78	90	83	91	86
SIU	486	93	99	97	98	97
3D US	679	100	100	100	100	100
MRI	24	100	100	100	100	100
Hysteroscopy Laparoscopy	Used as gold standard					

Adopted from Saravelos et al. [17]

genital tract malformations should involve only any of these four modalities.

Evolution of Estimates

When a clear definition of population, a consistent use of classification, and application of accurate investigations are *not* used, the estimates of prevalence of female genital tract malformations can be misleading. For example, analysing the prevalence from over half a million unselected women using all possible modalities from 1947 to 1990 gives an overall prevalence of female genital tract malformations of 0.16 % [1], which today we know is approximately a 50-fold underestimation. Similarly when analysing the reported rates of malformations for selected populations using different investigations from the last three decades, the reported rates vary significantly from 0.4–10.8 % for the general population [18, 19], to 1–48.9 % for the infertile population [20, 21], and from 0.5 to 65.8 % for the recurrent miscarriage population [22, 23] (Table 11.2). Of course, such a wide range of prevalence is rather meaningless.

Recent systematic reviews have therefore tried to tackle this issue. When looking at the three largest systematic reviews of the past 15 years, it is interesting to see the evolution of estimates for the prevalence of female genital tract malformations [17, 24, 25] (Fig. 11.1). The first conclusion is that in the recurrent miscarriage population there seems to be a consistent almost threefold increase in the prevalence compared with the general population across all three systematic reviews. The second conclusion is that the prevalence in the unselected/general population and the infertile population is higher than originally estimated in the two most recent reviews, probably owing to tighter inclusion criteria for the studies analysed. Finally, the third conclusion is that, in the latest most comprehensive review and meta-analysis, the infertile population appear to have a higher rate of female genital tract malformations which was not apparent in the two previous reviews.

Table 11.2 The variation of reported prevalence of congenial uterine anomalies in selected populations over the last 35 years

Population	Estimated prevalence (%)
General	0.4–10.8
Infertile	1.0–48.9
Recurrent miscarriage	0.5–65.8

References in-text

Prevalence and Different Subtypes

Using the two most recent critical reviews that controlled for the populations studied and the investigations used, the total prevalence of female genital tract malformations appears to be 5.5–6.7 %

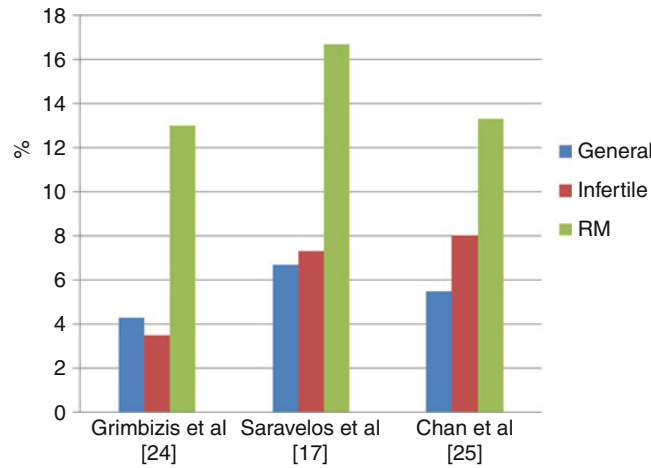

Fig. 11.1 The evolution of estimate of prevalence of female genital tract malformations in selected populations from three large systematic reviews

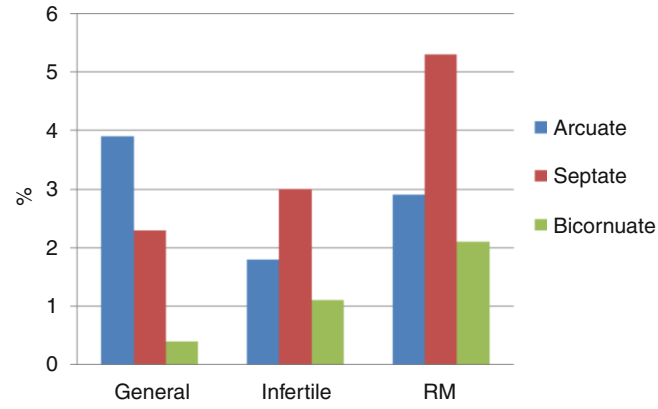

Fig. 11.2 Prevalence of different types of malformations according to the AFS classification in three different population groups. Data from Chan et al. [25]

for the general population, 7.3–8.0 % for the infertile population and 13.3–16.7 % for the recurrent miscarriage population [17, 25]. This would imply a possible association with infertility and a significant association with recurrent miscarriage. However, when assessing the prevalence of different types of female genital tract malformations, according the old AFS classification, the results are more confusing. Using the data from Chan et al. [25] (Fig. 11.2) it can be seen that the arcuate uterus is more prevalent in the general/unselected population, and less prevalent in the infertile and recurrent miscarriage population. On the other hand both the septate uterus and the bicornuate uterus are more prevalent in the infertile and recurrent miscarriage population, and less prevalent in the general/unselected population. Although this may imply an association between the septate and bicornuate uterus with infertility and recurrent miscarriage, the finding of a reduced rate of arcuate uteri in these populations is counter-intuitive. Why would the arcuate uterus – embryologically a variant of the septate uterus – be commoner in the general population compared to the infertile and recurrent miscarriage population? One possible explanation is selection and operator bias: as the AFS classification does not provide objective measures to diagnose and distinguish between a normal variant uterus, an arcuate uterus and a subseptate uterus, it could be that operators were more inclined to diagnose a septate uterus rather than an arcuate uterus in women with infertility or recurrent miscarriage. On the other hand, in unselected women of no reproductive concerns, the operators may have been more inclined to diagnose an arcuate uterus (which is considered by many specialists to be a normal variant uterus) when coming across a small subseptate uterus.

In order to reduce this bias, the prevalence of different types of malformations was reanalysed according to the ESGE/ESHRE classification. The 'arcuate' deformity was therefore merged with the Class U2 septate/subseptate uteri and the 'didelphys' deformity was merged with the Class U3 bicorporeal uteri. Following this, the commonest malformations appeared to be the Class U2 septate/subseptate uteri, followed by the class U3 bicorporeal uteri. Class U1 dysmorphic uteri, Class U4 hemiuteri and Class U5 aplastic uteri all had a prevalence of less than 1 % (Table 11.3). Interestingly, the Class U2 uteri were significantly increased in the recurrent miscarriage but not the infertile population, while the class U3, U4 appeared increased for both these population groups. The obvious limitation of this analysis is that the previous studies used to diagnose the 'arcuate' and 'septate' and 'bicornuate' uteri were not guided at the time by a classification that would allow for an objective measurement of parameters and diagnosis. Therefore, some arcuate uteri which will fall in the Class U2 septate/subseptate category may in fact be normal uterine variants according to the new ESGE/ESHRE classification. As a result the Class U2 uteri may be over represented.

Table 11.3 Estimates of prevalence of different genital tract malformations using the new ESGE/ESHRE classification

Population	Total (%)	Class U1 Dysmorphic (%)	Class U2 Septate (%)	Class U3 Bicorporeal (%)	Class U4 Hemi (%)	Class U5 Aplastic (%)
General	5.5–6.7	<0.1	5.9–7.2	0.3–0.7	0.03–0.1	<0.1
Infertile	7.3–8.0	0.1	4.8–5.4	1.0–1.4	0.4–0.5	–
Recurrent miscarriage	13.3–16.7	0.6	7.9–17.5	1.1–2.7	0.4–0.5	–

Data from Chan et al. [25] and Saravelos et al. [17]
Subclass percentages may not add up to the total estimate as some studies in the reviews evaluated only certain classes of malformations

Summary of Epidemiological Findings

The summary of the epidemiological findings are that:

1. Female genital tract malformations are common in the general/unselected population (~1:20 women)
2. Women with infertility may have a slightly higher rate of female genital tract malformations.
3. It is not clear whether Class U2 septate uteri are more common in women with infertility.
4. Female genital tract malformations and particularly Class U2 septate uteri are significantly increased in women with recurrent miscarriage.
5. There may be a bias in the literature of overdiagnosing septate uteri in favour of arcuate uteri in women with infertility and recurrent miscarriage.
6. There may be a bias in the literature of overdiagnosing arcuate uteri in favour of septate uteri in the general population.

Future

The epidemiological findings highlight some of the weaknesses that have been evident in the classifications and the investigations used in the past. It is clear that the lack of objective measurements to differentiate between the old subtypes of arcuate, septate and bicornuate uteri have hindered our understanding of the different associations between malformations and different types of complications in women from different population groups. The new ESGE/ESHRE classification is a positive step forward in this direction as it allows for the objective differentiation between the normal uteri, the Class U2 septate/subseptate uteri and the Class U3 bicorporeal uteri. Furthermore, the use of investigations such as 3DUS and MRI that can quantify measurements, will not only allow for malformations to be diagnosed accurately, but will also permit for data to be stored digitally for future analyses of different parameters. It could be that in the future, measurements such as septum lengths, widths, volumes will be introduced into the classifications as the investigations become more and more comprehensive. Ultimately however, treatment of the malformations will have to remain individualised, as the current epidemiological associations suggest that they are very common even in the general population, implying that not all them need to be treated when found.

Conclusion

The prevalence of female genital tract malformations in different populations of women has been very difficult to estimate in the past few decades owing to (a) use of classifications that do not provide objective measures for the diagnosis of subclasses of malformations; (b) use of inaccurate investigations; and (c) poor selection and definition of different patient populations. The most recent systematic reviews controlling for these factors estimate the prevalence to be 5.5–6.7 % for the general population, 7.3–8.0 % for the infertile population and 13.3–16.7 % for the recurrent miscarriage

population. However, there still appears to be an inconsistency when estimating the prevalence of different subclasses of malformations according to the AFS classification, suggesting that investigators in the past have overdiagnosed septate uteri in the infertile and recurrent miscarriage population at the expense of arcuate or normal variant uteri. Hopefully with the introduction of the new ESGE/ESHRE classification where clear objective distinctions are made between the normal uterus, the Class U2 subseptate/septate uterus and the Class U3 bicorporeal uterus, studies in the future will be able to provide more accurate estimations of prevalence without operator bias and subjectivity. This will certainly help to provide insight into which particular types of female genital tract malformations are associated with which pregnancy complications.

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12 Health Problems Related to Female Genital Malformations: Obstructive and Complex Anomalies

George Pados

Introduction

Female genital tract malformations consist an heterogeneous group of miscellaneous deviations from normal anatomy resulting from embryologic maldevelopment of mullerian or paramesonephric ducts, due to multifactorial, multigenic and familial mechanisms. The extent of health problems in this group of patients should be determined in relation to the extent of the malformations and patient's symptoms. Regarding health problems in obstructive anomalies, it is usually the pathology of the uterus, that is hemiuterus with rudimentary cavity (Class U4) and aplastic uterus with rudimentary cavity (Class U5) that is the focus of attention (Fig. 12.1) [1, 2]. As far as complex anomalies are concerned, it is usually the pathology of the cervix, that is cervical sub-classes C1 (septate cervix), C3 (unilateral cervical aplasia) and C4 (cervical aplasia), as well as vaginal sub-classes such as longitudinal obstructing vaginal septum (V2), vaginal septum and/or imperforate hymen (V3) and vaginal aplasia (V4) [1, 2]. Finally, it should be pointed out that female genital malformations are frequently associated with other abnormalities from other systems. In this context, health problems in the areas of urology, neurology, orthopedics and cardiology should be, also, considered. The practising gynecologist should be aware of the sequelae of these congenital abnormalities, since failure to manage these promptly may have long-term implications for the psychological, sexual and reproductive health of these patients. On the other hand, the involvement of a multidisciplinary team for the pre-operative management, surgical approach and follow-up is of utmost importance for the *lege artis* approach of these patients.

Cyclic Pelvic Pain

Patients with obstructive anomalies, which mainly include Class U4, U5 and complex ones, that is C1, C3, C4, V2, V3 and V4, are asymptomatic until they reach puberty. Then their main presenting symptom is amenorrhea and cyclical abdominal pain, although in cases of fusion defects of the genital tract (e.g. complete bicorporeal uterus with double cervix and longitudinal obstructing vaginal septum – U3b/C2/V2), menstruation from the unilateral horn of the uterus may still occur. Normal secondary sexual characteristics are present.

The accumulation of repeated menstrual content in the vagina creates a hematocolpos. When the obstruction is low enough, as it happens

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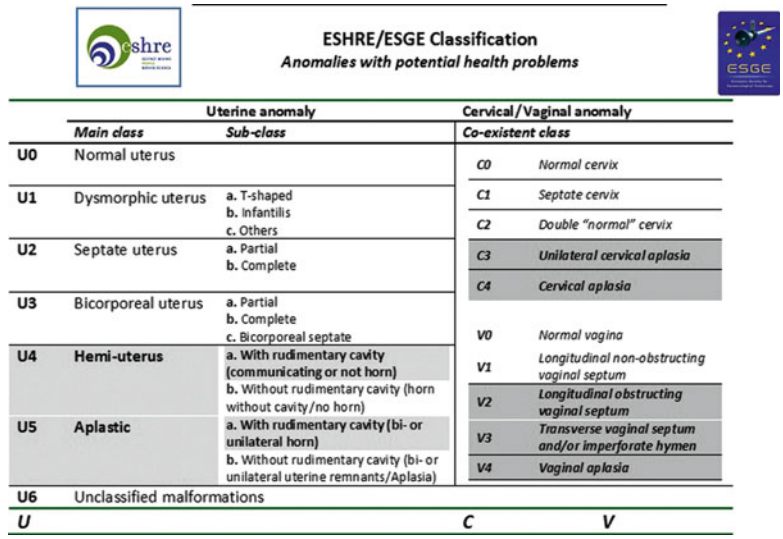

ESHRE/ESGE Classification

Anomalies with potential health problems

	Uterine anomaly		Cervical/Vaginal anomaly	
	Main class	***Sub-class***	***Co-existent class***	
U0	Normal uterus		*C0*	*Normal cervix*
U1	Dysmorphic uterus	a. T-shaped b. Infantilis c. Others	*C1*	*Septate cervix*
			C2	*Double "normal" cervix*
U2	Septate uterus	a. Partial b. Complete	*C3*	*Unilateral cervical aplasia*
			C4	*Cervical aplasia*
U3	Bicorporeal uterus	a. Partial b. Complete c. Bicorporeal septate		
			V0	*Normal vagina*
U4	**Hemi-uterus**	**a. With rudimentary cavity (communicating or not horn)**	*V1*	*Longitudinal non-obstructing vaginal septum*
		b. Without rudimentary cavity (horn without cavity/no horn)	*V2*	*Longitudinal obstructing vaginal septum*
U5	**Aplastic**	**a. With rudimentary cavity (bi- or unilateral horn)**	*V3*	*Transverse vaginal septum and/or imperforate hymen*
		b. Without rudimentary cavity (bi- or unilateral uterine remnants/Aplasia)	*V4*	*Vaginal aplasia*
U6	Unclassified malformations			
U			***C***	***V***

Fig. 12.1 ESHRE/ESGE classification of female genital tract anomalies indicating the classes and sub-classes that are associated with health problems

in case of imperforate hymen, the vagina has the capacity to expand considerably, so giving the impression of a pelvic abdominal mass. On the contrary, when the obstruction is high enough in the vagina, due to its restricted expansion capability, the retrograde menstruation is the main complication, which results in cyclic pelvic pain. It is at this time when children or adolescents with obstructive phenomenon come to diagnosis [3]. Sometimes, unilateral cyclic pain, followed by constant pain may be present. These symptoms are found in cases of obstructed hemivagina (V2), which present later than the other obstructing vaginal anomalies, because menstrual flow occurs from the non-obstructed hemi-uterus [4].

Patients who have any obstruction to menstrual flow, are at increased risk for endometriosis. In these cases, the retention of menstrual blood gives place to retrograde menstruation and the deposition of the blood in the pelvic cavity leads to the development of endometriosis, which may be severe and may result in the formation of endometriomas and destruction of pelvic anatomy (Fig. 12.2) [5]. After the relief of obstruction or removal of the non-communicating horn with functional endometrium endometriosis resolves, although it has been described that such removal does not reduce the risk of persistence or recurrence of the disease [6].

Ectopic Pregnancy

Unicornuate or Hemi-uterus accounts for approximately 10 % of all Mullerian anomalies and of these Class U4a represents 90 % of all unicornuate uterus [7]. This congenital anomaly is susceptible to many gynecologic and obstetric complications. Pregnancies in the rudimentary horn have been described, they occur when migration of a sperm takes place through the abdominal cavity and show a higher incidence for abortion or rupture of the horn. It has been reported that the incidence of ectopic pregnancy in the non-communicating horn is as high as 22 % [3]. On the contrary, no increase in the frequency of ectopic pregnancies in women with other uterine anomalies has been reported and the incidence in these cases is 1–2 % [8].

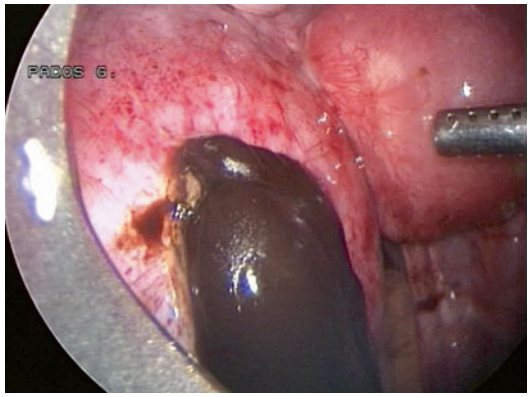

Fig. 12.2 Class U4a hemi uterus, with non-communicating left horn. Endometriosis lesions are noticed in the pouch of douglas (Courtesy of Pados G.)

A pregnancy conceived in a non-communicating horn has a 70 % chance of rupturing [9]. When rupture of the pregnant rudimentary horn occurs, it is almost always an emergency case. Rupture usually takes place between 10 and 15 weeks of gestation and causes heavy bleeding, thus threatening patient's life [3]. Although full-term pregnancies in the uterine horn have been reported as early as 1951 [10], its rupture is still a life-threatening complication in pregnancy. Since the incidence of ectopic pregnancies in patients with a non-communicating horn is high and its rupture is a serious complication, laparoscopic removal of the rudimentary horn and its tube is indicated when this uterine anomaly is diagnosed (Fig. 12.3) [7]. Sonographically guided hysteroscopic correction has been, also, proposed in a case report [8], but restoration management should not be considered an alternative approach for the following reasons: (a) there is a considerable variation in the anatomy of the non-communicating horns, so making extrapolation of restoration management not feasible in every case, (b) the muscle of the rudimentary horn is exceptionally thin and therefore placentation frequently pathological (i.e. placenta acreta) and (c) the blood supply of the horn is frequently compromised.

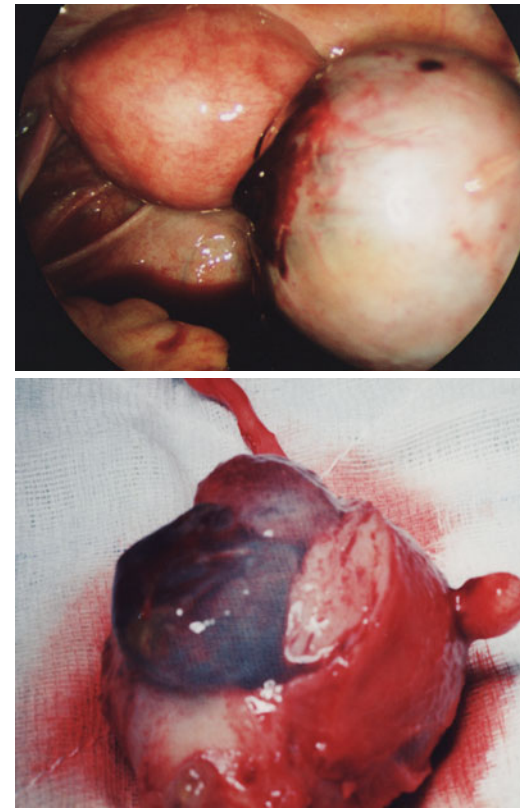

Fig. 12.3 Laparoscopic removal of the left rudimentary horn (Class U4a hemi uterus) with ectopic pregnancy within it (Courtesy of Pados G.)

Renal Abnormalities Occurring with Female Genital Malformations

The association of renal abnormalities with female genital tract malformations has been well recognized and therefore the adequate assessment of the renal tract consists an inevitable part of the routine evaluation of patients presenting with Mullerian anomalies. The incidence of renal anomalies in this group of patients is approximately 30 % [11], with unilateral kidney absence being the most common abnormality, while the incidence of unilateral kidney absence in the normal population is around 1 in 1,000 [12]. However, the incidence of this is not the same across the spectrum of Mullerian anomalies,

being the most common in uterus didelphis (U3 C2) [13]. Other less frequent but of clinical significance abnormalities include pelvic ureteric remnants, which insert ectopically, mainly in the vagina, ectopic ureters, which may cause incontinence and infection, scarred kidneys and dysplastic kidney. These abnormalities certainly have clinical implications not only concerning symptomatology, but also for scheduling complex multidisciplinary surgical interventions.

Psychological Aspects

The psychological management of the patients with Mullerian aplasia has the goal of eliminating the impact of the knowledge that these individuals have no vagina or even uterus and aims to the reduction of the emotional trauma of these adolescents. There are certainly two parties involved in this issue: the patient itself, which is usually a young adolescent and the parents. The school-age child may be embarrassed about the lack of menses onset compared with the other girls of the same age, questioning herself about its gender. Furthermore, the adolescent patient may have to deal with frustration and even depression with this condition, which may affect her female nature and future fertility. More often, the adolescent with a chronic pain syndrome, resulting either from dysmenorrhea or endometriosis, which does not get complete relief of symptoms from medical or even surgical intervention can be expected to be angry, depressed and feel totally helpless. Things are sometimes more complicated due to the denial and repressive behavior, which does not permit traditional interview and prompt counselling [14]. Evans and Poland [15, 16] described the emotional reactions of 54 adolescents with complex anomalies, which varied with the age of the patients and the relations to their parents. Quite interestly, the most important parameter was the ability to fulfill their role in future fertility rather than the expected difficulty with sexual intercourse.

The psychologic support of these adolescents will reduce the anxiety and depression they experience, will help them to adapt better to their congenital abnormality and help to prepare better for the appropriate surgical management.

Concluding Remarks and Issues for Further Clinical Research

The high incidence of health problems in patients presenting with obstructive and complex Mullerian malformations confer the need for a thorough investigation and additional gynecologic attention. Current practice suggests prophylactic removal of the rudimentary horn to reduce dysmenorrhea, prevent endometriosis and avoid gestation in it. Restoration management of the non-communicating horn should be an open issue for further research, taking into account the considerable variation in the anatomy of the non-communicating horn and often the defective function of the rudimentary horn.

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Fertility in Women with Uterine Malformations

13

Grigoris F. Grimbizis and Basil C. Tarlatzis

Introduction

Female genital anomalies are benign deviations from normal anatomy. They are the result of abnormal formation, canalization and/or fusion of the Mullerian (paramesonephric) ducts and/or of defective absorption of the midline septum [1, 2, 14]. Female genital anomalies could be the result of one or more embryological defects, in one or more stages of embryological development, affecting one or more organs of the female genital system [14]. This is expressed in a wide range of totally different possible anatomical variants, from the more simple to the more complex ones. Treatment requirements are depended on the clinical presentation and/or the possible effects on the reproductive potential of the women, which are related to the combined anatomical status of the female genital tract [14].

Congenital uterine anomalies (CUA) are the most common entities from the existed female genital tract malformations. They seem to be related with an impaired reproductive outcome, although their exact clinical impact as well as the effectiveness of their treatment is still considered debatable. Taking into account the high frequency of CUA and recognizing the need for a clear and clinically oriented categorization of the anomalies in a user's friendly way [14, 15], the new European Society of Human Reproduction and Embryology (ESHRE)/European Society for Gynecological endoscopy (ESGE) classification system uses uterine anatomy as the basic characteristic for the design of the main classes; main sub-classes are also based on different degrees of uterine deformity having clinical significance [16, 17]. Cervical and vaginal anomalies are classified in independent co-existent sub-classes, giving clarity in the anatomical representation of each anomaly [16, 17].

Uterus, hosting the developing embryo, plays a crucial role for implantation and evolution of pregnancy. Thus, the possibility that the anatomically defective endometrial cavity in cases of CUA could potentially impair implantation and, consequently, the achievement of pregnancy is an extremely interesting clinical question representing one of the more "hot" debates in the literature.

Aim

The aim of this chapter is to critically review the potential impact of CUA on the fertility potential of the woman. This will be based on: (1) indirect evidence coming from the analysis of their

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prevalence in the general and infertile population, (2) evidence from the achievement of pregnancy in patients having CUA and (3) additional evidence coming from other studies.

The ESHRE/ESGE classification system has an undoubted comparative advantage in the categorization of CUA and should be used as the research tool from now on; however, for the needs of the current chapter, the AFS [3] classification will be used since it is the most popular system utilized to date and, also, it was the classification used in most of the studies. It is important to note that anatomy and, largely, uterine anatomy is also the basis for the design of the main classes of the AFS system.

Prevalence of CUA and Distribution of Their Types in the General and Infertile Population

Potential differences in the prevalence of CUA in the general and infertile populations could indirectly reveal their role for the fertility potential of women having uterine abnormalities. The challenge to draw conclusions for the fertility potential of the women with CUA from the analysis of their prevalence in the general and infertile populations came from the fact that the observed prevalence of CUA in patients with recurrent pregnancy losses are higher than that observed in the general population being one of the more "hard" evidence of their role for the evolution of pregnancy [5, 13, 26].

The first attempt has been published in 2001; according to this publication the prevalence of CUA was found to be ~4 % in the general population and, also, ~4 % in infertile patients. The prevalence was higher (~12 %) only in patients with recurrent pregnancy losses or preterm deliveries [13]. The indirect conclusion was that uterine anomalies could not be considered as being responsible for infertility. However, the major limitation of this review was the fact that, for the estimation of the pooled incidence of CUA in the various populations, the researchers took into account all the studies without any attention to the method used to diagnose the anomaly.

In order to overcome this limitation, in a fore coming publication, another group of investigators tried to categorize the various available diagnostic methods according to their accuracy in diagnosing and differential diagnosing of CUA; high accuracy methods were considered those techniques having accuracy >90 % and, only endoscopy, hydrosonography (HSG) and three-dimensional ultrasound (3D US) fulfilled this criterion [26]. The estimated pooled prevalence of uterine anomalies in high accuracy studies was 6.7 % (95 % CI 6.0–7.4 %) in the general population, 7.3 % (95 % CI 6.7–7.9 %) in infertile population and 16.7 % (95 % CI 14.8–18.6 %) in recurrent aborters [26]. Even this more sophisticated study failed to reveal a significant difference between general and infertile population, highlighted again only the difference in the recurrent aborters (Fig. 13.1).

Three years later, another group has tried again to answer to the same question [5]; meanwhile more studies using high accuracy methods have been published. In their systematic review of high accuracy studies, the prevalence in the general population was found to be 5.5 % (95 % CI: 3.3–8.5 %), in infertile population 8 % (95 % CI: 5.3–12 %), in recurrent aborters 13.3 % (95 % CI: 8.9–20 %) and in women having infertility and recurrent pregnancy losses the impressive incidence of 24.5 % (95 % CI: 18.3–32.8 %) (Figs. 13.1 and 13.2) [5].

It seems, therefore, that with the accumulation of more data and experience in the diagnosis of uterine anatomy with the newer available techniques, the incidence of CUA is higher in infertile population although this is not, yet, statistically significant.

Apart from the possible adverse effect of CUA, in general, on the achievement pregnancy, another interesting topic for investigation is the possibility that the different types of uterine anomalies could exert a different impact on the fertility potential of the woman. This possibility could be related to the fact that, the various categories of uterine anomalies are associated with different degrees of endometrial's cavity deformity as well as with different structure and consistency of the myometrium.

Therefore, Saravelos et al. [26] reviewed the distribution and the prevalence of the various types of CUA in the different (general, infertile and recurrent aborters) populations based on the available data from the high accuracy studies. The prevalence of septate uterus in the general

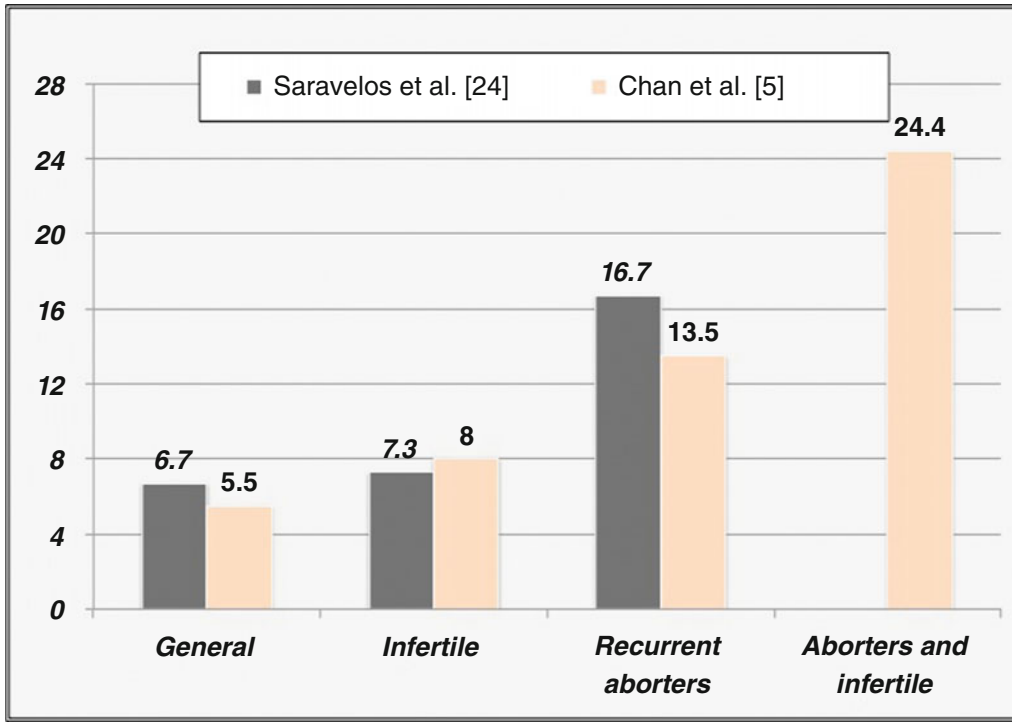

Fig. 13.1 Prevalence of uterine anomalies in the general and selected (infertile and recurrent aborters) populations (Data from Refs. [5, 26])

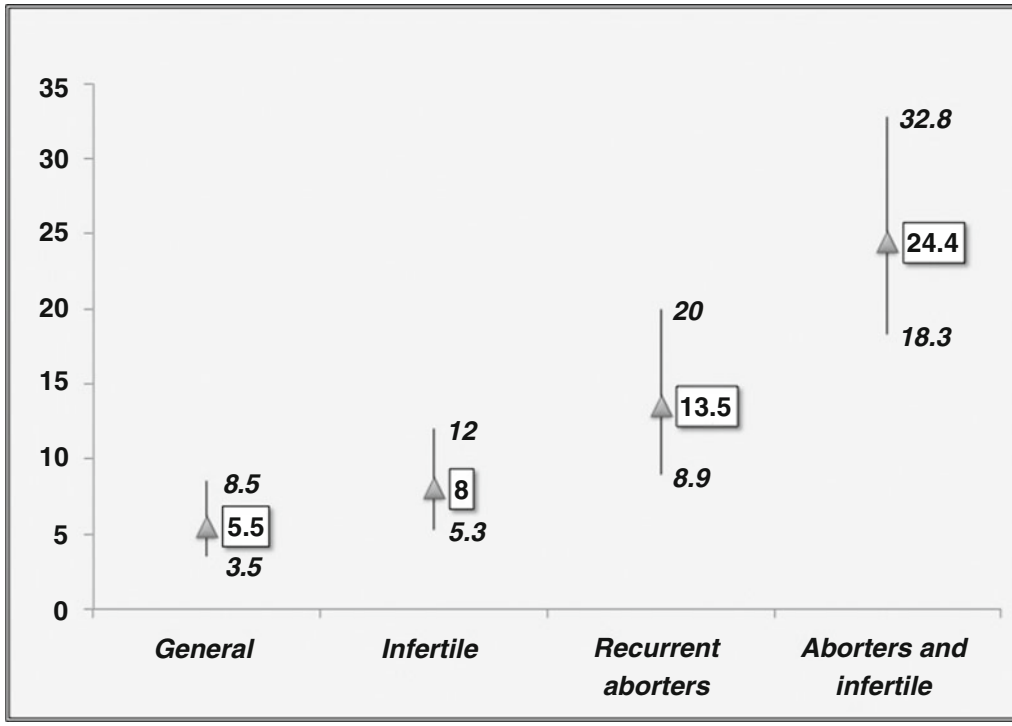

Fig. 13.2 Prevalence and estimated 95 % confidence intervals of uterine anomalies in the general and selected (infertile and recurrent aborters) populations (Data from Chan et al. [5])

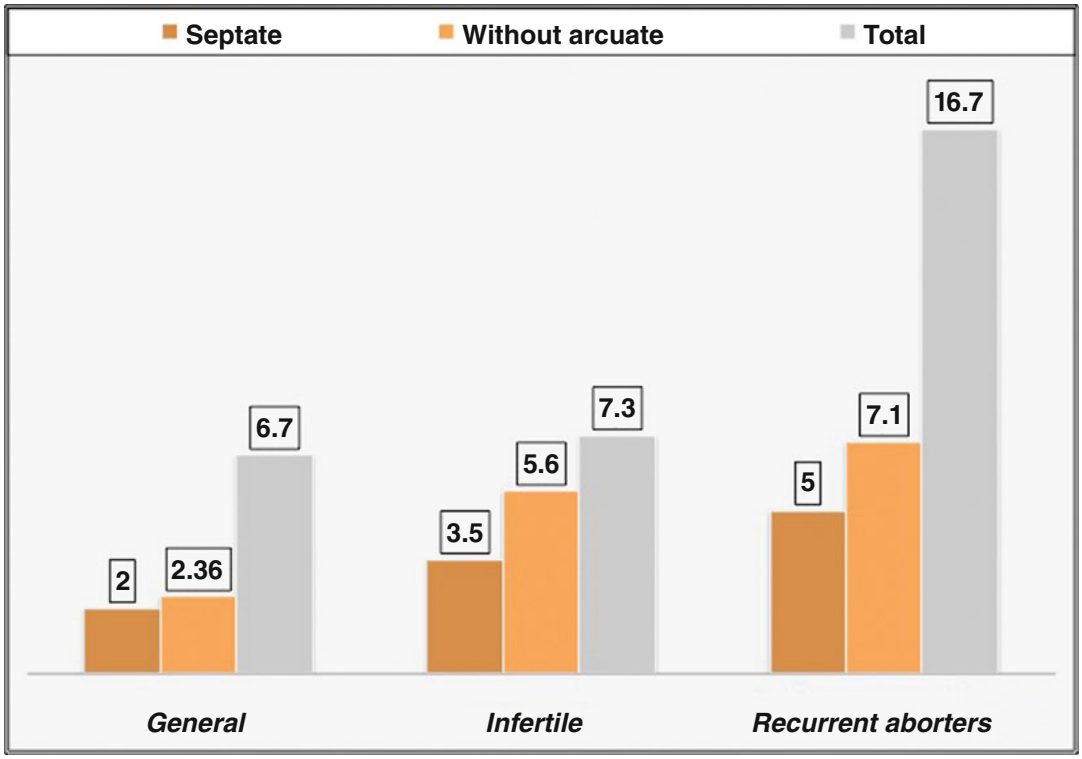

Fig. 13.3 Prevalence of uterine anomalies, uterine anomalies without arcuate uterus and septate uterus in the general and selected (infertile and recurrent aborters) populations (Data form Saravelos et al. [26])

population was found to be 2 %, in infertile population 3.5 % and in recurrent aborters 5 %; the high incidence of uterine anomalies in the general population was mainly due to the presence of "arcuate" uteri. The same tendency was observed for bicornuate uterus and the others more severe anomalies. Consequently, the prevalence of uterine anomalies without arcuate uterus was 2.36 % in the general population, 5.6 % (more than double) in infertile patients and 7.1 % in recurrent aborters (Fig. 13.3).

Chan et al. [5] observed a similar tendency in their systematic review. The incidence of septate uterus in the general population was found to be 2.3 %, in infertile population 3 %, in recurrent aborters 5.3 % and patients with infertility and recurrent abortions 15.4 %. The high incidence of uterine anomalies in the general population was again found to be due to the presence of "arcuate" uteri. Furthermore, the prevalence of uterine anomalies without arcuate uterus was 3.2 % in the general population, 5.8 % in infertile patients, 9.3 % in patients with recurrent pregnancy losses and 20.1 % in patients with infertility and recurrent pregnancy losses (Fig. 13.4).

Thus, the above-mentioned findings from prevalence studies represent indirect evidence supporting the notion that CUA could adversely impair fertility. Furthermore, it seems that the more severe the malformation of the cavity is, the more the possibility to play a role not only for the evolution but, also, for the achievement of pregnancy; septate uterus and more severe forms of uterine anomalies could adversely affect the fertility potential of the woman whereas this does not seem to be the case for arcuate uterus. It should be noted, however, that with the old AFS classification [3] the borders in the differential diagnosis between septate and arcuate uterus are not clear and the adoption of the new ESHRE/ESGE classification system could further elucidate this "hot" issue.

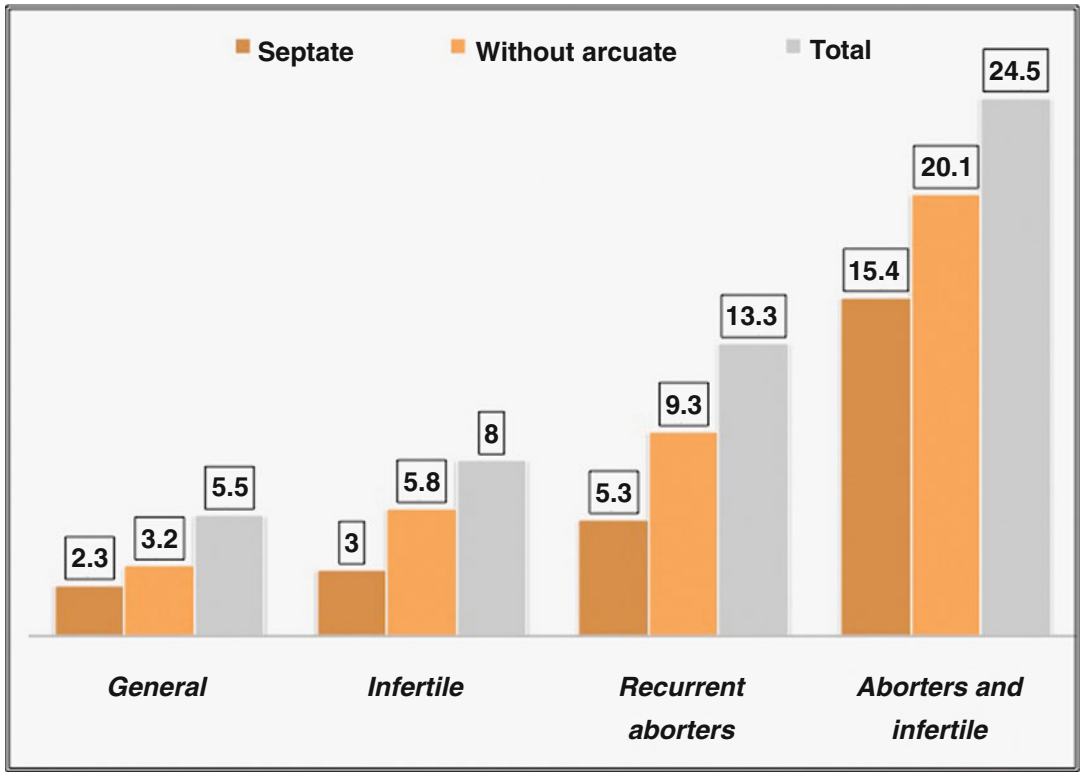

Fig. 13.4 Prevalence of uterine anomalies, uterine anomalies without arcuate uterus and septate uterus in the general and selected (infertile and recurrent aborters) populations (Data form Chan et al. [5])

Conception in Women with Congenital Uterine Anomalies

Evidence coming from the study of the prevalence of CUA in the general and selected populations is useful but it is indirect. More reliable conclusions could be drawn only from comparative studies. In a systematic review of the available comparative studies, Chan et al. [6] was found that patients with septate uterus as compared with normal controls was associated with a statistically significant decrease by 15 % in the conception rates (RR: 0.86, 95 % CI: 0.77–0.96), a statistically significant almost threefold increase in the abortion rates (RR: 2.89, 95 % CI: 2.02–4.14) and a statistically significant increase almost by twofold in preterm delivery rates (RR: 2.14, 95 % CI: 1.48–3.11). The authors failed to detect a difference in the achievement of pregnancy in women with unicornuate uteri but the available data for this research question could not be considered as sufficient [5].

In a more recent meta-analysis, Venetis et al. [28] examined the probability of pregnancy achievement in a larger cohort of meanwhile available studies and in both natural and assisted conception cycles. They failed to detect any statistically significant difference when data were analyzed separately in natural (RR: 0.96, 95 % CI: 0.89–1.04) and assisted cycles (RR: 0.66, 95 % CI: 0.37–1.19) in women with CUA as compared to those without CUA. However, the probability of conception, assisted or spontaneous, in women with congenital uterine anomalies (CUA) was found to be significantly decreased by ~15 % (RR: 0.86, 95 % CI: 0.74–1.00) when all data from natural and assisted cycles were analyzed together, thus, confirming the observation of the previous meta-analysis.

Most of the comparative studies available in the literature and included in the pre-mentioned meta-analyses are still retrospective and, thus, solid conclusions could not be, yet, drawn.

However, according to the best available evidence (level C/meta-analysis of retrospective comparative studies) the presence of CUA might be associated with a detrimental effect on patient's fertility potential decreasing the probability of pregnancy achievement by ~15 % (Class IIb Recommendation).

Fertility After Hysteroscopic Treatment

The results of hysteroscopic treatment of septate and bicorporeal septate uteri [9, 16, 17] could offer some additional evidence for the potential role of these anomalies on patients' fertility. However, the anatomic restoration of the cavity does not necessarily mean that it will accompanied by the restoration of normal fertility potential; treatment of septum is always associated with "trauma" and healing process of the cavity could impair the functional outcome of the procedure [13]. Hence, an increase in conception rates after surgical correction of the anomaly might be considered as an indirect proof of a harmful effect of the anomaly on woman's fertility whereas a neutral effect might not, since this could be due to the "trauma" following the procedure.

Thus, Mollo et al. [21] studied prospectively conception rates in infertile patient with septate uterus and otherwise unexplained infertility after septum resection compared to those of couples with unexplained infertility only; conception rates were found to be almost double in the group of infertile patients who underwent septotomy, thus supporting that notion that the presence of septum adversely affects fecundity.

Nouri et al. [22], in a review of all available observational retrospective studies, found a pooled post-operative pregnancy rate of ~60 % and live birth rate of ~45 % in infertile women who underwent septum resection. A "theoretical" group for comparisons could be also considered untreated infertile patients with unexplained infertility; the expected spontaneous pregnancy rates in this group do not exceed 35 % (The ESHRE Capri Workshop 1996) [10].

Venetis et al. [28] examined the value of hysteroscopic septotomy in a systematic review of all the published comparative studies. They found that surgical correction of uterine septa is associated with a ~60 % decrease (RR: 0.37, 95 % CI: 0.25–0.55) in the probability of miscarriage as compared to women that are not treated. This effect seems to be present, not only in women with a history of recurrent spontaneous abortions but also in infertile patients and in the non-specific population analyzed in the remaining studies. However, hysteroscopic removal of the septum was not found to lead to a statistically increased probability of pregnancy achievement (RR: 1.14, 95 % CI: 0.79–1.65) and delivering at term (RR: 0.66, 95 % CI: 0.29–1.49). However, the effect sizes observed in this analysis (that imply a beneficial effect) and the fact that both achievement of pregnancy and preterm delivery have been shown to be associated with the presence of a uterine septum, mandate the accumulation of further evidence in order to properly assess the value of hysteroscopic septotomy for these indications.

Thus, concerning the achievement of pregnancy after septum incision, it seems that it is still very early to draw definite conclusions. However, there is some indirect evidence mainly from the prospective study of Mollo et al. [21], that septum could adversely affect fertility.

Possible Biological Explanations

Although the association between CUA and suboptimal fertility potential seems, nowadays, to be accepted and supported by the evidence available, the exact etiology and the plausible biological mechanism underlying infertility and pregnancy loss remain still unclear. Several hypotheses have suggested in an effort to explain these findings.

Septate uterus is the more common anomaly and, mainly, its presence seems to be associated with impaired implantation. Thus, it was hypothesized that the endometrium overlying the septum might be a poor site for implantation because of the impaired blood supply, which is insufficient

to support placentation and embryo growth [4, 8, 11, 12, 20, 18, 19]. Therefore, pregnancy is less and miscarriage more likely to occur with embryos that implant on septum, explaining impaired fertility and evolution of pregnancy. However, although this explanation is attractive, it is not supported by the increased number of blood vessels in biopsy samples found by Dabirashrafi et al. [8] and the poorer pregnancy outcome (early and late pregnancy losses) observed by Kupesic [19] in patients with vascularized septa as compared to those with avascularized. Furthermore, if fertility is also impaired in other forms of uterine anomalies this hypothesis could not explain this.

Thus, it was hypothesized that once the epithelial/endometrial barrier has been overcome by the implanting conceptus, it is possible that the uterine vasculature and stroma carry out a subsequent barrier or 'interrogative' functions [7]. Hence, infertility and pregnancy losses in patients with uterine anomalies may be associated with abnormalities in the later, vascular stages of implantation. Different vascular beds differ in receptivity to invading trophoblast; uterine septum and/or uterine defective walls represent locations with alterations of endometrial vascularization indicating an impaired vascular bed [8, 11].

Another issue that gains attention for the pathophysiological explanation of decreased reproductive potential of women with CUA is the different structure of the uterine musculature as a result of the distorted uterine anatomy and the consequent alterations of normal uterine contractility. Altered uterine contractility could play a detrimental role in implantation and in the early stages of pregnancy development whereas miscarriage and preterm birth may result from more frequent or uncoordinated uterine contractions [8, 12, 19, 23–25]. The decrease of endometrial cavity volume and the resulted reduced uterine capacity could not be considered as being responsible for implantation failures; it might impair evolution of pregnancy during its later stages being a possible etiological factor for complications from second trimester on [12, 21].

Other, more sophisticated hypotheses, have been also suggested: the normal expression of HOX genes is important not only for the proper development of the female genital tract but also for the development of the endometrium, thus playing a major role in fertility [27]. Hence, a disrupted expression of HOX genes might be the link between CUA and impaired fertility in these women.

It is important to note that the accumulation of further relevant epidemiological data might elucidate the exact role of each type of uterine anomaly on reproductive potential of the woman, and enhance our understanding of the pathophysiology and the exact contribution of each proposed mechanism.

Conclusions and Issues for Further Research

According to the best available evidence, the presence of CUA seems to be associated with a detrimental effect on patient's fertility; the probability of conception, assisted or spontaneous, is decreased by ~15 %. However, it is not still clear whether all types of CUA have the same impact on woman's fertility. Thus, although some authors failed to detect a difference in the achievement of pregnancy in women with unicornuate uterus, indirect evidence coming from the analysis of the distribution of the various types of CUA in general and infertile population does not support this finding. On the other hand, based mainly in indirect evidence, it could be supported that the more severe the malformation of the uterine cavity is, the more the possibility to play a role for the achievement and evolution of pregnancy; septate uterus and more severe forms of uterine anomalies could adversely affect the reproductive potential of the woman. In view of this evidence, infertile patients should be investigated for the presence of CUA with high accuracy non-invasive diagnostic methods.

However, it should be noted that most of the studies available in the literature are still retrospective with serious restrictions in their design and, thus, the level of evidence of these conclusions

is not yet high (level C). There is still need of prospective well-designed studies; the new ESHRE/ESGE classification system could be a useful working basis for the design of those studies offering the crucial additional advantages of accurate diagnostic criteria and precise categorization of the anomaly type. It is important to note that the accumulation of further relevant epidemiological data might elucidate the exact role of each type of uterine anomaly on reproductive potential of the woman, and enhance our understanding of the pathophysiology and the exact contribution of each proposed mechanism.

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Pregnancy Outcome in Women with Uterine Anomalies

14

Carlo De Angelis and Donatella Caserta

Uterine malformations consist of a group of various congenital anomalies of the female genital system that have often been associated with increased miscarriage, preterm delivery and other adverse fetal outcome rates.

Uterine malformations are the result of four major disturbances in the development, formation or fusion of the Mullerian ducts during fetal life: (a) failure of one of the Mullerian ducts to develop (agenesis; AFS unicornuate uterus without rudimentary horn); (b) failure of the ducts to canalize; (c) failure or abnormal fusion of the ducts (AFS didelphys or bicornuate uterus); (d) failure of reabsorption of the midline uterine septum (AFS septate and arcuate uterus) [1].

Moreover, T-shaped uterus or hypoplastic uterus is a rare uterine malformation, except in woman exposed in utero to diethylstilbestrol (DES), an anti-abortive drug that used to be given to women with threatened miscarriage until the end of the Seventies [2]. The pathogenesis of this malformation remains unclear and its cause is still unknown.

The prevalence of congenital uterine anomalies in high-risk women is unclear as various diagnostic approaches have been applied to different groups of patients. In a recent, comprehensive systematic review Chan et al. [3] have identified 94 observational studies comprising 89,861 women. Pooled prevalence rates of uterine anomalies diagnosed by optimal tests are 5.5 % in the unselected population, 8.0 % in infertile women, 13.3 % in those with a miscarriage history and 24.5 % in those presenting miscarriage and infertility. That means that one out of four women with miscarriage and infertility harbor uterine anomalies.

Looking at the different classes of uterine anomalies, the so-called resorption or canalization defects, namely arcuate and septate uteri, have the highest prevalence rate (22.0 %) in high-risk patients with miscarriage and infertility, whereas unification defects have lower prevalence rates in the same patient population (bicornuate 4.7 %; unicornuate 3.1 %; Didelphys 2.1 %) [3].

The presence of a malformed uterus in a woman is thought to impair normal reproductive performance by increasing the incidence rates of early and late abortions, preterm deliveries and obstetrical complications. However, each uterine malformation may have a different effect on pregnancy outcome.

Hemi-uterus (AFS Unicornuate)

What is the probability for those patients to deliver a healthy child, and what specific obstetrics challenge will they face on the way to that desired endpoint? An investigation of the existing literature,

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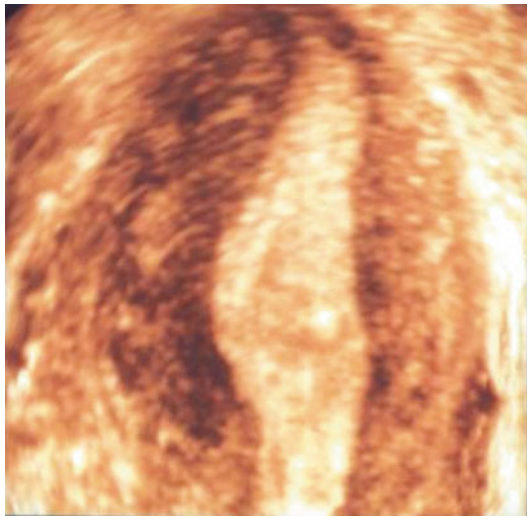

Fig. 14.1 3D ultrasound image of a hemi-uterus (ESHRE/ESGE Class U4)

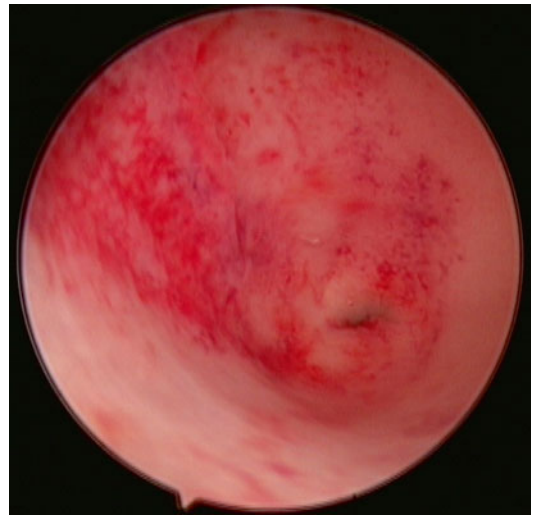

Fig. 14.3 Hysteroscopic view of a hemi-uterus

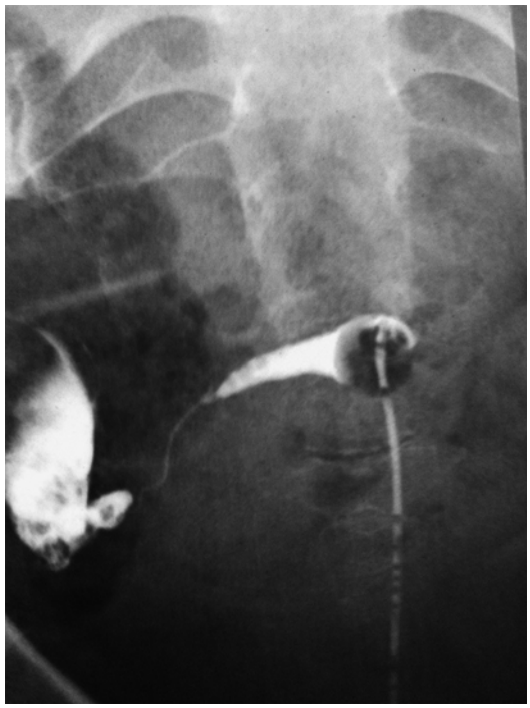

Fig. 14.2 Hemi-uterus (ESHRE/ESGE Class U4) at hysterosalpingography (HSG)

largely anecdotal and incomplete, relies heavily on case reports and case series to prognosticate for these patients. However, women with untreated unicornuate uterus (hemi-uterus; Figs. 14.1, 14.2, 14.3) seem to have a relatively poor pregnancy outcome, even though a successful pregnancy is possible [4–12].

The challenge faced by patients with unicornuate uterus has long been thought to be pregnancy maintenance rather than impaired fertility [5]. Patients with anomalies have higher frequencies of spontaneous abortions in the first and second trimester, preterm labor, and abnormal fetal presentations [6]. The assisted reproductive technology data, however, suggest that clinical pregnancy rates are reduced by 33 % in patients with unicornuate uterus, which contradicts the former statement [7].

Moreover, the rudimentary cavitated horn can be a site of implantation that results in horn gestation (ectopic pregnancy). This seems to be more likely in patients with AFS Class II a malformations (cavitated communicating horn) whose horn cavities are in direct communication with the primary uterine cavity. It is extremely uncommon to have an ectopic horn pregnancy in AFS Class Ib malformations, in which the rudimentary horn cavity does not communicate with the main uterine cavity, even though intra-abdominal sperm migration is a frequent occurrence in human reproduction [8]. Fedele et al. [9] have reported five cases of ruptured rudimentary horn containing ectopic pregnancy out of 49 patients with unicornuate uterus (10.2 %).

Table 14.1 Pregnancy outcome in patients with unicornuate uterus

	Studies	Patients	Pregnancies	Ectopics	Abortions	Preterm del.	Term del.	Live birth
Authors	N°.	N°.	N°. (%)	N°. (%)	N°. (%)	N°. (%)	N°. (%)	N°. (%)
Grimbizis et al. [1]	11	151	260	3 (1.2)	95 (36.5)	42 (16.2)	116 (44.6)	141 (54.2)
Reichman et al. [5]	20	290	468	28 (6.0)	114 (24.3)[a]	86 (18.4)	177 (37.8)[b]	232 (49.6)

[a]First-trimester abortion n. 84 (17.9 %); second-trimester abortion n. 30 (6.4 %)
[b]Intrauterine fetal death n. 16 (3.4 %)

In this chapter, we cover mainly on data derived from the two most updated systematic reviews on that issue, In the first review, Grimbizis et al. [1] have assessed 151 patients pooled from 11 studies published between 1953 and the late 1990s. Out of a total of 260 pregnancies, the following rates are recorded: mean abortion, 37.1 %; mean preterm delivery, 16.4 %; mean term delivery, 45.3 (%); and mean live birth, 55.1 %.

The second and most updated report is by Reichman et al. [5] who have evaluated the data from 20 papers published up to 2006. In total, they have examined 290 women with unicornuate uterus, for an overall number of 468 pooled pregnancies. Overall, 2.7 % of pregnancies are ectopic, 24.3 % end in first-trimester abortion and 9.7 % in second-trimester abortion. The preterm delivery prevalence rate is 20.1 %, term deliveries account for 44.0 %. A very high rate of intrauterine fetal death is reported (10.5 %) as against a lower-than 50 % live-birth rate (49.6 %).

Therefore, the data reported in most recent studies are even worst when compared to the earlier ones, with high prevalence of ectopic pregnancies and fetal death in utero, and a live birth rate lower than 50 % (Table 14.1). If we look at the different subclasses of unicornuate uterus, we can see that subclass b (no rudimentary horn) is associated with the absolute lowest pregnancy outcome.

Three main factors have been suggested as possible causes of such outcomes:

- diminished muscle mass: the unicornuate uterus walls are thinner than normal, myometrium diminishes in thickness as gestational age advances, causing inconsistencies over different aspects of the uterus [5]. This reduced myometrial muscle thickness is supposed to play a role in both second-trimester abortion and premature delivery, which accounts for up to 25 % of these patients;
- abnormal uterine blood flow: disturbance in the uterine blood flow caused by an absent or abnormal uterine or ovarian artery, which could explain growth restriction or spontaneous abortion. Poor vascularization could lead to impaired fetal nutrition, reduced fetal size and higher incidence of first-trimester abortion for compromised utero-placental blood flow [10];
- cervical incompetence: even though, as reported by Reichman et al. [5], it seems unlikely that it plays a key role given that the great majority of pregnancy losses in unicornuate uteri occur during the first trimester.

Bicorporeal Uterus (AFS Bicornuate and Didelphys)

Bicornuate uterus, which is rare in the unselected population (0.4 %), is significantly more prevalent in women with infertility (1.1 %) and miscarriage (2.1 %), particularly if these coexist (4.7 %) [3].

Nevertheless, the relative frequency of having a bicornuate uterus in women presenting with a first-trimester recurrent pregnancy loss and a divided cavity seems to be very low as reported by some authors [13]. Maneschi et al. [14] has compared 13 patients with bicornuate uterus who had not undergone corrective surgery and 8 women treated with metroplasty, namely the Strassman procedure. The cumulative pregnancy rates are 67 and 95 % in patients without surgical repair and 63 and 88 % in the surgery-treated group. The probability of giving birth to a live-born infant is as follows: with no corrective surgery 30, 58 and 79 % for the first, second and third pregnancy, respectively; after corrective surgery 71 and 86 % for the first and second pregnancy, respectively.

Fertility seems not to be impaired in patients with bicornuate uterus, whereas gestational

capacity is. A prognostic estimate of the likelihood of giving birth to a live-born baby can be formulated according to the number of pregnancies or surgical correction.

Based on the data reported in the literature on patients with untreated bicornuate uterus, even this malformation seems to have a poor pregnancy outcome. In the largest report published on the issue, out of 261 pooled patients from four studies with untreated bicornuate uterus for a total of 627 pregnancies, the mean abortion rate is 36.0 %, the mean preterm delivery rate 23.0 %, the mean term delivery rate 40.6 %, and the mean live-birth rate 55.2 %) [1].

In comparative studies on women with bicornuate uterus and normal controls, the pregnancy outcome in patients with bicornuate uterus is significantly poorer than that of patients with a normal uterus [15], whereas the miscarriage rate is significantly higher (41.8 % vs. 6.4 %; Risk ratio: 6.56) [16]. Even Shuiqing et al. [17] and Zlopasa et al. [18] have reported significantly high abortion rates in women with bicornuate uterus compared to controls (42.6 % vs. 9.1 %, risk ratio 4.69, and 27.5 % vs. 16.4 %, risk ratio 1.68, respectively).

Saravelos et al. [19] suggest that the miscarriage rate increases according to embryological severity of uterine anomalies. In 29 patients with bicornuate uterus they report a first-trimester miscarriage rate of 72.4 % (21/29) and a second-trimester miscarriage rate of 13.8 % (4/29) for a total miscarriage rate of 85.8 %. In this study, the pregnancy outcome in patients affected by bicornuate uterus seems to be really very poor, with a live birth rate of 13.8 %.

It is unclear if a complete bicornuate uterus has a poorer pregnancy outcome than partial bicornuate uterus since data in the literature are conflicting [15, 6].

As for Didelphys uterus, its prevalence is very low. According to Chan's review [3] it is 0.1 % in the unselected population, 0.5 % in women affected by infertility, 0.5 % in women with miscarriage and 3.1 % in women with mixed infertility and miscarriage.

The pregnancy outcome in women with didelphys uterus seems to be similar to that of women with bicornuate uterus. A review of 152 pregnancies by 114 pooled patients with untreated didelphys uterus has revealed a mean 32.9 % abortion rate, a mean 28.9 % preterm delivery rate, a mean 36.2 % term delivery rate with a mean 56.6 % live birth rate [1].

Therefore, according to these data, didelphys and bicornuate uteri seem to have a similar effect on reproduction, since the presence of the second cervix and of the second channel seems not to have a beneficial effect, from a functional point of view, on the reproductive capability of the uterus.

Nevertheless, there are some conflicting data on that issue. Heinonen et al. [20], in the largest single series on women with didelphys uterus and pregnancy (49 cases), reported a mean miscarriage rate of 21 %, ectopic pregnancies in 2 %, prematurity in 24 %, fetal growth retardation in 11 % and perinatal mortality in 5.3 %. A fetal survival rate of 75 % has led the author to conclude that fertility in women with didelphys uterus is not impaired significantly, pregnancy prognosis is comparatively good, while prematurity and fetal growth retardation indicate meticulous prenatal care. Even Shuiqing et al. [17] has found a low incidence of first-trimester miscarriage rate in women with didelphys uterus as against women with normal uterus (9.5 % vs. 9.1 %, risk ratio 1.05). In our opinion, a possible explanation for this discrepancy could be seen in the difficulty that sometimes occurs in a correct diagnosis of the anomaly. Also, differential diagnosis between didelphys uterus and complete septate uterus with duplicatio cervix, being the latter an anomaly not included in most previous classification systems, could sometimes be an explanation for conflicting data.

Actually, the most salient difference between the two subtypes of unification defects remains the opportunity for a bicornuate uterus to be treated surgically, i.e. with laparotomic or laparoscopic Strassman metroplasty (Table 14.2) [21–25].

Occasionally, a bicornuate uterus is combined with the septum, and in most of those cases treatment does not vary from that of a septate uterus alone.

Table 14.2 Pregnancy outcome after Strassman metroplasty for bicornuate uterus

	Patients	Pregnancies	Abortions	Live birth
Authors	N°.	N°.	N°. (%)	N°. (%)
Candiani et al. [21]	71	66	14 (19.7)	52 (73.2)
Maneschi et al. [22]	8	7	n.a.	7 (88.0)
Lolis et al. [24]	22	19	0 (0)	19 (86.4)
Rechberger et al. [23]	13[a]	10	2 (16.6)	8 (66.7)
Total	114	102	16 (14.1)	86 (75.4)

[a]One patient was lost at follow-up

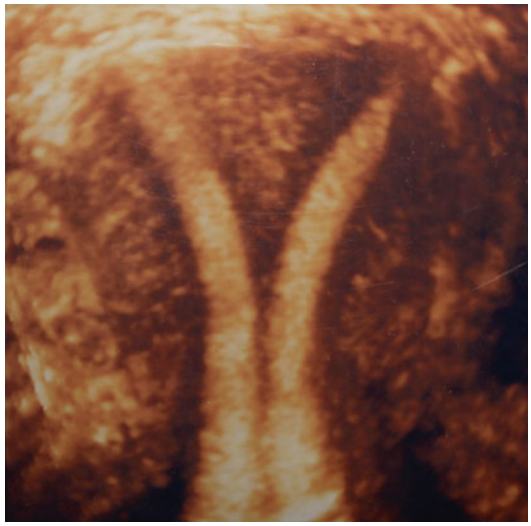

Fig. 14.4 3D ultrasound image of a complete septate uterus (ESHRE/ESGE Class U2b)

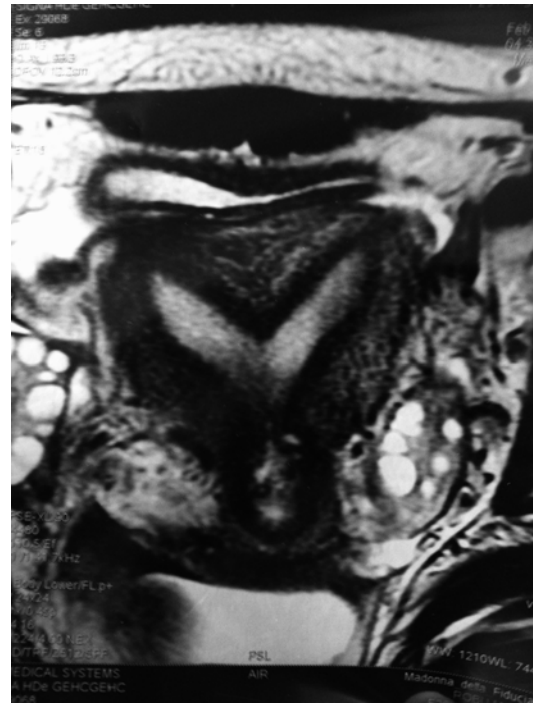

Fig. 14.5 MRI image of a partial septate uterus (ESHRE/ESGE Class U2a)

Septate Uterus

Canalization defects, namely subseptate or septate uteri, are significantly more common in women with miscarriage (5.3 %), especially if this is combined with a history of infertility (15.4 %) [3].

A septate uterus (Figs. 14.4, 14.5, 14.6) has generally been associated with the poorest reproductive performance, with fetal survival rates between 6 and 28 % and abortion rates up to 80 % [1]. The finding of a septate uterus per se is not a mandatory indication for surgery because it is not always associated with a severe reproductive performance [26, 27]. Ludmir et al. [28] have managed 42 patients with previously diagnosed but uncorrected uterine malformations: they have reported a 44 % pregnancy loss before the 25th week of gestation, 8 % premature deliveries, 48 % term deliveries and a fetal survival rate of 53 % in the septate group. Very similar to the latter are the data reported by Woelfer et al. [29]. in women with congenital anomalies detected incidentally by three-dimensional ultrasound. In this patient population considered at low risk of having an abnormal uterus, subseptate uterus is associated with first and second-trimester miscarriages in 45.6 % of cases and preterm labor in 10.5 % of cases. Nevertheless, the difference as against women with a normal uterus remains highly significant (Z =4.68).

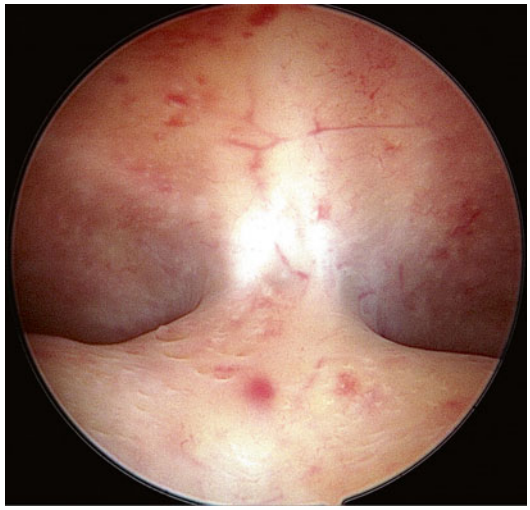

Fig. 14.6 Septate uterus (ESHRE/ESGE class U2) at hysteroscopy

In a survey on women with untreated septate uterus (four studies between 1982 and 1997, pooled patients/[1], the authors have reported a mean 44.1 % abortion rate, a mean 22.3 % preterm delivery rate, a mean 32.9 % term delivery rate and a mean 50 % live birth rate. These data suggest that pregnancy outcome in patients with untreated septate uterus remains significantly lower than in women with a normal uterus, even though not so low as reported in other studies [30], and it is close to that of women with an untreated bicornuate uterus.

Nevertheless, mention has to be made that the term 'untreated' means a woman who have not undergone/will not undergo corrective surgery, so that we could suppose it is the reproductive performance of a mixed group of patients with either asymptomatic and symptomatic infertility or miscarriage.

On the other hand, if we look at most studies concerning hysteroscopic metroplasty for septate uterus in women with infertility or miscarriage, the results are totally different from those reported in unselected untreated patients, with a very poor reproductive performance before surgery. In one systematic review [30] on 1,062 pooled pregnancies from 658 patients the miscarriage rate before hysteroscopic metroplasty is 88 %, preterm delivery rate is 9 %, and term deliveries rate is 3 %. In another review, [1] the data are very similar: out of 599 pooled pregnancies from 292 women the reported abortion rate is 86.4 %, preterm delivery rate is 9.8 %, term delivery rate 3.3 % and live birth rate only 6.1 %. Hence, we can suppose that in patients with a septate uterus who are symptomatic for infertility and/or miscarriage, wastage of the reproductive performance is an adverse reality.

Focusing on the most updated literature on the topic, we have found some remarkable studies published in the last 10 years, which supports the poor reproductive performance of selected patients with a septate uterus prior to hysteroscopic surgery. Gergolet et al. [31] has reported a miscarriage rate of 82.1 %, an ectopic pregnancy rate of 2.1 % and a live birth rate of 15.7 %; Saravelos et al. [32] have reached miscarriage, ectopic pregnancy and live-birth rates of 85.7, 4.7 and 9.4 %, respectively. Hollett-Caines et al. [33] and Pace et al. [34] have reported a nearly identical obstetrics history of their patients, with abortion and premature labor rates around 95 and 5 %. No data have been recorded on term delivery and live-birth rates, and we can presume it was nearly zero, as well as in the study by Venturoli et al. [35] who reported a 100 % abortion rate.

In conclusion, the review of the data seems to demonstrate a strong relationship between septate uterus and adverse reproductive outcome in selected patients with infertility and miscarriages.

Moreover, according to the systematic review and meta-analysis performed by Chan et al. [16], canalization defects (septate and subseptate uteri) are associated with reduced clinical pregnancy rates (R.R. 0.86) and increased rates of first-trimester miscarriage (R.R. 2.89), preterm birth (R.R. 2.14) and fetal malpresentation (R.R. 6.24).

It is unclear whether the length of the uterine septum can have an impact on pregnancy outcome in women with a septate uterus. Kupesic and Kurjak [36] have found no correlation between septal length and rate of obstetrics complications. Other authors suggest that pregnancy wastage, late first-trimester abortion or early second-trimester abortion could correlate with the length of the septum, with longer septae posing the highest risk) [37]. Nevertheless, most studies in the literature do not distinguish between septate

and sub-septate uteri in terms of reproductive outcome, which means that patients under consideration are usually included in the same study group.

Recently Gergolet et al. [31] have investigated prospectively whether hysteroscopic metroplasty in patients with a small septum could increase fertility and reduce the miscarriage rate as against metroplasty in a group of patients with a subseptate uterus that is having a septum of greater length. Both groups have shown very similar results: miscarriage rate respectively 94.9 and 82.1 % before metroplasty vs. 11.1 and 14.0 % after surgery; delivery rate 2.6 and 15.7 % before metroplasty vs. 88.9 and 84.2 % after the operation. The conclusion is that, according to the above results, there is no evidence to support that a small septum (indentation <1.5 cm) has a different effect on the reproductive outcome as against a subseptate uterus (indentation of 1.5 cm or more), either before or after surgical correction of the anomaly. In other words, the septum length seems to be ineffectual in determining the reproductive performance of those patients, being a little septum as detrimental as well as a long one.

In a series of 826 deliveries from 730 women previously treated with hysteroscopic metroplasty, Tomazevic et al. [38] have reported an improved pregnancy outcome after metroplasty both in the septate uterus and small septate uterus (arcuate) groups. They have concluded that clinical behavior of a small septate uterus is not different from that of a septate uterus.

Woelfer et al. [29] has found no correlation between the depth of fundal indentation in an arcuate uterus and first-trimester miscarriage, second-trimester miscarriage or preterm labor rates. In women with a subseptate uterus, the first-trimester miscarriage rate appears to decrease as the uterine septum length increases, but that finding has not reached statistical significance. Furthermore, there is no correlation between septum length and second-trimester miscarriage or preterm labor rates.

Actually, most recent studies seems to confirm the evidence: Paradisi et al. [39] found no differences in term of reproductive performance after hysteroscopic metroplasty in women with small partial uterine septum (<2.5 cm) and women with large partial uterine septum (>2.5 cm).

Therefore, further prospective controlled trials are needed in order to get to a definite conclusion on the issue, even though the most recent studies seem to contradict the importance of the internal indentation degree of the septum into the uterine cavity [40, 41] (Table 14.3).

Table 14.3 Pregnancy outcome in patients with septate uterus before hysteroscopic metroplasty: largest studies

	Patients	Pregnancies	Ectopics	Abortions	Preterm del.	Term del.	Live birth
Authors	n.	n.	n (%)	n (%)	n (%)	n (%)	n (%)
March and Israel [50]	91	240	0	212 (88.3)	21 (8.8)	7 (2.9)	12 (5)
Perino et al. [51]	24	27	0	24 (88.9)	3 (11.1)	0	3 (11.1)
Daly et al. [52]	70	150	0	130 (86.7)	13 (8.7)	7 (4.7)	10 (6.7)
Cararach et al. [53]	62	176	NR[a]	160 (90.9)	11 (6.2)	5 (2.8)	NR
Pabuccu et al. [54]	49	108	NR[a]	96 (88.9)	11 (10.2)	1 (0.9)	NR
Valle et al. [55]	115	299	NR[a]	258 (86.3)	28 (9.4)	13 (4.3)	NR
Grimbizis et al. [56]	57	78	2 (2.6)	69 (88.4)	2 (2.6)	5 (6.4)	NR
Venturoli et al. [35]	72	171	0	171 (100)	0	0	0
Hollett-Caines et al. [33]	26	70	0	66 (94.3)	4 (5.7)	NR	NR
Pace et al. [34]	51	120	0	114 (95.0)	6 (5.0)	NR	NR
Saravelos et al. [32]	29	106	5 (4.7)	91 (85.8)	NR	NR	10 (9.4)
Gergolet et al. [31]	72	140	3 (2.1)	115 (82.1)	NR	NR	22 (15.7)
Total	641	1.495	10 (1.1)[a]	1.326 (88.7)[b]	89 (7.1)[b]	38 (3.1)[c]	57 (6.8)[d]

Note: NR not recorded
[a]Total of 912 valuable pregnancies
[b]Including first and second-trimester abortions
[c]Total of 834 valuable pregnancies
[d]Total of 1.249 valuable pregnancies

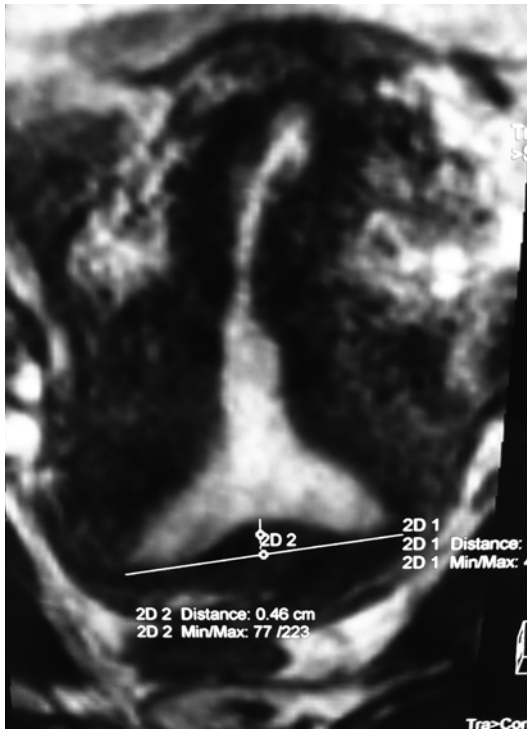

Fig. 14.7 MRI image of a T-shaped uterus (ESHRE/ESGE Class U1a)

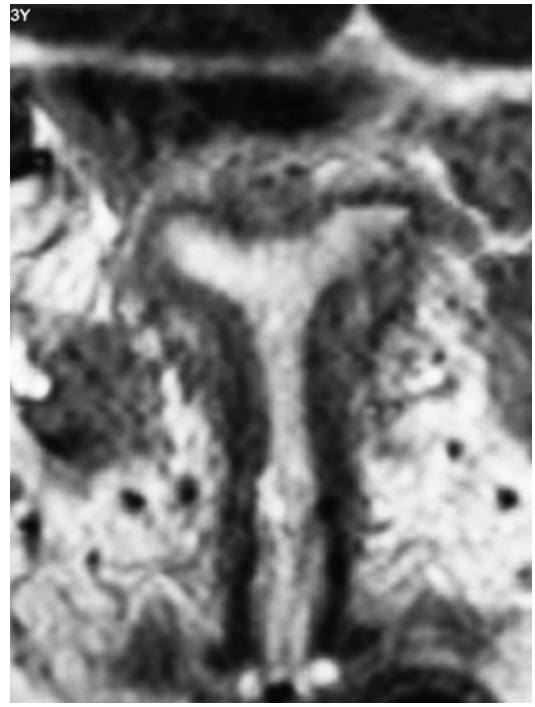

Fig. 14.8 MRI image of a uterus infantilis (ESHRE/ESGE Class U1b)

T-Shaped/Hypoplasic Uterus

Hypoplasia and dysmorphism of the uterine cavity (Figs. 14.7, 14.8) are unfavorable factors for fertility and pregnancy outcome. The etiology of uterine hypoplasia is generally unclear, apart from in-utero exposure to diethylstilbestrol (DES) [42]. DES was prescribed during the 1950s and late 1960s as a treatment for threatened miscarriage; it was given to some four million women in the USA while in France approximately 80,000 women were exposed to DES in utero [43]. On a group of 277 patients who underwent to HSG Kaufman et al. [44, 45] report abnormalities in 70 % of the DES-exposed women, whereas the most prevalent uterine anomalies are T-shaped uterus (19 %) and hypoplastic uterus (13 %) [46]. In addition, strictions, especially a constriction ring in the mid-uterus, irregular uterine contours and other anomalies can coexist.

Many studies have reported an increase in the infertility and miscarriage rates in women affected by T-shaped uterus or hypoplastic uterus. Kaufman et al. [47] has reported the risk for infertility increased by 1.49 in the presence of a T-shaped configuration, by 2.26 in the presence of mid striction, and by 2.63 when both anomalies were present. Even the pregnancy outcome appears often compromised, with higher rates of ectopic pregnancies, abortions and premature deliveries [43].

Katz et al. [48] have described eight women with reproductive dysfunction who had been diagnosed by hysterosalpingogram and hysteroscopy as having a "T-shaped" uterus and had been submitted to hysteroscopic metroplasty. Before the operative procedure, they had had ten spontaneous abortions (90.9 %) and one ectopic pregnancy (9.1 %), no term delivery. Garbin et al. [42] have reported on 15 women with a hypoplastic malformed uterus who had been exposed to DES in utero: before hysteroscopic metroplasty they had totalled 32 pregnancies without any live birth. Similar data are referred by Barranger et al. [49] on 15 women with hypoplastic uterus and 26

Table 14.4 Pregnancy outcome in patients with T-shaped/hypoplastic uterus before hysteroscopic metroplasty

	Patients	Pregnancies	Ectopics	Abortions	Preterm del.	Term del.	Live birth
Authors		n.	n.	n (%)	n (%)	n (%)	n (%)
Katz et al. [48]	8	11	1 (9.1)	10 (90.9)	0	0	0
Garbin et al. [42]	15	33	3 (9.1)	29 (87.9)	0	1 (3.0)	1 (3.0)
Barranger et al. [49]	15	26[a]	3 (11.5)	18 (69.2)	1 (3.8)	0	1 (3.8)[b]
Fernandez et al. [2]	97[c]	78	14 (17.9)	61 (78.2)	3 (3.8)[d]	0	0

[a]Two legal abortions
[b]Two deaths in utero
[c]Women with primary infertility or miscarriages
[d]All neonatal deaths

overall pregnancies before surgery: they have reported a first-trimester abortion rate of 61.6 %, a second-trimester abortion rate of 7.7 %, an ectopic pregnancy rate of 11.5 %, two cases of death in utero (7.7 %), and one preterm delivery before 32 weeks (3.8 %). No term deliveries and two legal abortions are referred (Table 14.4).

Fernandez et al. [2] have published the largest series on the reproductive outcome before and after surgical correction of a T-shaped uterus. They have presented a retrospective study on 97 women with a hypoplastic uterus, a cylindrical uterine cavity and bulging of the uterine side walls; while 63 had a history of DES exposure, the remaining 35 % had either a congenital malformation attributable to other causes or an acquired T-shaped malformation. On a total of 78 pregnancies before hysteroscopic metroplasty the miscarriage prevalence is 78.2 %, ectopic pregnancy 17.9 %, preterm delivery 3.8 % with all neonatal deaths and no live birth.

In conclusion, the pathogenesis of this congenital uterine anomaly remains unclear, apart from the exposition to DES in utero, and its cause is still unknown. When it is not treated surgically, it seems to be associated with a very poor pregnancy outcome.

In conclusion, it seems that those uterine malformations that cannot be surgically treated (Hemi-uterus and Bicorporeal uterus with double cervix – AFS Unicornuate and Didelphys uteri) are associated with poor reproductive performances, increased abortion rates and lower live birth rates, eventhough a successful pregnancy is possible in these women. On the opposite, septate uterus, hypoplastic uterus (AFS "T-shaped") and partial unification defects (AFS bicornuate uterus) are associated to the worst reproductive outcomes when untreated and to the higher reproductive performances after surgery.

If we look at the near future, some open issue could be developed: – the hypoplastic uterus (T-shaped/Uterus Infantilis) is an old/new congenital pathology to be taken into account, both for its increasing incidence and damage of reproductive outcome and for the promising results of hysteroscopic surgery in those patients; – further researches concerning new clinical and diagnostic parameters are also advisable, in order to individuate those subpopulations of patients with uterine congenital anomalies, i.e. women with septate uterus, that will benefit for sure of surgical procedure. Finally, focusing again on septate uterus, further controlled trials are needed in order to get to a definite conclusion on the issue of the length of the septum into the uterine cavity and the impairment of pregnancy.

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15 Cervical Weakness in Women Who Have Uterine Anomalies: Impact on Pregnancy Outcome

Feroza Dawood and Roy Farquharson

Overview of Uterine Anomalies

Uterine anomalies may be broadly grouped into congenital uterine anomalies (CUA) or acquired anomalies (such as leiomyomas, adhesions or polyps). Congenital uterine anomalies arise from aberrations or malformations of the female genital tract. The normal development of the reproductive tract is characterised by complex processes of differentiation, migration, fusion and subsequent canalization of the Mullerian system [1]. A spectrum of CUA ensues depending on when and how the embryological development of the Mullerian and paramesonephric ducts are affected.

The prevalence of CUA has been variably reported to be between 1 and 10 % [2]. The true population prevalence is difficult to assess because there is no universally agreed standardised classification system. We endorse the European Society of Human Reproduction (ESHRE)/European Society of Gynecological Endoscopy (ESGE) classification system of female genital anomalies that arose pursuant to a working group named CONUTA (CONgenital Uterine Anomalies) as this represents the most updated and clinically orientated version [3]. The detailed classification is discussed elsewhere in this book. Briefly, the main classes and subclasses are as follows: normal uterus, dysmorphic uterus, septate uterus (partial and complete), bicorporeal uterus, hemi-uterus, aplastic uterus and unclassified [3].

The modalities used to diagnose CUA typically include ultrasound, hysterosalpingography (HSG) or under direct vision with hysteroscopy. Laparoscopy and magnetic resonance imaging (MRI) may also be performed. Three- dimensional (3-D) and four- dimensional (4-D) ultrasound have the advantage of being non invasive and allow complete assessment of uterine morphology. In several studies, 3-D ultrasound has been favourably compared to HSG and laparoscopy in the diagnoses of CUA [4, 5].

Cervical Weakness and CUA

Cervical weakness (expressed hitherto in the literature as cervical incompetence) is a notoriously difficult entity to diagnose with certainty. The Euro-Team Early pregnancy protocol stated that there is no agreed definition of cervical weakness by absolute measurable or reproducible criteria [6]. Some define cervical weakness as the "history of painless dilatation of the cervix" resulting in

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second or early third trimester delivery coupled with the passage without resistance, of a size 9 mm Hegar dilator [6]. Other definitions include: a physical defect in the strength of the cervical tissue that is congenital or acquired [7] or recurrent second trimester or early third trimester loss of pregnancy caused by the inability of the uterine cervix to retain a pregnancy to term [8].

Since the most prominent clinical manifestations of cervical weakness are a history of spontaneous second trimester loss or preterm labour we focus on these in association with CUA. The possible hypothesis linking mid-trimester and preterm labour to CUA is that they may be an associated functional or anatomical weakening of the cervix.

Impact on Pregnancy Outcome

Although some CUA may have no impact on pregnancy outcome, others may contribute to miscarriage, intrauterine growth restriction and preterm labour [9, 10].

A recent review of CUA in a high-risk population, including miscarriage suggested a prevalence of 13.3 % [11]. In the recurrent miscarriage population, the prevalence of reported uterine malformations range widely from 1.8 to 37.6 % [12]. The septate uterus is the commonest congenital structural abnormality. A review of 24 studies suggested that the prevalence of CUA in the RM population is as high as 16.7 % compared to 6.7 % in the general population [13]. There are an abundance of studies describing CUA and miscarriage rates however few differentiate between early pregnancy or first trimester losses and mid-trimester loss (MTL) (between 12 and 24 weeks).

Mid-trimester Losses

Spontaneous mid-trimester losses may arise from cervical weakness alone or cervical weakness that is precipitated by the presence of a congenital uterine anomaly. A recent case-control study suggested a threefold increased risk of a MTL with a diagnosed septate or bicornuate uterus [13]. In a systematic review, the association between arcuate uteri and normally shaped uteri in terms of the risk of mid-trimester losses was analysed. Pooled analysis of four studies [14–17] revealed a significant increase in MTL in the women with arcuate uteri compared to women with a normal uterus (RR 2.39; 95 % CI .133–4.27; $p=0.003$). Other studies [15, 18] also demonstrated a doubling in the risk of MTL in association with a bicornuate uterus. The risk of MTL was described as being almost 10 % in another study evaluating women with a unicornuate uterus [19].

Preterm Delivery

A similar continuum of cervical weakness that causes spontaneous mid-trimester losses may lead to preterm delivery. A preterm delivery rate of 20 % was quoted in a study of 290 women with a unicornuate uterus [19], while in a smaller study; the preterm delivery rate was quoted as high as 66 % [20]. Another cohort study also concluded that women with any type of CUA had a higher chance of preterm delivery [21].

A systematic analysis of seven studies [2] demonstrated that the presence of an arcuate shaped uterus was not a risk factor for preterm delivery. However the limitation in this pooled analysis was a high degree of heterogeneity amongst the different studies. Five of these studies revealed a significant increase in preterm delivery (RR 2.14; 95 % CI 1.48–3.11; $p<0.001$) in women with canalization defects, particularly in women with subseptate and septate uteri [2]. There was also a significant association between increased preterm delivery and women with unification defects (RR 2.97; 95 % CI 2.08–4.23; $p<0.001$).

A more recent cohort study of 158 patients describe an increased risk of preterm birth in women with arcuate, septate and T-shaped uteri, and an even higher risk in women with unicornuate, bicornuate and didelphic uteri [22].

Management of Cervical Weakness and CUA

Opinions are divided regarding the role of hysteroscopic surgical uterine correction (metroplasty) in the presence of septate or subseptate uteri. While there are a number of uncontrolled small studies claiming improvements in future pregnancies following resection [23, 24], there are no randomised controlled trials to support these observations. A recent meta-analysis of the virtues of metroplasty to improve reproductive outcomes in patients with septate uterus found an overall favourable outcome [25]. Outcomes from the on-going TRUST trial (The Randomised Uterine Septum Transection Trial) comparing hysteroscopic metroplasty and expectant management in a miscarriage population are eagerly awaited [26].

Cervical Length Measurements

Ultrasound assessment of cervical length to detect cervical weakness has emerged as an effective prognosticator for preterm birth especially in women with a previous history [27]. Serial transvaginal cervical length measurements (CLM) are far superior and more reliable than digital cervical examination in assessing the length of the cervical canal, having an inter-observer and intra- observer variability of less than 10 % [28].

The risk of adverse obstetric outcome is inversely related to the length of the cervix and the gestational age at detection of a short cervix. Cervical length of less than 25 mm has been found in most populations to have the best predictive accuracy for preterm birth and mid-trimester loss and may be the most reliable threshold to define a high-risk population [29, 30].

A large randomised study of 47,000 low risk women was conducted where women were screened for cervical shortening at 23 weeks gestation [31]. The cervical length was measured at 15 mm or less in 470 women who were consequently randomised to cerclage or expectant management. The incidence of preterm delivery was similar in both groups; therefore the insertion of an ultrasound indicated cerclage was not deemed beneficial in women who have an incidental finding of a short cervix, in the absence of a previous mid-trimester loss or preterm birth [32]. Conversely women with prior obstetric risk may benefit from an ultrasound finding of a short cervix. A meta- analysis of four randomised controlled trials demonstrated that those women with a previous mid-trimester loss or preterm birth and a cervix of <25 mm had a better success rate of pregnancies continuing into the third trimester following insertion of cerclage [33].

Transvaginal Cervical Cerclage

The role and rationale for cerclage is an attempt to strengthen the internal cervical os to maintain a pregnancy. In the twentieth century, Shirodkar [34] and McDonald [35] described the two classical techniques of transvaginal cervical cerclage (TVC). The difference in technique is that with a Shirodkar cerclage, the bladder is reflected to enable the suture to be placed as close to the internal cervical os as possible per vaginum. The choice of technique is usually at the discretion of the surgeon. Evidence suggests that there is no significant difference in the preterm delivery rate when both the Shirodkar and McDonald technique are compared [36]. Cerclage is a common prophylactic intervention for mid-trimester loss and preterm delivery despite the lack of a well-defined population for whom there is clear beneficial evidence. Transvaginal cerclage is not without risks. The procedure is associated with an increased likelihood of medical intervention, hospital admission, puerperal pyrexia, induction of labour and caesarean section.

The largest study to evaluate the efficacy of transvaginal cerclage included 1,292 women at risk of preterm delivery [37]. The authors concluded that women with a history of at least three previous MTL's were the only group to derive a benefit from cerclage placement. The overall risk of preterm delivery reduced from 32 to 15 %.

Similar results were found in a multi-centre randomised controlled trial however the criteria for patient selection consisted of patients found to have a short cervix on routine transvaginal scanning at 22 weeks. Those women with a cervical length of 15 mm or below were randomised to cerclage or expectant management. The preterm delivery rate prior to 33 weeks was 22 % in the cerclage group compared to 26 % in the control group [38].

The CIPRACT trial recruited 35 women with a history suggestive of cervical weakness and CLM <25 mm before 27 weeks gestation. Preterm delivery prior to 34 weeks was 0 % when treated with cerclage compared to 44 % in the control group. The authors concluded that therapeutic transvaginal cerclage with bed rest reduces preterm delivery [8]. A further randomised controlled trial failed to demonstrate an improved perinatal outcome with transvaginal cerclage proposing ultrasonographic dilatation of the internal os and shortening of the distal cervix is a consequence of pathophysiological processes such as inflammatory and infective stimuli [7].

Another study that compared the application of transvaginal cerclage in women with a bicornuate uterus versus no cerclage describes a halving of the preterm delivery rate in the cerclage group. The same study also describes a 23 % reduction in the preterm delivery rate in women with an arcuate shaped uterus who were treated with cerclage versus no cerclage [20].

Transabdominal Cerclage

Transabdominal cerclage remains a valuable approach in the prevention of mid-trimester loss and preterm birth in cases of failed transvaginal cerclage or in cases where a transvaginal cerclage is deemed inappropriate. Examples include a short or absent cervix following surgery, congenital deformity or scarring as a consequence of obstetric trauma. Benson and Durfee first performed a transabdominal cerclage (TAC) in 1965 between 14 and 24 weeks gestation [39]. A midline incision was performed, the broad ligament was opened and with mobilisation of the uterine vessels, an avascular space was sought to pass a 5 mm Mersilene tape.

Although there are no randomised studies comparing the effectiveness of TAC with expectant management or TVC [32], a systematic review reported a better success rate of delivery >24 weeks in women with a TAC compared to those who had a repeat TVC [40]. Such outcomes were reiterated in a further study when TAC rather than TVC reduced the risk of preterm delivery [41]. Since then several studies have deemed TAC to be more successful than transvaginal cerclage in high-risk cases [40, 42, 43]. The efficacy and safety of TAC as a surgical procedure has been recently evaluated by a systematic review [42] and in terms of large single centre experience [44, 45].

Advances in minimally invasive surgery has led to a laparoscopic approach to TAC however there is no evidence to date to suggest that it is superior to open laparotomy [32]. A recent multicentre cohort study performed 66 preconceptual laparoscopic abdominal cerclages in women with at least one pregnancy loss in the second or third trimester and/or a short or absent cervix [46]. A total of 25 patients (71 %) delivered after 34 weeks gestation however three women experienced a further MTL. The peri-operative complication rate was 4.5 % [46].

A comprehensive review involving 31 eligible studies comparing laparoscopic versus open laparotomy TAC placement was published recently [43]. A cumulative number of 1,116 patients who underwent the open TAC were compared to 135 patients who underwent a laparoscopic placement. A high fetal survival rate of 94 % was achieved with pre-pregnancy TAC via open laparotomy and a fetal survival rate of 81 % was achieved via laparoscopic cerclage during pregnancy.

Conclusions

Until an international consensus is reached regarding the classification of CUA, in the first instance, it will be difficult to accurately determine the true incidence of the strength of correlation between CUA and cervical weakness. The evidence from the literature

is inherently flawed due to divergent definitions, heterogeneity and limitations of study groups. Furthermore, the quoted prevalence in the published literature is contingent upon the accuracy of the diagnosis of CUA.

Nevertheless, based on the historical classifications, there does appear to be an ostensible association between cervical weakness and the presence of different degrees of CUA. Furthermore, although not robust enough based on randomised controlled trials, there is evidence in the literature of improved pregnancy outcomes following interventions such as cerclage.

We advocate that the evaluation of women who present with a history suggestive of cervical weakness should include a thorough assessment to exclude the presence of a CUA. We opine that it would be difficult to justify not considering cerclage in women with a history of spontaneous mid-trimester loss or preterm birth, cervical weakness and an identifiable CUA.

What is certainly warranted is further research based on the ESHRE/ESGE definitions of CUA, and expounding the link between CUA and cervical weakness.

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Part IV

Treatment of Vaginal Aplasia/Techniques and Results

Frank Dilators

16

Lina Michala

Introduction

Vaginal dilation, first described in the 1930s by Robert Frank [1], remains a popular method to create a vagina in women with uterovaginal aplasia. It is in fact advocated as a first line treatment [2], being a successful and virtually risk free process, when compared to surgical vaginoplasties.

Indications

Women with Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome and Androgen Insensitivity Syndrome (AIS) are those most likely to benefit from vaginal dilation. Patients with other forms of Disorders of Sex Development (DSD) and uterovaginal aplasia, such as those with androgen biosynthesis enzyme defects, where a vaginal dimple is present, can also proceed with vaginal dilation. The process will not be suitable for DSD patients with a urogenital sinus or those with a flat perineum. It will also not be suitable for women with vaginal aplasia and a functional uterus, as this group of patients will require the surgical creation of a conduit for the passage of blood. In the latter cases however, dilation will be necessary postoperatively to maintain patency and vaginal girth, until the patient is able to have sexual intercourse.

Technique Description

The concept of vaginal dilation is based on the fact that the space between urethra and rectum is lined by supple connective tissue, leaving therefore a potential space for the vagina to be created or enlarged through application of pressure.

Vaginal dilation is most commonly performed using personal, graduated, plastic dilators that come in three different sizes, ranging between 10 and 30 mm in diameter (Fig. 16.1). Usually, a water based lubricant is used to facilitate the process. Initial pressure aims at enlarging the vaginal dimple away from the urethra, so as to avoid injuring it. Gradually, as the vagina lengthens, pressure is applied in an upward and slightly posterior direction, following the axis of the vagina. As the vagina grows in length, the second size dilator is used and finally the third, so as to simultaneously increase vaginal girth.

The process is considered successful and complete when the patient is able to comfortably insert the third size dilator or when she is able to engage in penetrative sexual intercourse with no problems.

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Fig. 16.1 Femmax® Dilators/Trainers, MDTI product

In the 1980s, Ingram modified the technique by attaching dilators to a bicycle saddle stool and asking the patient to position herself on the stool for 30 min to an hour a day. By this modification, the woman uses her body weight to exert pressure on the vagina, leaving her hands free, thus allowing her to engage in other activities during the dilation process, supposedly improving compliance with treatment [3]. The Ingram method, used mostly in America, is not widely available in Europe.

The appropriate time to commence vaginal dilation should be individualised. In most patients this will correspond with late adolescence to early adulthood. Professional psychological counselling will help identify the best time for initiating vaginal dilation, depending on time availability, motivation or the presence of a partner. Following completion of vaginal dilation, maintenance dilation is likely to be required, unless the patient is able to engage in regular sexual activity and this should be a factor to take into consideration when deciding whether to start vaginal dilation or not.

Interestingly, some women will present with a vagina of normal size, having achieved this through sexual intercourse alone. This may be an option for some patients that have a good starting vaginal length. However, it would not be reasonable to promote dilation through sexual intercourse as a first line approach for all, as pain at penetration may be traumatic enough to put the woman off from future sexual activity.

In patients with Complete Androgen Insensitivity Syndrome (CAIS), a commonly identified problem is vaginal dryness, due to decreased oestrogenisation, which may cause local irritation and discomfort during dilation. Symptoms will improve by using topical oestrogen regularly, alongside systemic oestrogen replacement.

Results

There are relatively few studies that look at outcome rates of vaginal dilation, particularly when compared to surgical vaginoplasty methods. The available literature suggests an anatomical success rate between 40 and 90 % [4–6]. It is unclear why some women are successful at vaginal dilation whereas some others are not. There is no evidence that a smaller starting size of the blind ending vagina would affect vaginal dilation success [4]. Also, there are no studies at present looking at anatomical or structural factors such as collagen or elasticity tissue levels that may play a role in vaginal dilation success (Table 16.1).

A number of studies have looked at psychosexual outcomes using validated questionnaires [4, 5, 7]. In a study by Ismail et al. [4] where 26 patients with MRKH or CAIS were monitored prospectively, 80 % completed dilation therapy in an average of 5 months. Patients were asked to complete the multidimensional sexuality questionnaire (MSQ), which measures sexual esteem, assertiveness, anxiety and depression, fear of sexual relation and satisfaction. Although all measures showed a general improvement trend, this only reached statistical significance for decreased depression and improved sexual satisfaction in women with CAIS. An earlier study looking at the Female Sexual Function Inventory (FSFI) in 60 women with MRKH that had completed vaginal dilation therapy, found them to have statistically significantly lower scores for orgasm and lubrication, when compared to controls and more likely to experience pain during sexual intercourse [7]. Overall, it appears that

Table 16.1 Details of studies looking at vaginal dilation since 2000

	Type of study	Place of study	Cause of vaginal agenesis	Year of publication	Range of age of participants	No. of participants	Successful	Success rate (%)	Median time required to achieve vaginal length (months)
Robson and Oliver [15]	Retrospective	Australia	MRKH	2000	14–19	39	25	64	
Ismail-Pratt et al. [4]	Prospective	UK	MRKH and CAIS	2007	18–24	26	21	81	5.2
Jasonni [16]	Retrospective	Italy	MRKH and CAIS	2007	13–18	104	41	40	6
Gargollo [17]	Retrospective	USA	MRKH	2009	14–35	69	50	72	18.7
Bach [5]	Retrospective	UK	MRKH	2011	16–27	32	25	78	5.6
Edmonds et al. [18]	Retrospective	UK	MRKH	2012	16–22	243	232	95	5.5

women with MRKH and CAIS, despite completing vaginal dilation, retain some difficulties during sex that may relate to the psychological impact of the diagnosis or may be attributable to vaginal anatomical factors.

Potential Complications

Vaginal dilation is a relatively risk free process, as it involves no anaesthetic and no hospitalisation. Short term risks, such as vaginal vault necrosis [8] or urethral damage and dilation [9] are relatively uncommon and usually are the result of unsupervised or forceful and protracted vaginal dilation.

Some women may present with urinary symptoms following completion of vaginal dilation and this is not surprising, given the close proximity between the vagina and the urethra. In a study of 19 women with MRKH or CAIS undergoing vaginal lengthening methods (vaginal dilation or laparoscopic Vecchietti procedure), there was a statistically significant increase in bladder emptying difficulty post treatment and a worsening in urinary frequency the longer the vaginal length achieved [10].

In the longer run, there are reports of vaginal vault prolapsed, although this appears to be rarer than with intestinal vaginoplasties. In those cases described in the literature, treatment to the prolapsed vaginal vault is either through a sacrospinous fixation or a laparoscopic sacrocolpopexy [11, 12].

There are no direct comparisons between surgical vaginoplasties and vaginal dilation, however, a recent study looking at depression and anxiety scores, as well as overall quality of life indices in women with MRKH having undergone surgery or dilation showed them to fare worse when compared to controls and women with the same diagnosis that had not received any treatment to their vagina [13].

This is not surprising, as vaginal dilation can be a lengthy process, which would remind an otherwise healthy woman of her abnormality. It can also cause some discomfort, although less so than when compared to postoperative pain relating to a surgical vaginoplasty.

Concluding remarks

Vaginal dilation, therapy should be undertaken in a controlled setting with emotional and professional psychological support and adequate coaching from a specialised nurse or gynaecologist that will guide and supervise the woman through the process. Providing the woman with ample information on how to perform dilation and scientific evidence that it is effective, giving her the opportunity to share her experience with other women with the same condition through support groups, along with frequent feedback on her progress have been shown to improve patients experience and compliance with treatment [14]. Cognitive techniques could also be used to improve pain perception during dilation therapy and reinforce motivation. Treatment, requiring frequent hospital visits. could be seen as an opportunity to discuss concerns about the implications of the condition on femininity, sexuality and fertility. This should improve the overall emotional wellbeing for women with a uterovaginal aplasia (Table 16.1).

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Vulvo-perineoplasty/Creatsas Vaginoplasty

17

George Creatsas and Maria Creatsa

Introduction

Mayer-Rokitansky-Küster-Hauser syndrome is a rare congenital abnormality of the female genital tract presented with aplasia of the uterus and the upper two-thirds of the vagina in an otherwise normal 46, XX individual. The incidence is approximately one case in 4,000 women. The syndrome is frequently associated with other nongynecological defects, such as: urinary tract anomalies, vertebral deformities and to a lesser extent auditory and cardiac lesions. Furthermore the absence of the vagina and the uterus have a profound psychological impact on the young woman's sense of femininity, so that the demand for a sexual life makes the creation of a neovagina strongly advisable. Several techniques of vaginal reconstruction, surgical or nonsurgical, have been reported such as the Creatsas vaginoplasty, the Franks procedure, the Williams vaginoplasty, the McIndoe operation, the Vecchietti technique and others [1, 2].

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Technique

The Creatsas vulvo-perineoplasty is a modification of the Williams' procedure. It is a simple, safe and quick operative method resulting in a functioning vagina, similar to normal. We developed our technique in 1981 and until now we have performed 221 cases. The operation starts with three incisions (using electrocautery) at the third, sixth and ninth o'clock positions of the hymen. This opening prevents postcoital bleeding during the first sexual intercourse. The vulval tissues are put under tension by four Allis clamps (Fig. 17.1a). A U-shaped incision follows on the labia (Fig. 17.1b). The upper edge of the incision ends 4 cm laterally to the external urethral meatus. After mobilizing the tissues, a meticulous hemostasis is required to avoid postoperative hematomas and tissue necrosis [3–5].

Closing of the inner skin margins followers. The knots are placed inside the created neovagina to avoid early decomposition, which could lead to wound opening.

A layer of sutures is followed to approximate the subcutaneous fat and the perineal muscles. Finally, the external skin is closed (Fig. 17.1d). For the closing of both the skin layers (Fig. 17.1b, c), interrupted absorbable 2-0 sutures are used, starting posteriorly and proceeding anteriorly.

The criterion for the success of the operation is the creation of a neovagina up to 10–12 cm in depth and 4–5 cm in width. The functional

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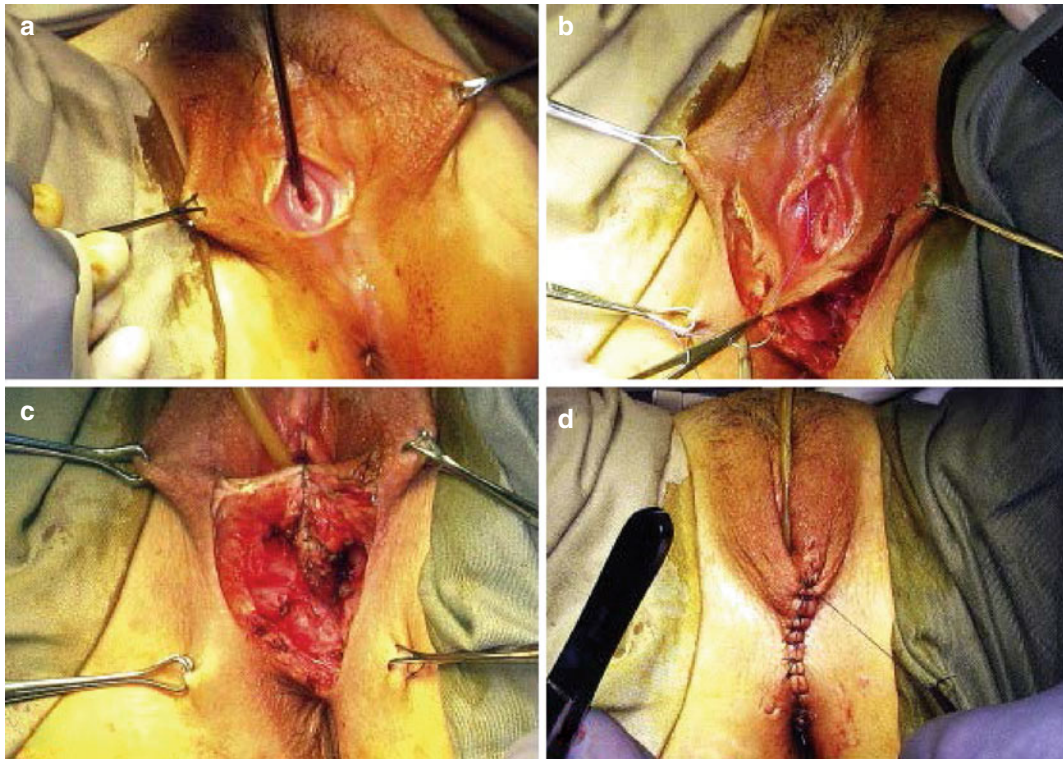

Fig. 17.1 (**a**) Placement of the Allis clamps and catheterization of the urethral meatus. (**b**) A U-shaped incision in the vulva, mobilization of the tissues and placement of the first suture. (**c**) Closing of the first layer with placed of sutures between the inner skin margins. (**d**) Closing of the second layer and completion of the operation [2, 3]

dimensions of the neovagina are measured using sonovaginography [1]. A clinical re-examination in 4 weeks and 6 months and then on a yearly basis is recommended (Fig. 17.2). Following our procedure, no significant postoperative complications were reported and all patients have had a satisfactory sexual intercourse. A mean hospital stay up to 6 days is required to prevent postoperative complications such as dehiscence and to maximize patient's compliance. Finally, there is no need for postoperative vaginal dilatations, which usually reduce the psychological impact on the patient [3, 6].

Comparative Advantages of Vulvo-perineoplasty

The McIndoe's vaginoplasty was a common used vaginoplasty among other available operative techniques. However, several complications were reported such as the risk of injuries of the neighboring organs. Also, graft shrinkage, due to the development of granulomatous tissue, caused neovaginal stenosis. The aesthetic outcome should be taken into consideration.

The Vecchetti's operation and its laparoscopic version are frequently performed in several European centers over the last years, with low perioperative morbidity and a short recovery period. Potential important complications may occur, namely passing the cutting needle from the abdominal wall to the retrohymenal fossa. Frequent follow-up evaluations to adjust the device tension and the use of dilators after the removal of the apparatus, are also required.

The sigmoidal colpoplasty is considered to be a major, complicated intraperitoneal operation that carries intraoperative risks and complications. Satisfactory anatomical and functional results have been reported by the use of pelvic peritoneum from the pouch of Douglas [7, 8].

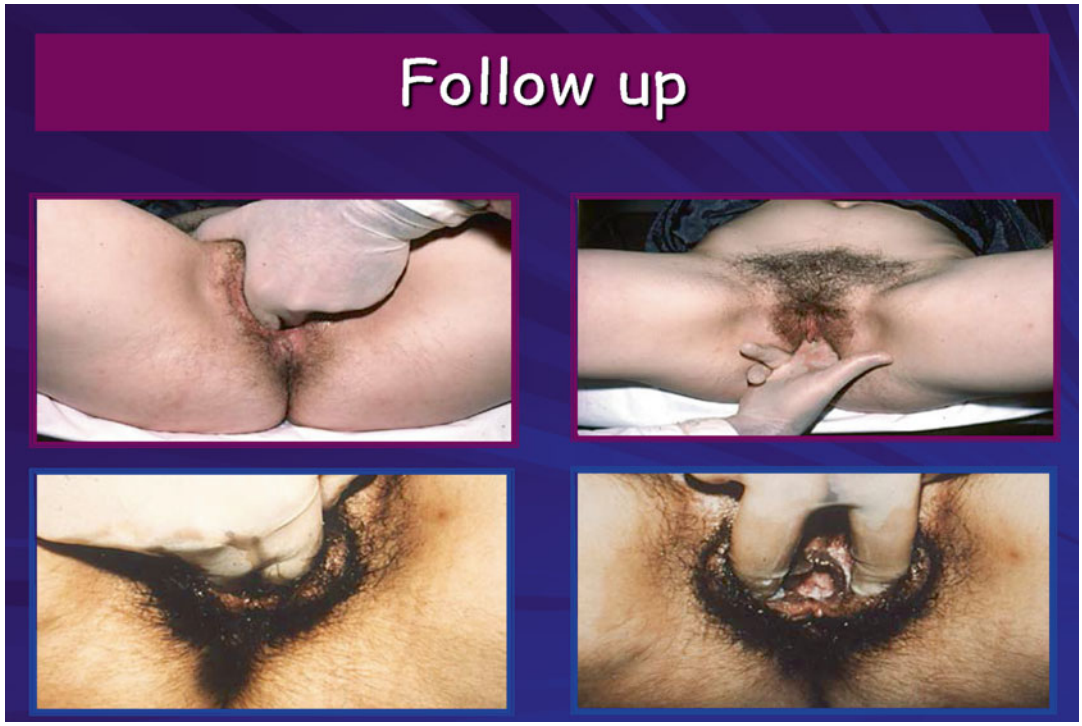

Fig. 17.2 Postoperatively results of Creatsas vaginoplasty

The Franks technique requires daily use of manually operated vaginal dilators for a long period of time. Despite the good results of the method and the absence of surgical and anesthetic risks, young patients often cannot maintain the required compliance.

In contrast to other grafting methods, Creatsas vulvo-perineoplasty provides elasticity of the tissues, formatting the lower part and the introitus. The neovagina allows for pleasant and uncomplicated sexual intercourse. The latter may be attempted shortly after the operation to alleviate the patient's stress [9]. Almost all of our patients described their sexual life as satisfactory or adequate, which shows that sexual satisfaction is usually achieved.

Conclusions and Proposals

In conclusion, the aim of all methods is the creation of a vaginal channel of adequate functional depth and width, with axial deviation similar to normal. Our experience shows that the Creatsas vaginoplasty is a simple, quick, and effective vulvo-perineoplasty that satisfies all the requirements.

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Neovagina Formation by Expansion of the Vaginal Vault

18

Sara Yvonne Brucker and Diethelm Wallwiener

Laparoscopically Assisted Neovaginoplasty: the Minimally Invasive Expansion Method

Introduction

This chapter discusses a laparoscopically assisted neovaginoplasty technique developed from the original pelviscopic Vecchietti procedure described by Gauwerky, Wallwiener, and Bastert in 1992 [1], the first reported laparoscopic expansion-based procedure for the creation of a neovagina in women with congenital vaginal aplasia. Our technique was subsequently optimized by improving surgical methods and developing a set of special instruments and devices [2, 3].

Essentially, our laparoscopic neovaginoplasty technique combines a minimally invasive surgical method with a stretching method, as does the classical laparoscopic Vecchietti procedure. However, our procedure differs fundamentally from the latter in that it is based on blunt perforation of the existing vaginal dimple, thus dispensing with vesicorectal tunneling from the abdomen to the vagina and dissection of the bladder and rectum. In our technique, the direction in which the blind-ended, short vaginal vault, or vaginal dimple, is perforated with the aid of targeted, laparoscopically guided imaging proceeds from the vagina to the abdomen, through the rectovesical septum, carefully avoiding any perforation of the bladder or rectum. A curved thread guide is used to subperitoneally feed two tension threads in a cranial direction before attaching them to a traction device positioned on the patient's abdomen. At the vaginal end, the two tension threads are joined to the proximal segment, or "olive", of a pluggable segmented dummy, which continuously exerts pressure on the vaginal dimple in the abdominal direction. Expansion of the vaginal dimple is subsequently achieved by daily tightening of the tension threads by means of the extracorporeal traction device under epidural anesthesia, thus creating a neovagina within a few days [3].

Our technique is appropriate in patients with congenital absence of the vagina and functional uterus. This occurs mainly in 46,XX individuals with Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, also called Müllerian agenesis Müllerian agenesis, a condition often additionally associated with renal anomalies (pelvic kidney, unilateral renal agenesis, and horseshoe kidney) and skeletal malformations of hitherto unknown etiology [4, 5].

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Our technique is also appropriate in patients with vaginal aplasia due to (complete) androgen insensitivity syndrome ((C)AIS), whose karyotype is 46,XY [6]. The main sign of congenital (utero) vaginal agenesis is primary amenorrhea without major abdominal pain. As the existing vaginal dimple usually is very short, sexual intercourse is frequently impossible, or very painful.

Treatment for MRKH syndrome and (C)AIS is the same [6]. The absence of the vagina requires correction to enable sexual intercourse [7, 8]. In addition to nonsurgical successive dilation according to Frank's dilator method [9], a number of invasive surgical procedures have been developed, for example the McIndoe and Davydov techniques using split-thickness grafts and peritoneum, respectively, and methods using ileum or sigmoid colon [6], see also the respective chapters in this book.

Indications

Laparoscopically assisted neovagina creation by expansion of the existing vaginal vault is primarily indicated in patients with congenital vaginal aplasia due to MRKH syndrome and AIS or CAIS. The skeletal and especially the renal malformations these conditions may be associated with do not constitute contraindications to the procedure. In particular, the presence of a single pelvic kidney is not a contraindication but does require skill and experience on the part of the surgical team.

Contraindications to the procedure include noncongenital absence of the vagina due to, e.g., cancer surgery, radiation therapy, or other interventions, and the patient's age, which should be at least 14 years.

The Laparoscopically Assisted Expansion Technique

Details of the purpose-designed set of devices and instruments, step-by-step descriptions of the procedure, and the preoperative and postoperative management of the patient have been reported elsewhere [10, 11]. The essentials of the procedure are described in the following.

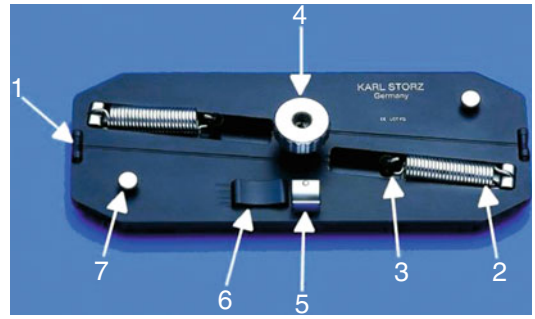

Fig. 18.1 The optimized traction device. *1* thread guide rail, *2* tension spring, *3* thread guide roller, *4* tensioning button, a single traction ratchet for even, stepwise tension via both threads to avoid dehiscence and tearing of the neovagina, *5* tension release lever, *6* locking mechanism to fix the traction ratchet and prevent inadvertent release, *7* pan-head screw for easy disassembly for autoclaving (Reproduced with permission from Brucker et al. [3])

Instruments and Devices

The neovaginoplasty technique described below requires a set of new instruments and devices developed specifically for this expansion-based technique. The set comprises the extracorporeal traction device, applicators, a pluggable segmented dummy, and vaginal dummies.

Extracorporeal traction device

The traction device shown in Fig. 18.1 consists of a base plate made of a biocompatible material with a flat, smooth surface. It lies snugly on the skin without creating pressure points. Via a guide rail, the thread, e.g. Terylene USP 4, is fed to the tension spring and passed over guide rollers on both sides. The direction of tension is thus defined whilst protecting the thread. The two thread ends are each tightened with a tensioning button, producing permanent tension by the spring force. A locking device with a sliding mechanism secures the tensioning button. Tension can be released in part or completely via the release lever at any time.

Applicators, pluggable segmented dummy, and vaginal dummies

The set of instruments developed for the technique as shown in Fig. 18.2. The straight and curved ***thread applicators*** with ergonomic handgrips are required for vaginoabdominal perforation

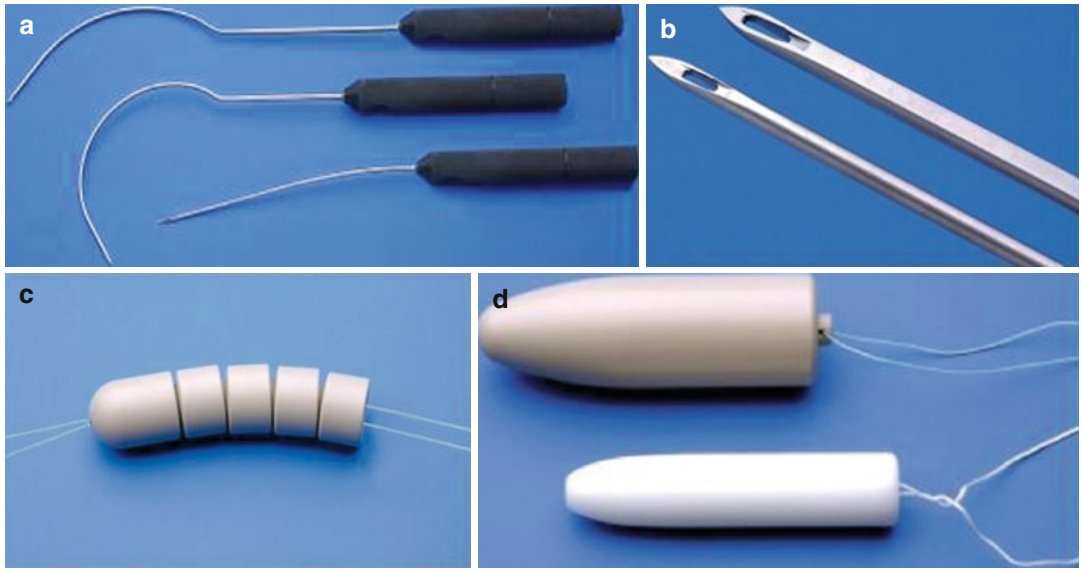

Fig. 18.2 Instruments and vaginal dummies for laparoscopically assisted neovagina creation by expansion. (**a**) Straight applicator for vaginal-abdominal perforation and curved tread guides for retroperitoneal feed-through of the tension threads, all equipped with ergonomic hand grips. (**b**) Sharp-edged applicator tips. (**c**) The pluggable segmented dummy for the traction phase with the "olive" as the top segment. (**d**) Vaginal dummies for postoperative maintenance of the neovagina. Lettering from *top left*, clockwise (Reproduced with permission from Brucker et al. [10])

(straight) and abdominovaginal perforation and peritonealization (curved). The sharp-edged applicator tips enable easy perforation of the vaginal dimple and retroperitoneal feed-through of the tension threads. The ***pluggable segmented dummy*** is designed to stretch the vaginal dimple into the abdominal cavity. The ***vaginal dummies*** used for postoperative maintenance of the neovagina have diameters of 2, 2.5, and 3 cm, and lengths of 10 and 12 cm.

Laparoscopic instruments and equipment

The procedure requires a standard set of laparoscopic instruments comprising a 0° endoscope, a Veress needle, and two trocars (10 and 5 mm in diameter). It further requires a xenon light source and a thermoflator. A 3-chip camera with integrated control buttons, zoom, and focusing is needed for imaging. The video camera system and monitor should have full high-definition (HD) quality (1,920 × 1,080 pixels) for visualization of fine structures. Lastly, the procedure requires a minimum of two grasping forceps, including a sharp forceps to enable secure gripping the uterosacral ligaments.

Preoperative Management and Preparations

Before surgery is considered, it is essential to confirm the diagnosis of MRKH syndrome or (C) AIS by chromosome and hormone analysis and ultrasonography, and establish the indication for the chosen procedure. In addition, magnetic resonance urography (MRU), and in some cases diagnostic laparoscopy, may be necessary to exclude other malformations of the urogenital tract. The patient and her parents or legal guardians need to be educated about all available treatment options, surgical and nonsurgical, and discuss the patient's expectations of surgical treatment. With regard to laparoscopically assisted neovaginoplasty, the procedure, the immediate postoperative course, and the necessity to wear a vaginal dummy for a prolonged period to maintain neovaginal function and to see the specialist for regular check-ups should be discussed in detail.

Preoperative anesthesiologic evaluation should be performed and thrombosis prophylaxis achieved using low-molecular weight heparin and compression stockings. Bowel preparation is mandatory.

A first or second-generation cephalosporin should be administered for antibiotic prophylaxis less than 30 min preoperatively and maintained postoperatively until the traction device is removed.

Surgical Technique

For surgery, the patient is placed in the ***Trendelenburg position*** with her legs resting on sufficiently padded leg holders to enable unhindered access to the perineum. The patient is prepped and draped in a standard sterile manner, allowing simultaneous access to both the abdominal and the vaginal region. The procedure is performed under ***general anesthesia***. Immediately before surgery, epidural anesthesia is additionally administered for postoperative pain control.

Laparoscopically assisted neovaginoplasty is a technically demanding procedure that takes a team of two surgeons, one or (ideally) two assistants, and a scrub nurse 1–2 h to complete.

Prior to laparoscopy, the future ***position of the traction device*** just below the umbilical fossa is determined and marked with a pen, as are the future puncture points to the left and right of the traction device.

Laparoscopy is initiated, a pneumoperitoneum is created, and the optical trocar and telescope are introduced. Following inspection of the initially intraabdominal site, the suprasymphyseal auxiliary trocar is placed. The procedure requires only a single suprapubic trocar.

Next, the direction of the perforation necessary for the introduction of the traction threads through the vaginal dimple into the abdominal cavity is determined diaphanoscopically using simultaneous laparoscopy and cystoscopy in the picture-in-picture mode. The future neovaginal apex needs to lie dorsally on the connecting fibrous band of the rudimentary uterus, exactly dorsally to the uterosacral ligaments.

Controlled digital pressure from the left forefinger is then applied to the vaginal dimple, pushing it in the direction of the abdomen, until the vaginal dimple is almost perforated, as shown in Fig. 18.3. Simultaneously, the straight thread guide is inserted under this guiding finger together with the two threads attached to the dummy, following the guiding finger to the proximal end of the dimple while the left middle finger is used to distance the rectum dorsally. It is crucial during this step to grasp the uterosacral ligaments at

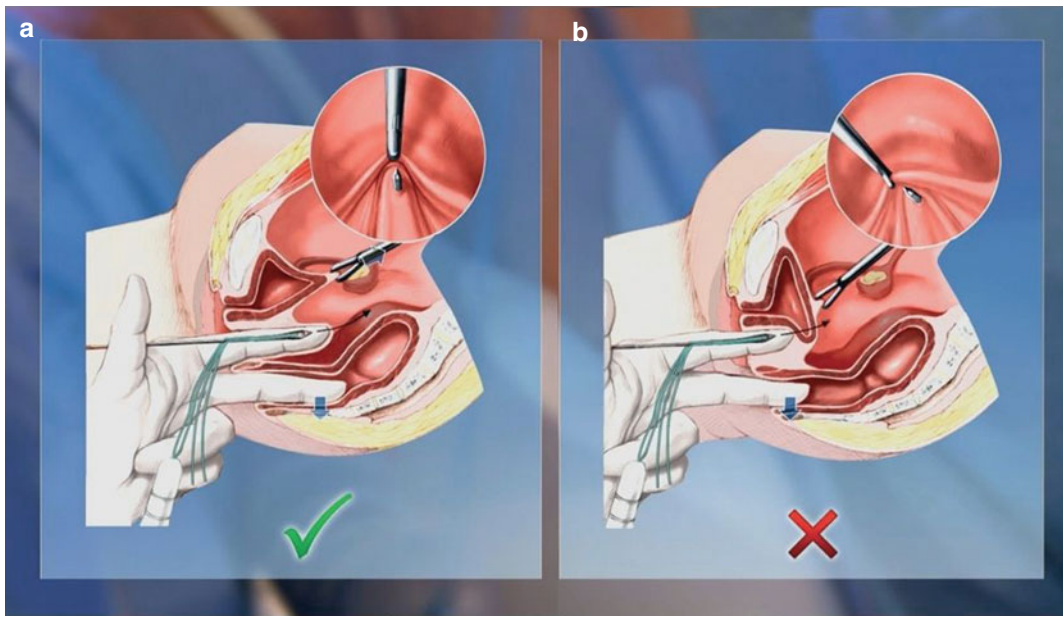

Fig. 18.3 Correct (**a**) and incorrect (**b**) finger and forceps positions during transvaginal perforation of the vaginal dimple (Reproduced with permission from Brucker et al. [10])

their union using a laparoscopic forceps and to draw them as far as possible in the cranioventral direction. This ensures that the bladder cannot be punctured because it is stretched and flattened and removed from the point of perforation. Fig. 18.3 illustrates the correct and incorrect finger and forceps positions.

Perforation of the vaginal dimple then introduces the threads into the abdominal cavity. Unlike other Vecchietti-based techniques, our procedure thus obviates the need for tunneling of the vesicorectal space.

Intraabdominally, the threads are detached from the straight thread guide, which is then retracted. Injury to the bladder and rectum is excluded by cystoscopy and rectal palpation.

After the bladder is filled to 200–300 mL, the curved thread guides are successively inserted at the marks previously made on the right and left side of the abdomen and then retroperitoneally advanced to the upper end of the vagina, as shown in Fig. 18.4. After intraabdominally threading each thread into the guide, it is drawn back behind the peritoneum and out through the abdominal wall, as illustrated in Fig. 18.5.

Under cystoscopic control, a suprapubic catheter is then inserted and the transurethral catheter removed to prevent pressure from the dummy causing urethral necrosis. The suprapubic catheter remains in place until removal of the traction device. This change of catheters can be dispensed with if only the top segment of the pluggable dummy, the olive (Fig. 18.2c), is used. In this case, urethral necrosis will not occur because as a rule the olive will reach its final position behind the urethra within hours.

Finally, the traction device is positioned as far cranioventrally as possible, with its cranial edge bordering on the lower edge of the navel, as shown in Fig. 18.6. This achieves the greatest potential for maximization of neovaginal length and the best possible anatomical axis. Each thread is fed via a thread guide on the tension device to the spring opposite the thread exit point and inserted into the slot in the tensioning wheel shaft. The threads are secured by attaching the tensioning wheel with an audible click. The wheel is gradually turned until the necessary tension has been built up and then secured with the locking mechanism. This tensions the two threads simultaneously and uniformly.

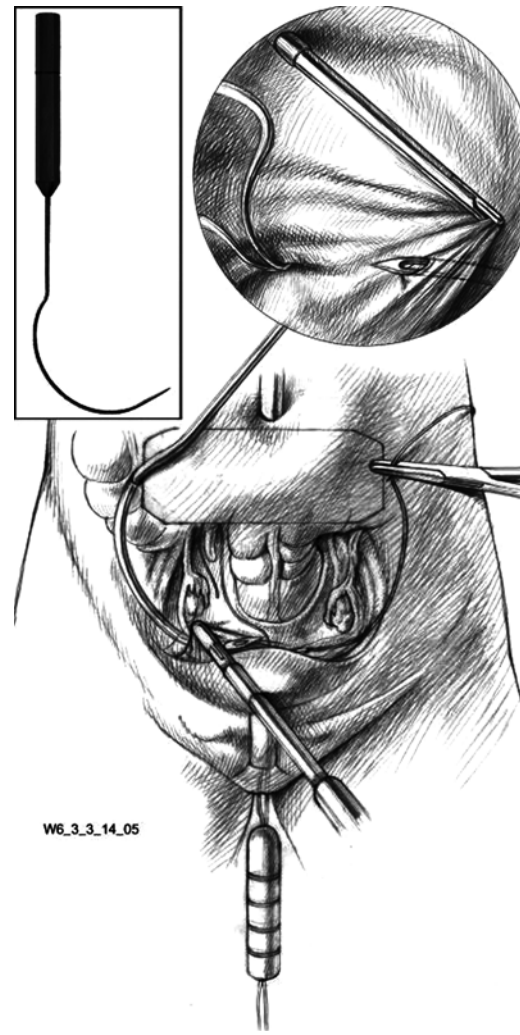

Fig. 18.4 Insertion of the curved thread guide, down to the cranial end of the vagina (Reproduced with permission from Brucker et al. [3])

Postsurgical Management

After surgery, daily tightening of the threads using the traction device requires pain control via an indwelling epidural catheter. Once expansion has created a neovagina of approx. 10 cm in length, usually 4 or 5 days after surgery, the tension threads are loosened slightly and cut close to the abdominal wall to enable removal of the traction

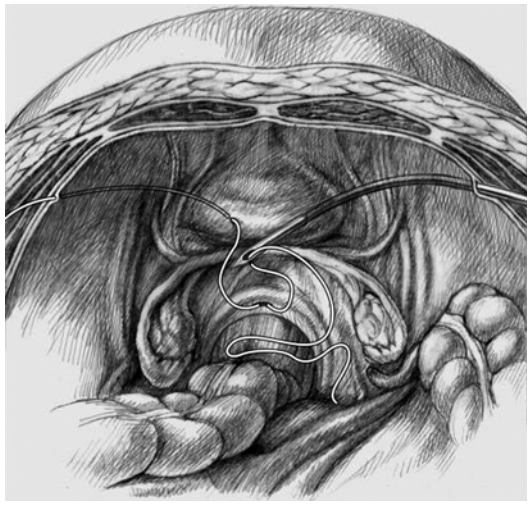

Fig. 18.5 Retroperitoneal drawing of the threads through the abdominal wall (final result on the left). The right side shows the thread about to be retroperitoneally drawn to the exterior (Reproduced with permission from Brucker et al. [3])

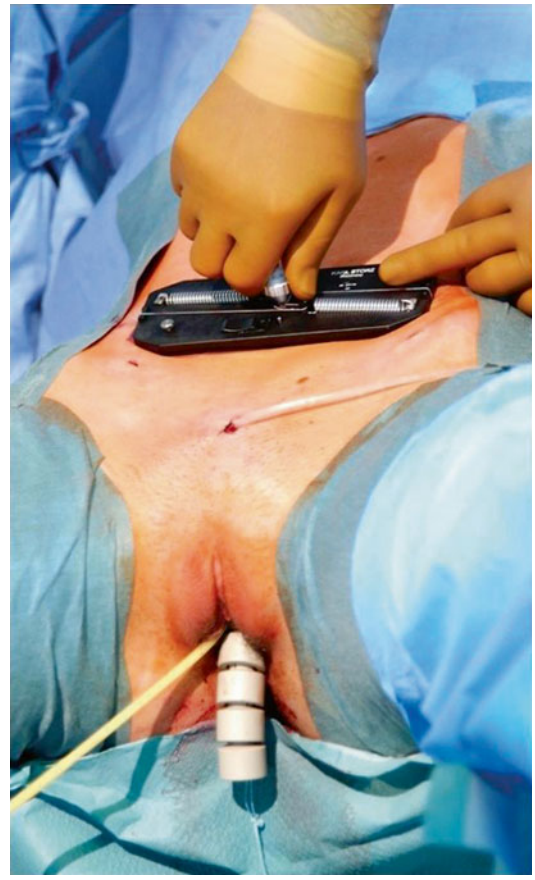

Fig. 18.6 Using the traction device to tension the threads postoperatively (Reproduced with permission from Brucker et al. [10])

device and segmented dummy. The latter is extracted vaginally together with the intracorporeal portion of the threads.

To maintain the neovagina and speed up epithelialization, a vaginal dummy must be worn for several weeks after surgery. Insertion is facilitated by generously coating the dummy with estrogen-containing cream, which also promotes epithelialization. In the absence of regular intercourse after this phase, it is advisable to continue wearing the dummy several times a week to prevent neovaginal shrinkage.

Modifications

The surgical technique described above encompasses a number of fundamental modifications to the original procedure using a traction device to create a neovagina by vaginal dimple expansion as first described in patients with congenital vaginal aplasia by Vecchietti in 1965 [12]. The then novel original procedure involved laparotomy to access and dissect the vesicorectal space. With the advent of laparoscopy, it became possible to replace laparotomy, obviating the morbidity open surgery entails. Thus the first laparoscopic Vecchietti neovaginoplasty procedures were reported by Gauwerky et al. in 1992 [1] and Fedele et al. in 1994 [13], the former technique being based on vesicorectal tunneling, the latter already replacing this dissection step by vaginoabdominal perforation of the rectovesical septum, thus further reducing morbidity.

Our current technique is the result of the substantial further development and optimization of both the instruments and devices required for the procedure and the surgical technique of laparoscopically assisted neovaginoplasty.

Essentially, our technique involves three major modifications to the original Vecchietti technique. First, it replaces abdominal open surgery by

laparoscopically assisted minimally invasive surgery. Second, it dispenses with the need for dissection of vesicorectal space by using the vaginal approach to introduce the tension threads into the abdominal cavity by vaginoabdominal perforation of the rectovesical septum. Third, in our technique, the traction device is positioned just below the umbilical fossa rather than in the suprapubic region as in the original technique. This is an important modification as it greatly reduces the danger of the olive being drawn too ventrally in the direction of the bladder, potentially resulting in injury to, and even perforation of, the bladder, as has been reported by others [14, 15]. At the same time, the more cranial positioning of our traction device also enables better anatomical results in terms of both neovaginal length and an anatomically correct axis.

Review of the Literature

The following review of the literature will focus on the post-operative functional results of neovagina formation by laparoscopically assisted expansion of the existing vaginal vault. The essential data from relevant publications are summarized chronologically in Table 18.1, updating a recent review by Brucker et al. [6] that discusses the wide range of treatment options available to patients with congenital vaginal aplasia and other malformations of the female genitalia. This section will focus on Vecchietti-derived techniques since the nonsurgical dilation method originally developed by Frank and the other surgical procedures, e.g. those using skin grafts (McIndoe), peritoneum (Davydov), or bowel, particularly sigmoid colon, are discussed in detail elsewhere in this monograph.

After early studies by Gauwerky et al. focusing on the technique of the laparoscopic Vecchietti procedure as such in 1992 [1] and the technique with case reports on five patients in 1993 [16], Fedele and colleagues [13] in 1994 published a study in two patients with MRKH syndrome who underwent a laparoscopic modification of the Vecchietti procedure without dissection of the vesicorectal space, yielding very good results in terms of anatomic and sexual function in both patients.

In 1996, Fedele et al. [15] reported that a mean vaginal length of 8.1 ± 1.1 cm was achieved without surgical complications in an open non-comparative clinical study in 14 MRKH syndrome patients, of whom 93 % showed satisfactory results.

Borruto and colleagues in 1999 [17] published a retrospective comparative analysis of Vecchietti's operation by laparoscopy vs. laparotomy in MRKH patients. Seven patients underwent the laparoscopic procedure vs. 69 who underwent laparotomy. Average neovaginal length was 7.5 cm and all seven laparoscopy patients reported satisfactory results after follow-up periods of 1–60 months.

A retrospective study published by Fedele and colleagues in 2000 reported their experience of the laparoscopic Vecchietti procedure in 52 patients with MRKH syndrome [18]. They reported a traction time of 7 days, a vaginal length of >7 cm, and satisfying results in 94.2 % of patients [18].

Brun et al. [19] published a retrospective study in 2002, reporting comparable mean operative times for the laparoscopic Vecchietti procedure in three women relative to conventional Vecchietti procedures by laparotomy in 17 patients. Mean operative time was 55 min and the traction period was 7.7 days, ultimately resulting in a neovaginal length of 8.3 cm and a width of 2.7 cm.

A 2006 descriptive comparative technical study by Fedele and associates [20] reported operating 26 MRKH patients with new (12 patients) and conventional instruments (14 patients) without any intraoperative complications. Traction times and neovaginal lengths for the two groups were reported as 8.3 ± 1.2 and 6.2 ± 1.1 days and 6.2 ± 0.4 and 7.5 ± 0.6 cm, respectively. No details were reported as to the follow-up period and whether the results were satisfactory.

Folgueira and colleagues reported outcomes in 18 patients with MRKH syndrome who underwent creation of a neovagina by the laparoscopic Vecchietti procedure with technical modifications, including abdominovaginal perforation of

Table 18.1 Selected publications, in chronological order, reporting expansion-based laparoscopic or laparoscopically assisted neovaginoplasty techniques and their outcomes

Author (year) [Reference]	Type of study	Patients, N (technique)	Indication (n)	Age, median [range] or mean ± SD, years	Operative time, median [range] or mean ± SD, min	Intraoperative complications, no. of patients (%)	Traction time [range], days	Neovaginal length, median [range] or mean ± SD, cm	Satisfactory results, n/N (%)	Follow-up, median [range] or mean ± SD, months
Gauwerky (1992) [1]	Technique	n.d.	MRKH	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Gauwerky (1993) [16]	Technique and case reports	5 (Vecchietti with VRT)	MRKH (2) AIS (2) Other (1)	27.3 [23–33]	n.d.	0	15 [12–19]	9.6 [8–12]	5/5 (100)	91 [72–108]
Fedele (1994) [13]	Technique, case report	2	MRKH						2/2 (100)	
Fedele (1996) [15]	Open noncomparative clinical study	14	MRKH	[15–34]	n.d.	0	n.d.	8.1 ± 1.1	13/14 (93)	[6–24]
Borruto (1999) [17]	Retrospective analysis of laparoscopy vs. laparotomy	7 (laparoscopic vs. 69 laparotomic Vecchietti procedures)	MRKH	n.d.	n.d.	0	n.d.	7.5	7/7 (100)	1–60
Fedele (2000) [18]	Retrospective analysis	52	MRKH	16.9 [15–34]	22	3 (5.8)	7	>7	49/52 (94.2)	37 [6–64]
Brun (2002) [19]	Retrospective analysis of long-term results	3 (laparoscopic and 17 laparotomic Vecchietti procedures)	MRKH	19.3 [18–21]	55	0	7.3 [7, 8]	8.3 [8, 9]	3/3 (100)	27 [24–30]
Fedele (2006) [20]	Descriptive comparative technical study	26 (12 new +14 with conventional instruments)	MRKH	21.5 ± 3.7 and 21.3 ± 3.1	n.d.	0 and 0	8.3 ± 1.2 and 6.2 ± 1.1	6.2 ± 0.4 and 7.5 ± 0.6		
Folgueira (2006) [21]	Descriptive study of technique and outcome	18	MRKH	20.1 [15.9–27.1]	45 [40–55]	0	6.3 [5–9]	11.3 [6–13]	17/18 (94.3)	25 [6–60]
Ismail (2006) [22]	Descriptive comparative technical study, case reports	5 (3 Vecchietti (MRKH), 2 Davydov (AIS))	MRKH (3) AIS (2)	25 [15–49]	n.d.	0	7	7.6	n.d.	10.6 [6–30]

Brucker (2008) [3]	Prospective comparative study	101 in 3 subgroups:	MRKH (93) AIS (8)			4/101 (3.9)				
		12 (conventional instruments, with VRT)		19.2 ± 6.1	113		11.7	8.9 ± 2.0	8/12 (67)	n.d.
		18 (conventional instruments, no VRT)		20.1 ± 5.2	93.5		7.5	7.8 ± 1.6	11/12 (92)	37.7 ± 15.5
		71 (new instruments, no VRT)		21.5 ± 6.4	47.5		4.8	9.6 ± 1.3	33/33 (100)	15.5 ± 9.1
Fedele (2008) [23]	Follow-up study	110	MRKH	17	20–45	6 (5.5)	6–9	>6	Functional success: 103/106 (97)	n.d.
Fedele (2010) [24]	Retrospective descriptive study	11 (9 Vecchietti, 2 McIndoe)	MRKH (10/11 with a solitary pelvic kidney)	21.8 (mean, SD not given)	32 ± 6.4	0	7 (mean, SD not given)	6.9 ± 0.4 after surgery, 7.4 ± 0.6 at 4-year follow-up	8/9 (89)	48
Bianchi (2011) [25]	Retrospective comparative study	45 (15 Vecchietti, 30 Davydov)	MRKH	20.4 ± 3.4	30 ± 9.6	0	n.d.	6.3 ± 0.7	Inadequate information	≥12
Viola (2013) [28]	Technique, case report	1	MRKH with pelvic kidney	45	n.d.	0	n.d.	7	1	n.d.
Rall (2014) [26]	Combined retrospective and prospective long-term follow-up study	240	MRKH (223) CAIS (15) Other (2)	18.7 [14.5–49.7], 20.5 ± 5.6	n.d.	n.d.	n.d.	At ≥11 months: anatomic length 8.0 [6.0–12.0], 8.0 ± 1.7; functional length 10.0 [6.0–13.0], 9.5 ± 1.5	Median scores on 10-point scale for overall patient-reported satisfaction: 8.5 (neovaginal length) and 8.0 (quality of sexual intercourse)	16 [11–141]

Modified from Rall et al. [27]
AIS androgen insensitivity syndrome, *CAIS* complete androgen insensitivity syndrome, *MRKH* Mayer-Rokitansky-Küster-Hauser syndrome, *n.d.* no data, *VRT* vesicorectal tunneling. Data are only shown for expansion-based procedures

the pseudohymen instead of dissection of the vesicorectal space. Outcome was reported as an average vaginal length and diameter of 11.3 and 2.4 cm after an average traction period of 6.3 days with satisfactory results in 17 (94.3 %) patients [21].

In 2006, Ismail et al. [22] reported on a descriptive comparative technical study of 5 patients, three with MRKH and two with AIS. The former underwent laparoscopic Vecchietti procedures; the latter underwent neovagina creation according to the Davydov method. With the Vecchietti procedure, during which there were no complications, traction time was 7 days, yielding an average neovaginal length of 7.6 cm after surgery and 6.2 cm after 6 months' follow-up.

Our own optimized laparoscopically assisted neovaginoplasty procedure described in detail above was investigated in a prospective comparative interventional study in a large cohort of 101 patients [3]. This three-arm study compared our optimized technique and new instruments with the laparoscopic conventional technique using the Vecchietti instruments with and without dissection of the vesicorectal space. In particular, the modified traction device provided a stable direction of traction and prevented unintentional release and ripping of the threads, complications typically observed with the conventional Vecchietti procedure. With our technique and the new instruments, mean operative time decreased by 58 % to 47.5 min from 113 min for conventional instruments and vesicorectal tunneling. Moreover, bladder lesions were reduced significantly and no bowel lesions occurred when the new instruments were combined with vaginoabdominal perforation instead of vesicorectal tunneling. Similarly, mean traction time was reduced from 11.7 to 4.8 days. No instrument-related complications occurred with our new set of instruments. Six months after surgery, neovaginal length with our technique was 10.6 cm, which was 2.5 cm more than obtained with the conventional method. No lubricants were required and intercourse was not painful. Once the traction device and segmented dummy were removed, patients were advised to wear a vaginal dummy 24 h a day for 4 weeks before reducing the wearing time over the next 5 months or until becoming sexually active. Resulting in fewer surgical complications, shorter operative and traction times, and better functional results than with vesicorectal tunneling using conventional instruments, the combination of our optimized technique with the new instruments yielded a safer, shorter, more effective, and less traumatic procedure than with conventional instruments and vesicorectal tunneling [3].

In 2008, Fedele and colleagues reported long-term follow-up results achieved with the laparoscopic Vecchietti technique, demonstrating anatomic success in 104 of 106 (98 %) and functional success in 103 of 106 (97 %) patients [23]. The traction device was removed 6–9 days after surgery. To prevent vaginal stenosis patients postoperatively performed noncontinuous vaginal dilation for up to 6 months or until epithelialization. A neovaginal length of at least 6 cm and easy introduction of two fingers within 6 months after surgery were the criteria for anatomic success. Scores on the Female Sexual Function Index (FSFI) were comparable with those of controls [23].

In a retrospective descriptive study published in 2010, Fedele et al. [24] compared the results of nine Vecchietti and two McIndoe procedures. No complications were observed with either technique. Mean operative time was considerably shorter for the Vecchietti procedure, 32 ± 6.4 vs. 190 ± 14.1 min. Twenty-four months after surgery, iodine-positive vaginal-type epithelium coating of the neovagina was 100 %. At 4-year follow-up, 8 of 9 (89 %) Vecchietti patients had a mean neovaginal length and width of 7.4 ± 0.6 cm and 4.2 ± 0.5 cm. At long-term follow-up of 14 years, both patient groups had a mean neovaginal length and width of 8.2 ± 0.4 cm and 5 cm. All patients then also reported having a normal satisfactory sexual life and no dispareunia or long-term urologic complications. The authors considered that the modified Vecchietti approach, in addition to producing optimal functional results and being safe and effective, also yielded good anatomical and esthetic results whilst being shorter than the McIndoe procedure in terms of both operative time and hospital stay.

Bianchi et al. retrospectively compared the Vecchietti (15 patients) and Davydov (30 patients) procedures in their 2011 study [25]. They reported durations of surgery as 30 ± 9.6 and 134 ± 24 min,

respectively. The two procedures did not differ with regard to intraoperative complications. Neovaginal epithelialization at follow-up was 60 and 80 %, respectively, at 6 months and 100 % in both groups at 12 months after surgery.

The long-term results achieved with our optimized laparoscopically assisted neovaginoplasty technique over a period of 14 years have recently been reported by Rall et al. [26]. This combined retrospective and prospective study assessed the long-term anatomical and functional outcome of our technique in 240 patients with vaginal agenesis, predominantly due to MRKH (93.3 %) or CAIS (6.3 %), over a median follow-up period (range) of 16 (11–141) months. Essentially, common long-term complications such as neovaginal prolapse, dysplasia or malignancy, or loss of neovaginal length were not observed. Granulation tissue, which was readily treated by cauterization, and infections with human papillomavirus persisting to long-term follow-up were rare (<2 %). Mean functional neovaginal length remained stable at 9.5 cm in all patients, even if they had not had sexual intercourse and had stopped wearing the vaginal dummy, with median dummy wearing time being 8.6 months. On average, epithelialization increased from 34 % at the 1-month visit to 93 % at the long-term assessment and depended on time of onset and frequency of sexual intercourse. Median total Female Sexual Function Index score at long-term follow-up was 30.0, which was comparable with similar-aged general-population controls. The study demonstrated the technique to be fast, effective, and minimally traumatic, creating a neovagina of adequate size and secretory capacity for normal coitus. Long-term complication rates were very low and long-term functional results completely satisfactory. Postoperatively, no prolonged period of dilation is necessary, even in the absence of sexual intercourse.

In summary, outcomes achieved with laparoscopic modifications of the Vecchietti procedure since the early 1990s have been found to be comparable with the results of the conventional Vecchietti procedure performed by laparotomy. Moreover, in Europe, the laparoscopic Vecchietti procedure has since come to be considered the corrective surgical treatment of choice for MRKH syndrome-related vaginal aplasia in Europe [17]. Overall, the body of available data directly comparing various modifications of the Vecchietti procedure with one another or with other, more invasive neovaginoplasty methods is very limited, particularly with regard to prospective studies.

Potential Advantages and Limitations of the Technique

Every technique, whether surgical or nonsurgical, has advantages and limitations. The advantages of our surgical expansion technique include the following.

Advantages

The general advantage of Vecchietti-based neovaginoplasty techniques is that the neovagina they create has a normal anatomy, histomorphology, and functionality without the need for extraneous tissues such as skin, peritoneum, or intestine. In addition, no plastic surgery is required, which can cause scarring, and functional results are rapidly achieved [3].

The laparoscopically assisted neovaginoplasty technique we developed dispenses with dissection of the vesicorectal space by employing vaginoabdominal perforation of the rectovesical septum, a fundamental modification from the Vecchietti technique, which proceeds from the abdomen to the vagina and involves dissection of the bladder and rectum, making it a surgically more complex and demanding procedure that is more invasive and takes longer to complete than our procedure [3].

Our surgical technique offers all the advantages of laparoscopic neovagina creation, including markedly reduced operative times (approx. 40 min on average), a shorter traction phase, a short hospital stay (6–7 days on average), excellent functional results in terms of average vaginal lengths of 10–11 cm and a satisfying sexual life. The rare cases of treatment failure observed at our institution have been attributable mainly to failure to wear the dummy rather than surgical technique. Long-term results of our technique also include a histomorphologically normal

vaginal epithelium, normal lubrication, a normal vaginal flora, and the absence of scar formation and cosmetic defects [3]. There is no problem with odorous discharge as may occur after neovagina creation using sigmoid colon.

Limitations of the Technique

Given that MRKH syndrome occurs approx. in 1 out of 4,000–5,000 female births, the annual incidence in Germany with a population of approx. 82 million is about 70–100 cases. This calls for specialist centers where these patients can be offered the experience and multidisciplinary expertise required to comprehensively diagnose and provide appropriate treatment options, be they surgical or nonsurgical. Therefore, the widespread use of laparoscopically assisted neovagina creation as described in this chapter is discouraged. As success rates decrease with each subsequent surgery, our procedure should only be performed at tertiary referral centers where the technique is routinely performed by experienced surgical teams.

Despite the advantages our technique offers, there are a number of risks associated with it, particularly if it is carried out incorrectly (see Fig. 18.3, left) due to lack of experience on the part of the surgical team. Risks include injuries to the intestine, bladder or rectum, bleeding, and hematoma formation. Rare complications include injury to the iliac vessels during peritonealization, and peritonitis. Urethral necrosis, dehiscence of the neovagina, luxation of the olive, and injury to the abdominal wall caused by the traction device are extremely rare. Postoperative urinary infections are more common, whereas persistent granulation tissue rarely occurs.

Conclusion

In summary, the available evidence from published studies in our opinion strongly suggests that the expansion-based surgical techniques, including the optimized technique developed by ourselves, offer a number of advantages, provided the indications and contraindications are observed and the crucial steps are performed correctly. Vaginoabdominal perforation is less invasive than dissection of the vesicorectal space or skin-graft tunneling and is not associated with odorous discharge as may occur with the sigmoid colon technique. The technique we have developed is also fundamentally different from the conventional open and laparoscopic Vecchietti procedures in that it replaces dissection of the vesicorectal space by vaginoabdominal perforation.

In experienced hands, our laparoscopically assisted neovaginoplasty technique is a short, on average 40-min procedure, creating an approx. 10–11 cm long neovagina in the anatomically correct axis within 4–5 days. The neovagina is functional, allows the patient to have satisfying sexual intercourse within 3–4 weeks, and becomes fully epithelialized within less than 6 months. Factors crucial to the success of our technique include a comprehensive diagnostic evaluation of the patient, appropriate perioperative and postoperative care, and an experienced specialist surgical team working at a center for the diagnosis and correction of malformations of the internal and external female genitalia.

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Neovagina Creation with the Use of the Pelvic Peritoneum

19

Leila V. Adamyan and Assia A. Stepanian

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is the most common form of vaginal agenesis. It is described in 90 % of patients with congenital absence of the vagina, uterus, and fallopian tubes and results from the failure in embryologic development of the mullerian ducts. The incidence of vaginal agenesis is 1:4,000 to 1:10,000.

The condition of vaginal agenesis can cause significant psychological trauma to the patient and her family. Although multiple operations for correction of vaginal agenesis are currently implemented, no standard method for colpopoesis exists. Introduced by D. O Ott in 1898, the method of neovagina creation with the use of the pelvic peritoneum underwent multiple modifications, including vaginal colpopoesis by M.I. Ksido (1933) and A.G. Kurbanova and Y.V. Kravkova (1969), A.A. Verbenko and M.P. Shakhmatova (1976) and abdomino-vaginal colpopoesis by S. N. Davydov in 1977 [1]. In 1984 N.D. Selezneva and A. N. Strijakov involved the principal of the "lighted" window in creation of vesico-rectal space. L. V. Adamyan developed laparoscopic-assisted peritoneal colpopoesis in 1992, and it was first described in an international publication in 1993; [2, 3] in this technique 3 out of 6 of the main steps of the procedure are performed laparoscopically [2–9].

Our experience in the treatment of mullerian anomalies includes over 2,000 cases and resulted in the morpho-functional classification of mullerian anomalies in 2009 [10]. Seven hundred and eighty nine of those patients have MRKH syndrome or other forms of vaginal agenesis. Three hundred and twenty four of these patients underwent laparoscopic-assisted peritoneal colpopoesis using Adamyan's technique.

This method has the advantage of all of the following characteristics at once: it provides the immediate presence of a neovagina of normal size (Fig. 19.1); spares patients' organs for neovagina creation and avoids grafting or the need for therapeutic dilation and traction; employs the benefits of laparoscopy; provides for support at the vaginal apex via the approximation of the fibro-muscular streaks; minimizes the hospital stay and postoperative use of narcotics; allows for the establishment of normal vaginal epithelium within 3 months of surgery (Fig. 19.2); within a short time allows patients to have intercourse with sexual satisfaction compatible with that of women in the control group with normal vaginal development; results in no scars other than laparoscopic incisional scars.

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Technique

Preparation for Surgery

Preoperative evaluation is focused on defining congenital abnormalities of the genital system and on evaluating for the presence of, and the extent of, potential associated abnormalities, as well as attention to patients' social support and the presence or absence of sexual partners. 94.4 % of our patients have a sexual partner prior to colpopoesis [11].

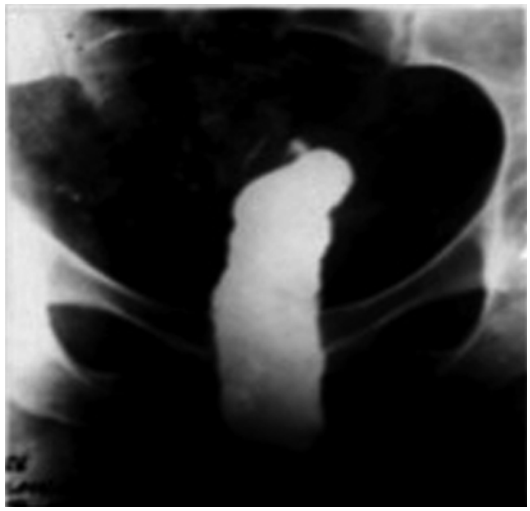

Fig. 19.1 The neo-vagina of a normal size formed during surgery

In each patient, we performed a physical and pelvic and abdominal ultrasound examinations, karyotyping, biochemical profile, CBC, amenorrhea hormonal profile. When needed, magnetic resonance imaging (MRI), intravenous pyelography (IVP), and X-ray of the spine are used. If indicated, extensive counseling is applied. The presence or absence of rudimentary uterine horns and functional endometrium are established.

During pelvic examination, careful attention is given to the position of the urethra, orientation of the vaginal dimple, especially in patients with previous colpoelongation or other techniques, and state and symptomatology related to the fibrotic tissue in patients with previous surgical intervention.

A step-by-step description of the surgery, methods, and the results of studies are provided to the patient, as well as postoperative expectations, especially related to maintenance dilation or intercourse and follow up examinations.

Description of the Operation [2–9]

The surgery is performed utilizing the Adamyan's laparoscopic-assisted technique of Davydov's colpopoesis.

After the positioning the patient in lithotomy position with legs in stirrups and the administration of IV antibiotics, evaluation under anesthesia takes place (Fig. 19.3) and diagnostic laparoscopy is conducted in order to identify/confirm the state

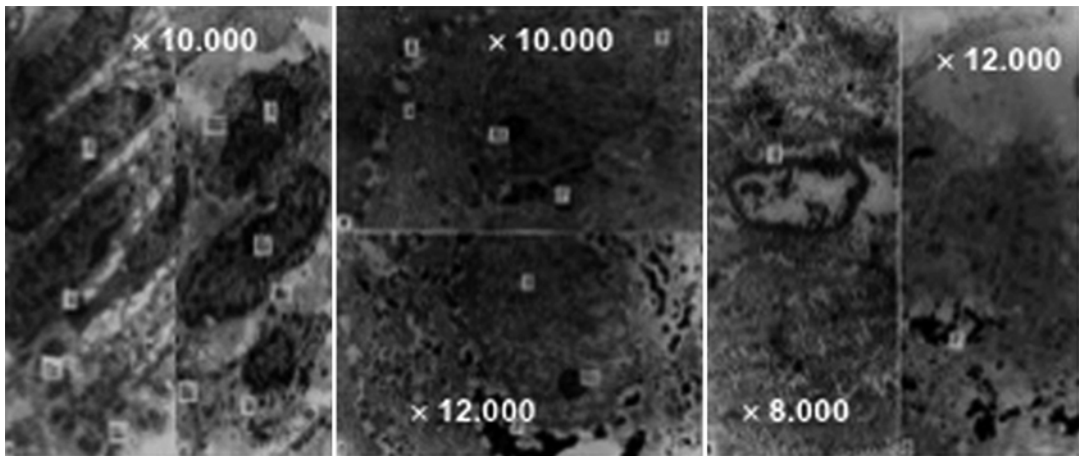

Fig. 19.2 Squamous vaginal epithelium formed in 1.5 months after peritoneal colpopoesis

of the pelvic peritoneum, pelvic organs, presence or absence of the adhesive process, inflammation, endometriosis, or other pathology, as well as mobility of the peritoneum and the state of the vesico-rectal space. During laparoscopy special attention is also given to presence, prominence, and location of the fibro-muscular streaks and the ovarian and tubal appearance (Fig. 19.4).

With the laparoscope in place for assistance and guidance of vaginal dissection, a transverse incision is made between the lower aspects of the labia minora (Fig. 19.5). With a preference for blunt dissection and, when necessary due to previous scarification, combined sharp and blunt techniques, the channel is formed in the space between the urethra and the bladder and the rectum (vesico-rectal space) (Fig. 19.6).

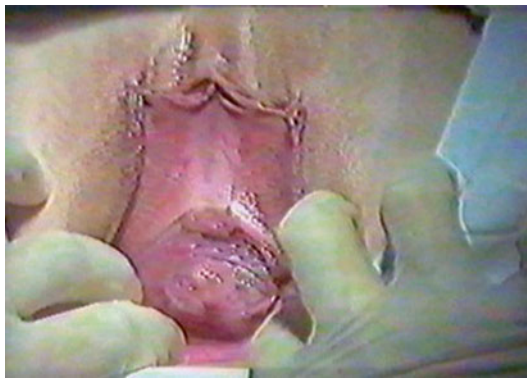

Fig. 19.3 Examination of the external genitalia in the beginning of surgery

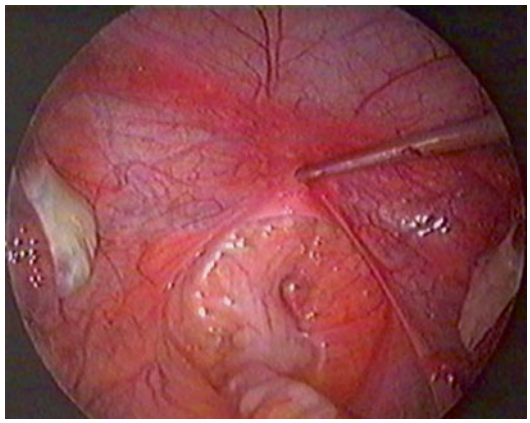

Fig. 19.4 Identification of the most mobile aspect of the peritoneum

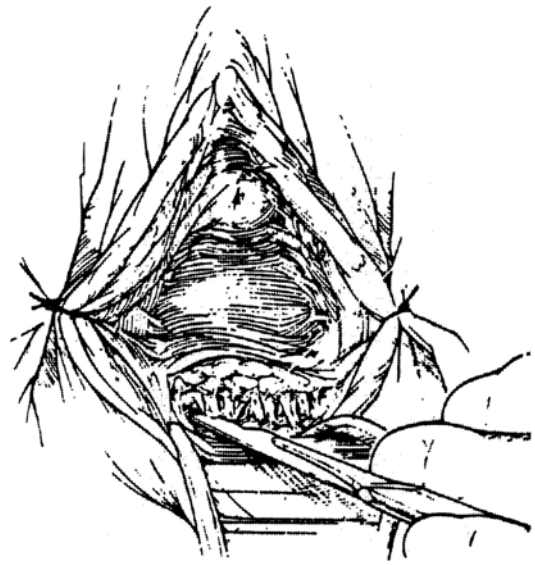

Fig. 19.5 Transverse perineal incision

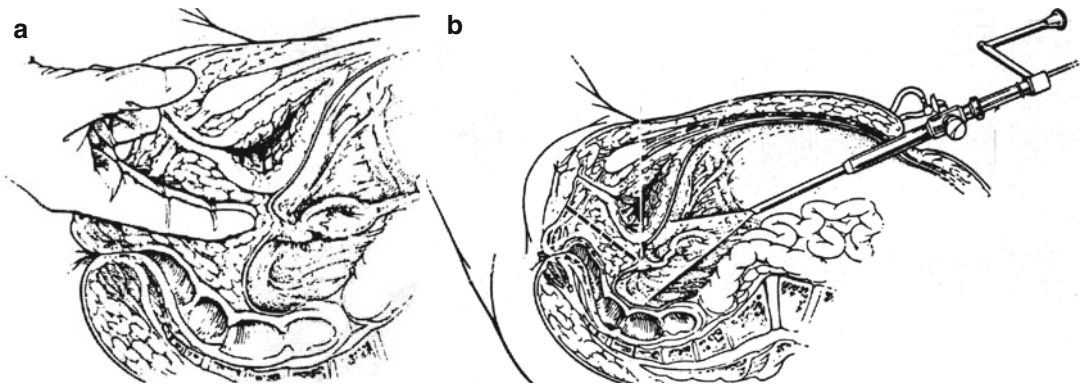

Fig. 19.6 (**a**) Blunt dissection under (**b**) laparoscopic guidance in formation of the neo-vaginal channel in the vesico-rectal space

The most mobile aspect of the pelvic peritoneum is introduced into the formed channel with the use of the laparoscopic manipulator and the laparoscope itself (Fig. 19.7a, b). This step is exceptionally important in order to prevent of excessive vaginal tension and labial shifting, as described in the literature [12]. The peritoneum is then grasped with hemostats, and the peritoneum is incised between them using scissors (Fig. 19.8a, b).

The edges of the peritoneum are further pulled into the formed channel and are attached to the dissected skin of the perineum using interrupted stitches of 3.0 Vicryl. Should the elasticity of the pelvic peritoneum be reduced by previous procedures, laparoscopic placement of this stitch can be employed. Should the peritoneum be prematurely entered due to excessive pressure on it during peritoneal introduction into the perineal incision, the suture including the lateral corners of the pelvic peritoneal incision may be placed and delivered to the perineal incision in order to facilitate the approximation of the perineal and peritoneal incisional edges. A 16-French Foley catheter and a double roll of 4-in. Kling or inflatable vaginal dilator, lubricated with estrogen vaginal cream or a combination of Vaseline and antibiotic cream, is employed.

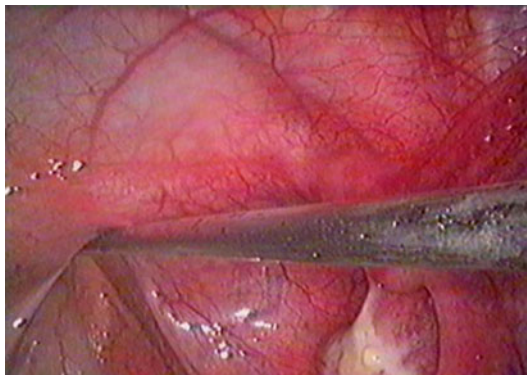

Fig. 19.7 (**a**, **b**) Presentation of the most mobile aspect of the peritoneum into the perineal incision

The apex of the vagina is formed by laparoscopic placement of one or two pursestring stitches of 0 or 1 Proline at a distance of about 11–13 cm from the opening of the neovagina, depending on the patient's pelvic length and corresponding dimensional anatomy. This stitch involves the peritoneum overlying the bladder, the fibro-muscular streaks, the peritoneum overlying the pelvic sidewall, and serosa of the sigmoid colon or perirectal gutter (Fig. 19.9a, b). A neovagina is thus created (Fig. 19.10a, b). The apical support is provided by the approximation of the fibro-muscular streaks in the described pursestring stitch. Minimal manipulation of the peritoneum is advised.

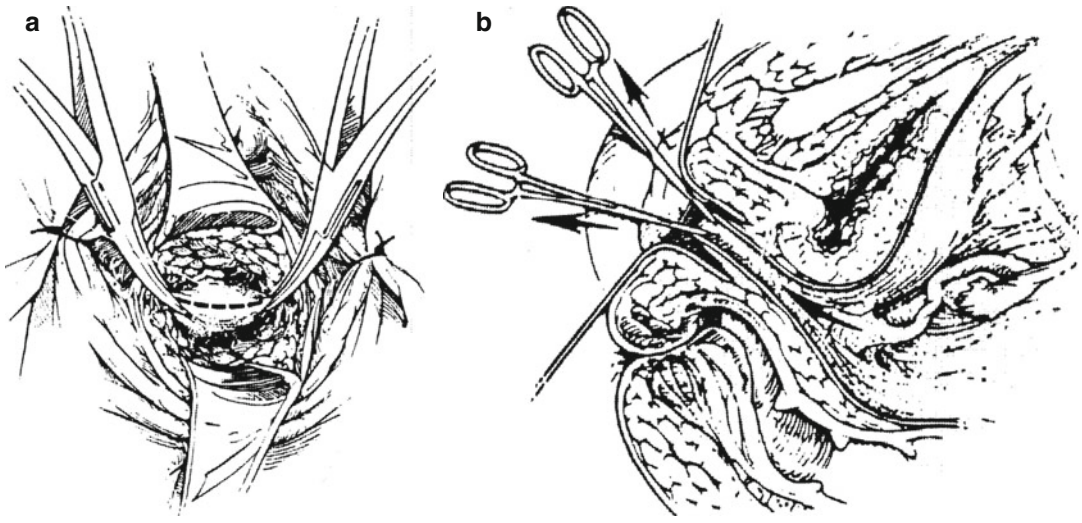

Fig. 19.8 (**a**) Peritoneal incision followed by (**b**) the flow of pneumoperitoneal gas

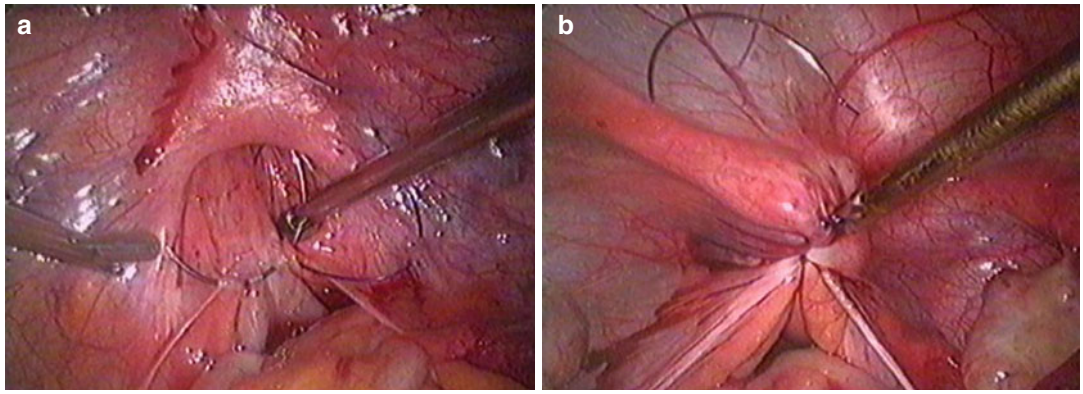

Fig. 19.9 (**a**, **b**) Formation of the vaginal apex via laparoscopic pursestrings stitch

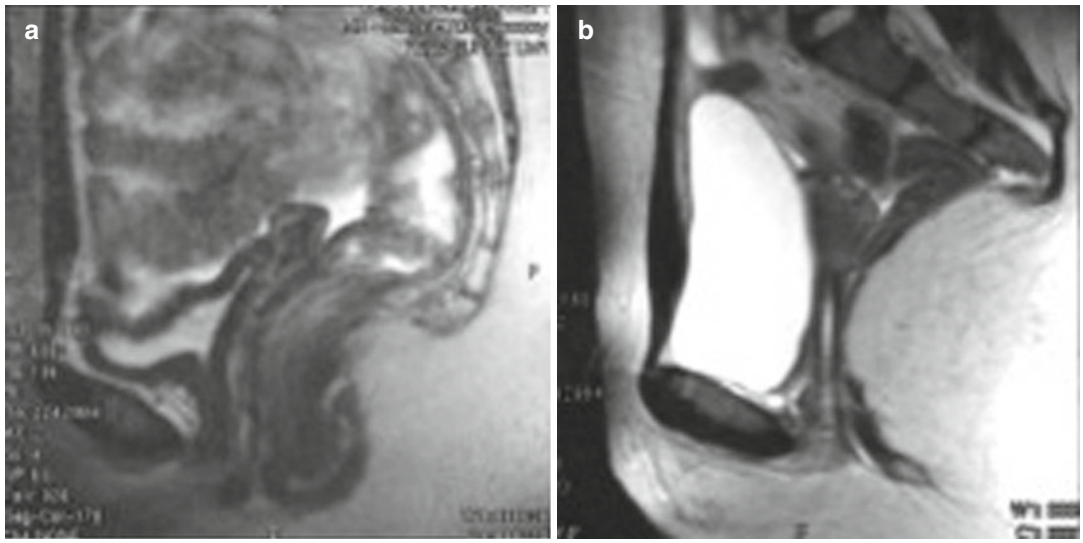

Fig. 19.10 (**a**) MRI image of the congenitally closed vesico-rectal space. (**b**) MRI image of the newly formed vagina using Adamyan's technique.

Postoperative Management

Patients are mobilized in 3–6 h after the surgery and go home on the same day or the next morning with the instructions to follow a regular diet and for pelvic rest as the only restrictions in their activity. In our experience, patients who present from far regions of Russia or other countries, prefer to stay at the hospital until at least the removal of the vaginal tampon (Kling) or inflatable dilator.

Oral antibiotics are used while Foley catheter is maintained until removal of the vaginal packing in 36–48 h. At 36–48 h the tampons are removed and the vaginal walls are carefully examined. Each patient is guided in the performance of her first digital neovaginal examination, followed by focused individualized postoperative counseling, centered on the maintenance of the neovagina with dilation and counseling of the patient on perioperative experience.

At 1 week patients are reexamined with attention to the tissue reaction, vaginal width and length, the condition of the vaginal apex, and the state of the suture line. The aspects of sexual engagement at 4 weeks or thereafter as well as sexual satisfaction are introduced.

We uniformly recommended that sexual intercourse occur not earlier than 4 weeks after the procedure—when the glove or dilator that the patient uses for the maintenance of the neovagina no longer shows evidence of bloodstaining. No maintenance dilation is needed after initiation of regular intercourse.

Surgical Results

Operative time has ranged between 25 and 45 min for all patients without previous surgery or perineal structural abnormality. Median blood loss has been less than 25 cc.

The main characteristics of the neovagina are evaluated at 3–4 months after the surgery. During the gynecologic examination the peritoneo-perineal suture lines are not visible, the length of the neovagina is 11–12 cm, the walls are adequately stretchable, and the width is comfortable to the patients. The walls of the vagina are rougated and moisturized. Conducted with 43 women, morphological and electronomicroscopic evaluation established the presence of the normal vaginal epithelium at this time during postoperative period [11].

The review of the long-term results of our original technique of laparoscopically assisted peritoneal colpopoesis studied functional aspects of formed neovaginas in patients with MRKH as compared with a control group of women who have no somatic pathology, who have regular sexual activity, and who have no history of surgery involving pelvic organs or the pelvic floor [13].

Two hundred and sixty nine patients operated on between 1995 and 2013 responded to our questions with included Female Sexual Function Index (FSFI). 57, 90, and 111 responders underwent surgery between the years 1995 and 2000, 2001 and 2006, and 2007 and 2013, respectively, allowing for 15–10, 9–5, and 4–1 year follow up accordingly.

The average functional length of neovagina (TVL) was higher than reported in the existing literature and equaled 12.46 ± 1.16 cm (range 5–14 cm); the anatomic vaginal length measured when no pressure applied to the neovaginal apex by the ring forceps was 10.87 ± 1.0 cm with a range of 5–13 cm. Two women with 5 cm of vaginal length were not sexually active after surgery, and did not perform maintenance dilation.

Fourteen out of 269 patients (5.2 %) were not sexually active for reasons not associated with their satisfaction with their sexual experience. Two hundred and twenty three women were satisfied with the results of their surgeries, composing 87.8 % of 255 sexually involved patients and 82.9 % of all 269 women in the study, as compared with 38 (76.0 %) of 50 women in the control group. Out of these women, 166 (65.1 %) were satisfied with their sexual life and 57 (22.7 %) were very satisfied, achieving long-term highly sustainable functional results due to laparoscopic-assisted colpopoesis with the use of pelvic peritoneum.

The questions related to libido, excitability, lubrication, orgasm, and satisfaction identified no significant statistical differences between the patients and the control group based on FSFI scores ($p > 0.05$). Gestational surrogacy was undertaken by and successful in 36 patients.

In addition to the use of this surgery for primary surgical correction, it can be successfully applied to patients after previous graft-involving colpopoesis if satisfactory results were not achieved. It is our estimation that 12 % of the patients operated in our group had previous surgical correction of vaginal agenesis with the use of the grafting. A crucial aspect of the surgery involves the meticulous dissection that allows the surgeons to minimize the risk of injury to the rectum and the bladder/urethra. It also allows for achievement of adequate results (length, width, and the possibility of future sexual satisfaction).

In one of the cases patient had 6 previous surgeries, including an initial skin graft involving operation followed by 5 Z-flaps. The initial vaginal length of 3.5 cm was increased to 12 cm at the time of surgery immediately and to 11 cm at the 6-month follow up. The length of surgery was 1.5 h with blood loss of less than 25 cc. This patient is happily engaged with her fiancé and considers her sexual life/intercourse very comfortable and fulfilling.

In rare cases, should adequate vaginal parameters be not achieved by peritoneal colpopoesis and short-course therapeutic dilation not be feasible, careful laparoscopic-guided vaginal dissection followed by maintenance dilation can be performed.

Complications

Since introduction of the laparoscopic-assisted peritoneal colpopoesis in 1992, the complications of the current peritoneal colpopoesis (324 women) included rectovaginal fistula formation in 1 patient (0.3 %), rectal injury in 1 patient (0.3 %), achievement of <6 cm of vaginal length in 2 patients cases (0.6 %), vaginal stricture uniformly resolved with therapeutic dilation in 6 patients (1.85 %), and dyspareunia in 12 patients improved with local therapy (3.7 %). No pelvic prolapse, abscesses, or urethral damage were reported in our patients group [10, 11].

Rectal injury was repaired at the time of surgery with no sequelae for the patient. Rectovaginal fistula in a different patient resolved after surgical treatment. Both vaginal stricture and failure to achieve of the appropriate vaginal length occurred in patients who did not perform maintenance dilation and did not engage in regular intercourse.

Discussion

Laparoscopy is involved in 3 out of 6 steps of laparoscopic-assisted peritoneal colpopoesis. The other laparoscopic technique was introduced by L. Fedele [14] and was based on Vecchietti's abdominal technique [15, 16].

The operation described by G. Vecchietti involves the use of an invagination technique by traction achieved with an acrylic olive that is positioned over the vaginal dimple, and can be performed with abdominal or laparoscopic approaches [15–19]. Traction is achieved with the use of a traction device placed over the lower abdomen and attached to the olive via laparoscopically placed subperitoneal sutures. The neovagina was created in 7–9 days, followed by active dilation until onset of regular sexual activity. 52 women of the original series reported 100 % anatomic and 98.1 % functional success [17]. Anatomic success was defined as achievement of a neovagina of ≥6 cm in length and easy introduction of 2 fingers vaginally within 6 months of surgery. An 89 % satisfaction rate was reported in a different study [17].

The comparative analysis of two laparoscopic techniques was described [20]. Authors observed that laparoscopic Davydov's allowed for achievement of the longer vagina at 12 months of surgery (stated 8.5 ± 1.6 cm), twice shorter need in postoperative analgesia, earlier removal of the urinary catheter (day 2 as compared with day 8.6 days in laparoscopic Vecchietti), earlier epithelization at 6 months. Dyspareunia was observed in 11 out of 80 patients (13.75 %) as compared with 8 out of 80 patients (10 %) in Vecchietti group. FSFI scores in both groups demonstrated no statistically significant differences.

The Fedele method was further modified by S. Y. Brucker et al. [21] and required no surgical tunneling, resulting in a reduction of the operative time to 47.5 min, a reduction of tractional time to 4.8 days, and an increase in neovaginal length to 10.6 cm at 6 months after the surgery. Epithelization of the neovagina was achieved after a mean of 10.1 months. The mean time to intercourse was 4.3 and 5.7 months in subgroups without surgical dissection and with surgical dissection [21].

The data in this series is compatible with those of our series if vaginal length presented here is anatomic as opposed to functional. Functional vaginal length in our series of laparoscopic-assisted peritoneal colpopoesis is 12.46 cm, exceeding the anatomic length of 10.87 cm.

Out of 89 patients, the complications in the modified Vecchietti surgery [18] included 3 (3.4 %) patients with recognized and repaired bladder injuries, 2 patients with hematoma of the bladder with no vesicular lesions found on cystoscopy, and 1 patient with self-resolved necrosis of the urethra. The injury rate appears to be higher with this surgery, yet likely statistically not significant.

The sexual function after laparoscopic-assisted peritoneal colpopoesis was compatible with patients without gynecologic disorders, as measured by composite scores for desire, arousal, lubrication, orgasm, satisfaction, and pain [22].

Additional Concerns Regarding Peritoneal Colpopoesis in the Literature

Concerns were raised about limitations in the management of potential postoperative failure of laparoscopic technique of Davidov [20]. In our observation, failure of laparoscopic-assisted peritoneal colpopoesis is extremely rare. Two patients who have not been sexually active and did not maintain their vaginal length through dilation had a vaginal length of 5 cm [11]. Improved vaginal length in one of them was achieved through therapeutic dilation and careful vaginal dissection that released excessive formations of apical fibrotic tissue and achieved maintained vaginal length of 12 cm after surgery that lasted 35 min, demonstrating that in the rare events of failure of laparoscopic-assisted peritoneal colpopoesis, excellent results can be achieved with additional intervention.

Possible limitations in uterine transplantation in patients with laparoscopic-assisted peritoneal colpopoesis were mentioned in the literature as well [20]. While no uterine transplantation after Adamyan's technique of Laparoscopic Davydov surgery has been performed so far, we believe that success of transplantation will not be altered in such patients as no significant pelvic sidewall anatomic changes and changes to pelvic vascular anatomy occur and dissection of fibro-muscular streaks is possible when needed.

Concerns related to the development of pelvic organ prolapse in patients after the treatment for vaginal agenesis have been noted. So far we have not identified papers or reports that indicate development of pelvic organ prolapse after peritoneal colpopoesis. Suspension of the neovagina has been described using abdominal sacral colpopexy and sacrospinous ligament suspension [23–25]. Potentially, approximation of the fibrous streaks employed in our method decreases the risk of apical prolapse, while absence of patient-performed therapeutic dilation prevents potential for incorrect vector of dilation and reduces the risks of cystocele and rectocele in these patients.

Conclusions

In our experience, consistent with many observations in the literature, laparoscopic–assisted peritoneal colpopoesis presents multiple fundamental advantages at once: it results immediately in the creation of a neovagina of normal size and elasticity; spares skin and the sigmoid colon; reduces dependency on tractional devices; employs the benefits of laparoscopy; reduces the time of postoperative bed-rest and reliance on a low-residue diet; limits the use of postoperative analgesics; allows for early commencement of satisfying sexual activity; demonstrates epithelization within 3 months after surgery; and minimizes the risk of pelvic-organ prolapse. In our experience, it reduces operative time, hospital stay, blood loss, and minimizes complication rates. The results of the surgery are sustainable. While the use of vaginal dilators is essential postoperatively, the purpose of their use is maintenance of the vaginal parameters achieved during surgery until regular sexual intercourse takes place.

The immediate and long-term results of the surgical correction of the vaginal aplasia in women with MRKH demonstrated that both physical and functional qualities of the neovagina formed with our laparoscopically assisted peritoneal colpopoesis technique are compatible with the qualities of the vagina of normal original structure. Somewhat higher sexual satisfaction rate in the group that underwent surgery can be attributed to potentially higher attention of these women to their sexual habits and experiences.

Laparoscopic-assisted peritoneal colpopoesis requires delicate dissection and needs to be performed in the centers with experience in managing these patients. In view of rare incidence of MRKH in general gynecologic practice, the referral to specialized centers for evaluation and both surgical and non-surgical

treatment is of a significant benefit to the patient.

While continuous work on technical improvement is always beneficial, special attention should be given to the identification of all possible etiologic factors in an effort to prevent these events during the gestational stage of human development and to advise a couples planning gestational surrogacy. Further studies that track the effects of materials used in formation of the neo-vagina on general health of a woman as well as their local effect, such as malignancy and others, may be necessary. Additionally, what can we learn about endometriosis in patients with vaginal agenesis and other obstructive anomalies.

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Neovagina Formation with the Use of Bowel

20

Daniel Raudrant, Caroline Carrard, and Eddy Cotte

Introduction

The techniques for the creation of a neovagina in women with Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome derive from the fertile imagination of surgeons. They probably vary so widely precisely because none is perfect.

The first neovagina made from the bowel was constructed with rectal tissue by Sneguireff FW [1] in 1892 and with sigmoid or ileal sections by Baldwin in 1904 [2]. Serious complications, some of them lethal, rapidly led to the abandonment of these intestinal vaginoplasties, but advances in gastrointestinal surgery have enabled their reintroduction.

At what age should surgery take place?

The woman must be fully-grown and want to have sexual relations. Our patients have had a mean age of 20 years (range: 14–41 years).

Preoperative work-up for MRKH syndrome

This work-up includes karyotyping and magnetic resonance imaging (MRI) of the pelvis. The pelvic MRI makes a preoperative diagnostic laparoscopy unnecessary. It also allows an assessment of the presence of rudimentary, nonfunctional uterine horns.

The renal compartments must be visualized; if not, renal ultrasound may be necessary. In cases of renal abnormalities, including a single kidney or pelvic kidneys, computed tomography (CT) is performed for urologic imaging, to visualize the path of the ureter or ureters.

Radiography of the cervicodorsal spinal column is necessary to look for associated vertebral malformations. In our series, 22 % of patients had renal malformations, and 14 % skeletal abnormalities. In all, 69 % of patients had isolated MRKH syndrome.

Different intestinal grafts can be used

While sigmoid sections are the most common intestinal graft, other intestinal segments have been used, including ileocecal segments [3, 4], the cecum [5], the jejunum [6], and the distal ileum [6, 7]. In 2009, W. Schneider described an ileal J pouch [7]: "*a 23 cm long segment of the distal ileum pedicled on the ileocolic artery is excised, intestinal continuity is restored with an ileoileostomy. The excised ileal segment is curved to create a J pouch…with a linear cutter device. The neovagina is constructed from an ileal J pouch anastomosed to the vaginal stump*."

These techniques are described for vaginoplasties, either for women with MRKH syndrome or

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for vaginal reconstruction after pelvic exenteration. The series are often small and report good results for sexual function [6].

Technique

Technique for Sigmoid Vaginoplasty

According to the guidelines of the American College of Obstetrics and Gynecology first issued in 2002 [8] and renewed in 2006 [9] and 2013 [10] and French guidelines issued in 2012 [11], surgical vaginoplasty is recommended only as second-line treatment after the vaginal dilatation (Frank's) method has failed or been refused [12].

From 1992 through April, 2014, 88 women were referred to our gynecological surgery department for sigmoid vaginoplasty. Twenty-five were redirected toward Frank's method, and 63 had a sigmoid vaginoplasty. In two of these cases, the sigmoid vaginoplasty was not the first procedure used to create a neovagina: one woman had already had an unsuccessful split-thickness skin graft, and another had already undergone two previous procedures (a McIndoe procedure followed by a Vecchietti operation).

We have performed 59 sigmoid vaginoplasties by laparotomy and more recently 4 by laparoscopy.

The technique has evolved over time. All procedures were performed by the same surgeon (DR), assisted for the four totally laparoscopic procedures by a gastrointestinal surgeon specialized in laparoscopy.

We still use mechanical intestinal preparation.

For the 59 operations with an abdominal Pfannenstiel incision, the mean operating time was 183 ± 3 min. For the last three laparoscopic procedures, the mean operating time was 240 min.

We describe here the laparoscopic technique, which should become the reference technique. It reproduces the laparotomic technique but with better dissection, less blood loss, and simpler recovery for the patient, even though the duration of the procedure is currently longer.

For laparoscopy, four trocars must be placed, one transumbilical for the camera, one on each side, and the third in a right paramedian location.

Step One: Removing the Rudimentary Uterine Horns and the Septum

After verifying the anatomy of the internal genital organs, the rudimentary uterine horns and the upper part of the fibromuscular median septum are removed with the ultracision Harmonic™ scalpel (Ethicon Endosurgery, Cincinnati, OH), as previously described [13, 14]. The medial septum is then dissected from the bladder. It is essential to avoid damaging the ureters, which are closer to the midline than when the uterus is present. The septum is dissected from between the bladder and the rectum and cut approximately 1 cm above the trigone of the bladder.

Dissection continues between the septum and the anterior rectum, to the level of the vaginal cupula, which is exposed with a translucent dilator lit from the perineum. It then continues laterally to the levator ani. The excision of the rudimentary horns and the medial septum makes it possible to create a large channel between the bladder and rectum. We no longer use the vaginal route for the dissection.

The incision of the vaginal stump is made laparoscopically, during step 3, after the sigmoid graft has been removed and intestinal continuity reestablished. This sequence avoids CO_2 leaks.

Step Two: Sigmoid Vaginoplasty – Preparation of the Sigmoid Graft

First, the sigmoid and descending colon are mobilized, but mobilization of the splenic flexure is generally not useful. The distribution of blood vessels in the colon mesentery is then carefully analyzed. A 15–20-cm segment is needed for the sigmoid vaginoplasty. This segment is generally the distal part of the sigmoid colon, just above the rectosigmoidal junction and is pedicled on a single artery. The arcade of Riolan and the colon mesentery are divided at each end of the sigmoid segment. Only the last sigmoidal artery is preserved

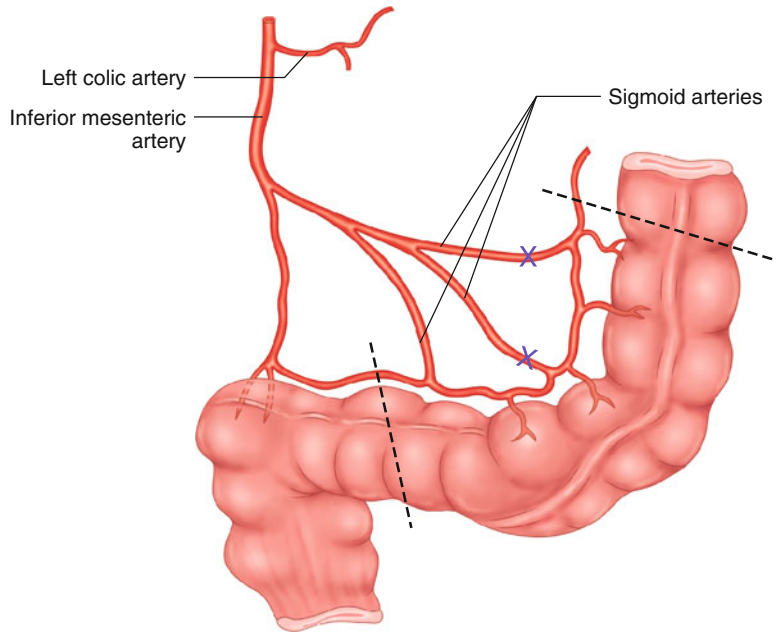

Fig. 20.1 Ligation and section of the superior sigmoid arteries, conservation of the inferior sigmoid artery, and the Riolan arcade

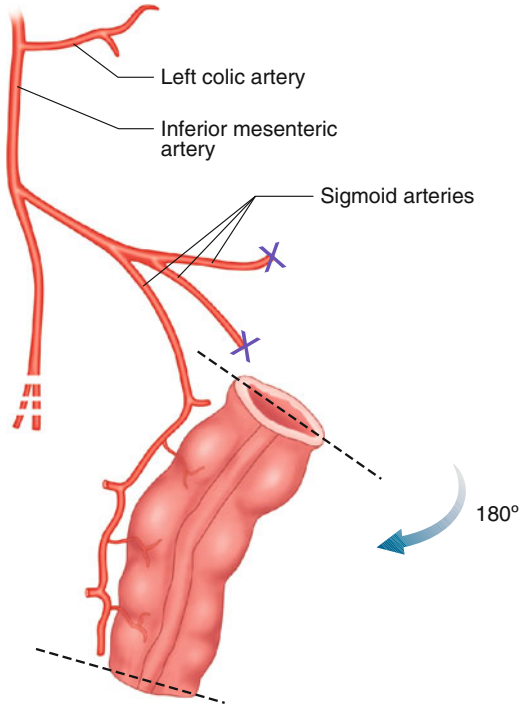

Fig. 20.2 Rotating the graft 180° for a colovestibular anastomosis without tension

with the arcade of Riolan (Fig 20.1). Any other proximal sigmoid artery vascularizing this segment is divided at its origin to enable the graft to be rotated 180° on its mesentery, without any tension (Fig 20.2). The colon is divided at each end of the segment with a linear stapler device (Echelon Flex™ ENDOPATH® Staplers with a green cartridge, Ethicon Endosurgery). An end-to-end circular stapled colorectal anastomosis is prepared (ENDOPATH® ECS 29, Ethicon Endosurgery). The lower left port is enlarged (3–4 cm) and the distal part of the descending colon is extracted through a wound protector in order to place the anvil of the circular stapler. The anastomosis is then performed under laparoscopic control, and an anastomotic air leak test is performed.

Step Three: Colovestibular Anastomosis

A U–shaped incision is made in the vaginal stump laparoscopically, to protect the urethra and to provide a flap large enough to allow for colovestibular anastomosis (Fig 20.3). The sigmoid graft is turned 180°. The colovestibular anastomosis is performed through the perineal

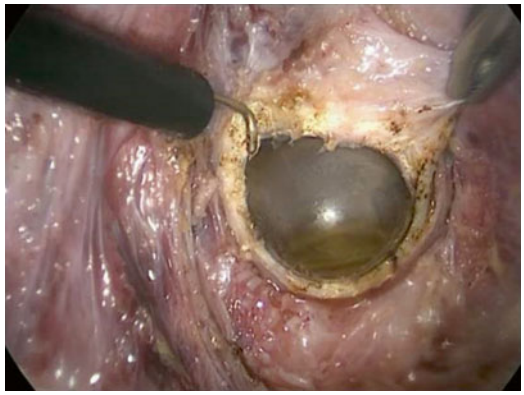

Fig. 20.3 A U-shaped incision is made in the vaginal stump laparoscopically

route with Vicryl 3-0 sutures, after the staples are removed.

Step Four: Graft Sacropexy

To prevent a prolapse of the sigmoid transplant, the end of the neovagina is fixed to the sacral promontory with two nonresorbable stitches, and the laparoscopy is completed.

Step Five: Assessment of Anatomical and Functional Results

Anatomical results are assessed by a first clinical examination under general anesthesia 1 month after surgery. We use Hegar dilatators (n° 28–32) to assess wound healing and vaginal patency.

Afterwards, the patient must practice dilatation of the graft until she begins sexual activity.

Complications

Immediate Complications

Two women developed a major complication: a pelvic hematoma due to bleeding in the perineal cleavage. It required surgical re-exploration and hemostasis.

Rectal injury occurred in two patients during the perineal route. The wound was detected immediately and sutured without any further complication. Four complications resulted from using the peritoneal route for cleavage.

Later Complications

Anatomical results of sigmoid vaginoplasty were good. Shrinkage of the graft remains the primary complication (17 %). It is, however, easy to repair with a dilatator. Prolapse of the neovagina occurred in 4 % of the patients in our series and has been described by other authors [15, 16]. We have had no such cases since making the sacropexy a systematic part of the procedure.

Excessive mucus production has been reported [17, 18]. It can be reduced by choosing a short graft and by vaginal douching. Colitis of the bowel graft has also been described [17, 18], and, in one cases, MUCINOVS adenocarcinoma [17, 18]. We had one such case in our series, 11 years after the graft. The graft has been removed, but hepatic metastases have developed.

In the case of persistent bleeding, an endoscopy and biopsies of the graft must be considered.

Functional Results and Sexual Function

Materials and Methods

In 2010, a questionnaire analyzing sexual function was sent to the women included in our series since 1992.

Two standardized questionnaires were used: the Female Sexual Function Index (FSFI©) [19] and the Female Sexual Distress Scale – Revised (FSDS-R©) [20, 21]. These questionnaires were addressed to 11 women for whom vaginal dilatation was recommended and to 48 who had had a sigmoid vaginoplasty.

Rosen's FSFI included 19 items analyzing 6 separate domains of the functional aspect of female sexuality: desire, arousability, orgasm, lubrication, comfort, and quality of sexual life. The total FSFI score, which had a maximum of 36, was obtained by summing the six domain scores. Patients with a total score $\leq$26.55 were defined with sexual dysfunction [19]. The next 13 questions of the questionnaire came from the FSDS-R (Female Sexual Distress Scale-Revised) [20, 21] and assessed psychological distress in

women with hypoactive sexual desire disorder, as described by Derogatis. A score above 11 (maximum: 52) suggested sexual distress.

We included 12 additional questions concerning details on sexual intercourse, vaginal discharge, pelvic pain, self-esteem, depression, and gestational surrogacy.

Functional Results

The women's mean age at the time they completed the questionnaire was 24 years, and the mean time after surgery was 6 years (range: 10 months–17.8 years).

In all, 40 (68 %) women responded to the questionnaire: 35 (73 %) of the 48 who had surgery and 5 (45 %) of the 11 treated by vaginal dilatation. Six (10 %) were lost to follow-up and 13 (22 %) did not return the questionnaire. One wrote to state that the subject was too intimate to be discussed in a mail questionnaire.

Table 20.1 shows the FSFI and FSDS-R scores.

Table 20.2 summarizes responses to the additional questions concerning intercourse frequency, vaginal discharge, pelvic pain, self-esteem, depression, and surrogacy.

Sigmoid Vaginoplasty Group

In the surgical group, one patient responded only in part to the questionnaire so that the FSDS-R was the only interpretable score. Three women had never had sexual intercourse, and another had not been sexually active for several years. Among the other 30, 22 (73 %) had regular sexual intercourse (at least two to three times a week). The mean time before the first sexual relation after surgery was 7 months (range: 1–42 months).

The mean FSDS-R was 21. Only 15 % had a score <11, indicating the absence of anxiety related to sexuality.

The mean total FSFI score was 28 in the surgical group (excluding patients who had not yet or did not currently engage in sexual intercourse). There were 21 patients (70 %) with a score >26.55. When we look at each domain's mean score, women with MRKH syndrome treated by sigmoid vaginoplasty can be considered "normal" in terms of desire, arousability, lubrication, orgasm, and global sexual satisfaction. However, discomfort or pain scores are higher in these patients ($p = 0.06$). Only 20 % of patients said they never experienced dyspareunia and 35 % had never had abdominal pain. We note that the comfort score of patients whose graft had shrunk was similar to that of other patients (4 and 3.9, respectively). Unsurprisingly, the only significant difference between the groups was in terms of discomfort due to vaginal discharge.

Vaginal Dilatation Group

In the group treated by the Frank procedure, one patient had never had sexual intercourse, but 75 % of the remaining patients had regular sexual activity. The mean time before the first sexual relation after the first dilatation was 5 months (range: 2–12 months).

The mean FSDS-R score was 18. Two woman had a score <11, which indicated an absence of sexual distress.

The mean total FSFI score was 30 and each domain score was similar to that for normal women. Three women (75 %) had a score >26.55.

Two patients had dyspareunia and one abdominal pain.

The FSFI and the FSDS-R scores conflicted in 38 % of cases, in the vaginoplasty group as well as in the group treated by vaginal dilatation. This demonstrates that the two scales analyze different aspects, which is why we chose to use these complementary questionnaires. The FSFI evaluates the functional aspect of sexual disorders, while the FSDS-R aims to detect psychological distress linked to sexuality.

Psychological Results

Within the two groups, 28 % of women showed signs of depression (based on a positive response to questions 27 and 28 of the questionnaire). In terms of body image, 70 % of the women who had had sigmoid vaginoplasty said they felt "completely feminine" compared with 60 % of

Table 20.1 Functional results (FSFI and FSDS-R scores) of women treated by sigmoid vaginoplasty or Frank method

			FSFI©							FSDS-R®
Procedure	No. of patients	No. of responses	Desire	Arousability	Lubrication	Orgasm	Satisfaction	Comfort	Total score	
Sigmoid vaginoplasty	48	35 (73 %)	4.36	4.74	5.18	4.44	5.35	3.93	**28.00**	21.35
			±0.9	±0.7	±0.9	±1.1	±0.6	±1.2	±3.1	±12.2
Franks method	11	5 (45 %)	4.65	5.10	5.10	4.80	5.40	5.20	**30.25**	18.40
			±1.3	±1.0	±1.1	±0.9	±1.2	±1.1	±6.2	±15.4
Total	59	40 (68 %)	–	–	–	–	–	–	–	–
p (Wilcoxon exact Test)	–	–	0.64	0.34	0.93	0.61	0.57	0.06	0.13	0.72

Table 20.2 Answers to additional questions concerning intercourse frequency, vaginal discharge, pelvic pain, self-esteem, depression, and surrogacy

Questions		Sigmoid vaginoplasty	Frank method	All patients	p
Mean time before first intercourse after treatment (in months)		7	5	–	0.54
Frequency of vaginal intercourse	*Occasionally*	8 (27 %)	1 (25 %)	–	–
	1–2/week	12(40 %)	0	–	–
	2–3/week	7 (23 %)	2 (50 %)	–	–
	Daily	3 (10 %)	1 (25 %)	–	–
Vaginal discharge discomfort		23 (68 %)	0	–	–
Abdominal pain	–	22 (65 %)	1 (20 %)	–	0.69
Dyspareunia	–	24 (80 %)	2 (50 %)	–	0.22
Considering adoption	–	27 (79 %)	3 (60 %)	30 (77 %)	1.00
Considering surrogacy	–	27 (79 %)	5(100 %)	32 (82 %)	0.57
Signs of depression	*Feel depressed or desperate*?	10 (29 %)	1 (20 %)	11 (28 %)	1.00
	Decreased interest or pleasure in everyday life?				
Feeling of femininity	–	24 (70 %)	3 (60 %)	–	0.59
Changes in body image since treatment		15 (44 %)	3 (60 %)	–	
Body image perception	*Positive*	17 (50 %)	2 (40 %)	–	–
	Neither positive nor negative	13 (38 %)	3 (60 %)	–	–
	Negative	4 (12 %)	0	–	–

those who had vaginal dilatation (p = 0.59). Approximately half of the women (44 % of those treated surgically and 60 % of those without surgery) (p = 0.65) estimated that their treatment had "almost or entirely" changed their body image and that they perceived this change as "positive" (50 % of those with and 40 % of those without surgery).

Most wanted children: 77 % wished to or had already applied to adopt, and 82 % (32/39) said they would consider surrogacy. It should be noted that among the 11 women with signs of depression, 4 had good FSFI and/or FSDS-R scores, which suggests psychological distress linked to a cause independent of their sexuality. One patient emphasized that her depression had "nothing to do with her sexuality" and six others said that it was due to their unfulfilled desire for motherhood. We should point out that gestational surrogacy remains forbidden in France.

Advantages and Disadvantages

Although vaginal discharge is sometimes perceived as uncomfortable, sigmoid vaginoplasty is the only technique providing natural lubrication of the neovagina [22].

Whereas techniques of passive dilatation require an average delay of 11.8 ± 1.6 months [23] before the first sexual intercourse, sigmoid vaginoplasty allows sexual activity after 1 month. It can also be supposed that surgery is often chosen because it is psychologically complicated for these young patients to go through repeated self-dilatations which they sometimes experience as embarrassing or shameful [24].

Our results for sexual function are equivalent or better than those published for the other techniques, specifically those of Davydov [25], Vecchietti [26], and McIndoe [27].

Furthermore, as the laparoscopic approach increasingly replaces laparotomy, postoperative

disadvantages should gradually be reduced, as long as surgeons have extensive experience in both gynecological and gastrointestinal laparoscopic surgery [28, 29].

Ph. Communal et al. [13] analyzed the first 16 patients of this series and found that the functional results of their sigmoid vaginoplasty were good and similar to those of normal women, with the exception of the comfort criterion. Our report, based on a larger series, confirms these findings with slight differences: the mean total FSFI score is 28 ± 3.1 among patients who had surgery, i.e., slightly lower than in the previous investigation. The mean FSDS-R of 21 ± 12.1 indicates that psychological distress is related to sexuality.

Several factors may explain these results. First, one may question the relevance of comparing patients to the normal population. Pre- and post-operative results should be evaluated instead, to provide a more precise indication of the effect of the surgery.

Psychological results may also explain the relative weakness of these scores. In fact, the responses to the questions relating to depression and to body image show that neither the vaginal dilatation nor surgery, even if satisfactory, solve all problems.

As underlined by Berman et al. [30], a non-negligible number of patients perceive their body negatively with a weak sense of femininity (here in 10 % of the cases), despite achieving satisfying sexuality. Signs of depression are frequently encountered: infertility and the frustration concerning the difficulties of having children certainly play a role in these findings. In a recent study involving women treated by sigmoid vaginoplasty, Labus et al. [31] reported a 22 % rate of depression. Other authors have found that, regardless of their treatment, patients with MRKH have worse scores in terms of depression, anxiety [32], psychoticism, psychological distress, and self-esteem [33]. Thus, it is evident that multidisciplinary management with emphasis on psychological support is indispensable for these women [15]. Whatever technique is chosen, psychological care should be proposed at diagnosis, with the possibility of prolonging treatment over several years.

Conclusion

As recommended by the Committee Opinion of the American College of Obstetrics and Gynecology since 2002 [9–11] non-surgical vaginal dilatation (the Frank procedure) procedure must be proposed as a first-line treatment to the extent possible. In case of failure or of refusal by the patient, sigmoid vaginoplasty appears to be an attractive alternative, presenting rapid and satisfactory anatomical and sexual results. It requires a surgeon with experience in laparoscopic gynecologic surgery and in gastrointestinal surgery, or two specialists working together.

Further studies should now be carried using pre- and post-treatment evaluation to examine functional results more specifically and to improve the identification of women who might benefit from this technique. Regardless of the method used to create a neovagina, we believe that the psychological impact of the diagnosis and its treatment must be managed by a multidisciplinary team to improve, by a global approach, both psychosexual and anatomical results.

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Vaginal Aplasia: Critical Overview of Available Treatment Options

21

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Introduction

Vaginal agenesis or aplasia usually presents in combination with uterine agenesis as part of Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome [2] or Complete Androgen Insensitivity Syndrome (CAIS) [16]. More rarely, it can be an isolated anomaly, combined with a functional uterus, where blood collecting within the uterine cavity will lead to a haematometra and cyclic pain. Vaginal anomalies requiring vaginoplasty will also be encountered in patients with a urogenital sinus, as part of a disorder of sex development (DSD), the complexity of which will depend on the extent of the common urogenital channel. XX DSDs such as congenital adrenal hyperplasia or in utero androgen exposure, and XY DSDs such as partial androgen insensitivity syndrome (PAIS) or androgen enzymatic defects may require vaginal dilation, vaginoplasty or a urogenital sinus mobilization [17].

Any classification attempt of the neovagina formation should take into account: the invasiveness of the method, the distortion of the female pelvic anatomy, the type of mobilization of neighboring tissues (peritoneum, skin) or other functional healthy organs (ileum, colon) to the perineum or the use of heterologous tissues or biomedical devices [6, 22]. Therefore, the treatment options could be classified as: (1) those expanding the vaginal dimple non surgically (e.g. Frank, Ingram), (2) those focusing in vulvo-perineal reconstruction allowing the expansion of the vaginal vault after plication of flaps from the labia and the perineum (e.g. Williams and/or Creatsas vulvo-perineoplasty), (3) those expanding the vaginal vault surgically with application of pressure to the vaginal dimple (e.g. Vecchietti), (4) neovagina formation after surgical creation of the space between bladder and rectum and lining with epithelium of neighbouring tissues (e.g. Davydov/peritoneum, McIndoe-Reed/skin flaps), (5) formation of neovagina between the bladder and the rectum using intestinal tissue (e.g. intestinal vaginoplasty).

Evaluation of the various types of vaginoplasties is based on (1) the anatomical outcome, (2) the functional outcome, (3) the complication profile, and (4) the cost-effectiveness of each technique. Anatomical success is considered as a

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post-intervention vaginal length >6 cm although vaginal length >7 cm seems to be associated with better functional results [1, 6, 15, 20] (Table 21.1). Functional success is described as "full genital performance during heterosexual intercourse" [31] and measured in questionnaire scores such as the FSFI (Female Sexual Function Index; [27]). However, in the existing studies, a lot of different definitions have been used for the evaluation of the vaginoplasty results.

Expansion of an Existing Vaginal Vault

Non Surgical Expansion of the Vaginal Vault: Vaginal Dilation

In most cases of MRKH and CAIS vaginal dilation is all that will be required to create a vagina. Vaginal dilation, first described by Frank [13], is a virtually risk free method with reported success rates ranging between 40 and 90 % (see Chap. 16) [6, 26]. It entails the insertion of moulds of increasing sizes within the vaginal dimple and applying pressure. Depending on the motivation and psychological support available, treatment could be completed in weeks, but will usually take as long as few months [18]; the median reported time to achieve a sufficient vaginal length varies between 6 and 18 months. This may be one of the drawbacks of the method, as it often requires a long commitment that may be psychologically taxing for some patients. For the small percentage of women where dilation will not be successful, being familiar with dilators will prove useful following a surgical vaginoplasty, when the patient will be asked to use them postoperatively, to prevent constrictions and stenosis.

Being non-invasive and risk-free, vaginal dilation could be recommended as a first line treatment option for patients having a vaginal dimple present. For those cases that will fail, or where anatomically there is no vaginal dimple on the perineum or where a complex anomaly exists, a surgical procedure will be required.

Surgical Traction of the Vaginal Vault

The Vecchietti method was first described as an open procedure in the 1960s [32] and has since been modified into a minimal access one [5, 11]. The anatomical success rates, defined as the achievement of a post-operative vaginal length >6 cm, are reported to be as high as ~99 %, associated with functional success rates of ~95 % [6]; the mean post-operative neovagina length has been measured ~7.9 cm [22]. This technique involves the insertion of an acrylic bead in the vaginal dimple that is attached via the peritoneal cavity onto a traction device positioned on the abdominal wall that will gradually pull the vaginal vault upwards. The patient usually remains an inpatient for a week, at the end of which the traction device, bead and threads are removed. Postoperatively, the patient will have to maintain vaginal length with dilation or through coitus.

Risks of the procedure relate to the laparoscopic procedure itself and the possible injury to the bladder during insertion of the threads into the peritoneal cavity [10]. A variation of the Vecchietti technique involves the introduction in the introitus of an inflated Foley's balloon, instead of an acrylic bead, the advantage being that a better vaginal width can be achieved as compared to the one obtained through the Vecchietti method [9].

Vulvo-perineoplasty: Williams "Vaginoplasty" and Creatsas Modification

The Williams vaginoplasty [34] and the Creatsas modification [7] are simple surgical procedures, whereby the labia majora are sutured to form a neovaginal pouch, whose axis is parallel to the perineum. The anatomical success rates are reported to be as high as ~97 % associated with functional success rates ~95 %; the mean postoperative neovagina length has been measured ~11.5 cm [6].

Table 21.1 Evaluation of the various types of vaginoplasties

	Vaginal dilation	Vulvo-perineoplasty	Traction vaginoplasty	Peritoneal vaginoplasty	Skin vaginoplasty	Bowel vaginoplasty
Complexity	Low	Medium	High	High	High	Very high
Indications						
No vaginal dimple	–	+	–	++	++	++
Previous surgery	–	–	–	++	+	++
Anatomical outcome						
Anatomical success	75 %	97 %	99 %	92 %	91 %	95 %
Mean neovagina length (cm)	6.6	11.5	7.9	8.9	8.8	12.9
Functional outcome						
Successful intercourse	74 %	95 %	96 %	93 %	89.5 %	90 %
Functional success (FSFI score)	21.6–30.3	N.A.	29.0–30.2	21.4–31.8	N.A.	24.8–30.0
Complication profile						
Invasiveness	None	Minimal	Medium	Medium	Medium-high	High
Hospitalisation	None	+	++	++	+++	+++
Perioperative complications						
Donor site	–	–	–	–	+++	+++
Postoperative complications	–	+	++	++	+++	+++
Long-term complications						
Vaginal stenosis	–	+	–	+	+++	–
Vaginal discharge	–	+	–	–	+++	+++
Need for vaginal lubrication	–	++	–	–	+++	–
Neovagina prolapse	++	–	++	+	+	+
Morbidity	+	+	++	++	+++	+++
Mortality	–	–	–		+	+
Cost–effectiveness						
Inexpensive	+++	+	–	–	–	–
Time consuming	+++	–	+	–	–	–
Patient compliance	–	+	+	+	+	+
Options for further Treatment	+++	+++	+	+	+	+
Dilation needed	+++	+++	++	+	+	+

Based on data from Callens et al. (2014) and McQuillan et al. (2014)

The non-anatomical vaginal axis is a major disadvantage of the method, although it has been shown that through coitus, the space between urethra and rectum is eventually dilated. It seems that the external pouch acts as a sheath for "natural dilation" during normal intercourses, thus leading to the described expansion of the vaginal dimple. A further drawback to this method is that it leads to scar formation on the perineum whereas hair growth within the neovagina can be distressing.

Neovagina Formation in the Space Between Bladder and Rectum

Lining with Peritoneum: Davydov Technique

The Davydov vaginoplasty was first presented [8] as an open operation that has since been modified into a laparoscopic one [15]. The anatomical success rates, defined as post-operative vaginal length of >6 cm and in some studies >8 cm, are reported to be >92 % associated with functional success rates ~93 % [6]; the mean postoperative neovagina length has been measured approximately 8.9 cm [22]. This technique involves the mobilization and positioning of peritoneum within the neovaginal space, created bluntly between urethra and rectum. The peritoneal lining is then anastomosed to the introitus or onto perineal skin. The roof of the peritoneal neovagina is usually then closed with a purse-string suture.

The Davydov, as is the case with the Vecchietti method, may lead to intraoperative injury to the bowel or bladder. It is surgically a more complex operation than the Vecchietti procedure, which however has the added advantage that it can be performed even in cases where there is no vaginal dimple, such as for example in certain cases of XY DSDs.

Lining with Skin

The McIndoe-Reed technique [21] involves the creation of a split thickness skin graft, usually taken from the thigh or the buttocks, which is then inserted in the neovaginal space. The anatomical success rates are reported to be ~91 % [6], and the mean postoperative neovagina length has been measured ~8.8 cm [22]. Problems with this technique relate to the visible scars on the donor skin site. Also, there is often concern with vaginal dryness and stricture formation.

Other Options for Lining

Other tissues used to line the neovagina are freeze-dried human amnion [4, 12] and autologous in vitro cultured vaginal mucosal skin [25]. The former has fallen into disuse due to the risk of blood borne infection transmission. In the Wharton-Sheares-George method [33] no tissue is used to line the neovagina, as neo-epithelization of the neovaginal space occurs by leaving a mould in place.

Neovagina Formation with the Use of Bowel: Intestinal Vaginoplasty

Neovagina formation with the use of bowel involves the isolation of a short segment of ileum or sigmoid colon, extensive upwards dissection of this segment in order to connect it with the perineum in the space between bladder and rectum with minimal tension. The anatomical success rates are reported to be ~95 % associated with a mean reported functional success rate of ~90 % [6]; the mean postoperative neovagina length has been measured approximately ~12.9 cm [22]. Ileum, jejunum or colon have been used with variable success [3, 19, 28]. The greatest advantage of the method is the fact that vaginal caliper is maintained with stenosis affecting only the level of the perineal anastomosis. Lubrication is usually satisfactory, however in some patients mucous overproduction can be particularly distressing. Diversion colitis [30] and prolapse of the bowel mucosa [14]) have been increasingly presented in the literature as possible risks. Furthermore, although the proce-

dure may be performed laparoscopically, it usually involves a laparotomy, with increased intraoperative and postoperative risks, including bowel anastomosis leakage. However, bowel and skin graft vaginoplasties are favored over the Davydov procedure in cases where prior extensive abdominal surgery will not allow peritoneal mobilization.

Both the Mcindoe and Bowel vaginoplasties have been associated with the development of squamous or adenocarcinoma of the neovagina respectively [24, 29]. Patients and their physicians should therefore remain vigilant about this complication.

Proposed Algorithm

Studies comparing vaginoplasties are few and data are poor in quality, in order to allow an evidence-based approach in defining the best treatment option for vaginal aplasia. However, in 2007 a multidisciplinary team from UCLH proposed an algorithm, to facilitate decision-making with regards to choice of vaginoplasty [23]. It encompassed vaginal dilation as a first line treatment for MRKH and CAIS; surgical methods such as the Vecchietti and Davydov procedures with bowel vaginoplasty being indicated as a second or third line option. Practices may vary, but any tertiary referral centre should be able to offer a series of vaginoplasties to accommodate different patient's needs, according to pathology.

An important principle to choosing the appropriate treatment modality is to escalate procedures from less invasive to more complex and risk prone. Furthermore, the expected outcome of each technique in terms of anatomical and, mainly, functional success is very important in the decision-making process; the aim of any vaginoplasty technique is the creation of a neovagina for an enjoyable intercourse [23]. Two groups of investigators have tried to systematically review the results of the various techniques [6, 22]; the mean anatomical and functional success rates as well as the mean post-operative vaginal length achieved with various methods were previously mentioned. However, the studies included in those reviews were not prospective and, most importantly there are no randomized comparisons and different definitions for anatomical and functional success have been used.

The proposed algorithm is based on UCLH algorithm, although the authors of this chapter have integrated growing available experience in this field based on available scientific data (Fig. 21.1).

The proposed algorithm consists of the following steps:

1. Vaginal dimple present, no previous perineal surgery: proceed to vaginal dilation
2. Failed vaginal dilation, vaginal dimple present, no previous perineal surgery: Vechietti method or Davydov procedure
3. Failed Vecchietti, no vaginal dimple present: Davydov Procedure
4. Previous surgical abdominal or perineal procedure: McIndoe or Bowel vaginoplasty

In all cases, maintenance vaginal dilation is required if the woman is not sexually active.

Conclusion

The debate regarding the superiority of any vaginoplasty remains open. There is a need for objective comparisons and non-biased long term follow up studies. Until then, it seems reasonable to proceed with non-invasive and less complex procedures first, particularly with patients with MRKH and CAIS. Bowel and skin vaginoplasties pose long-term risks and may lead to unpleasant symptoms and, thus, should probably only be used for cases where dilation or the Vecchietti and Davydov procedures cannot be performed due to previous abdominal surgery.

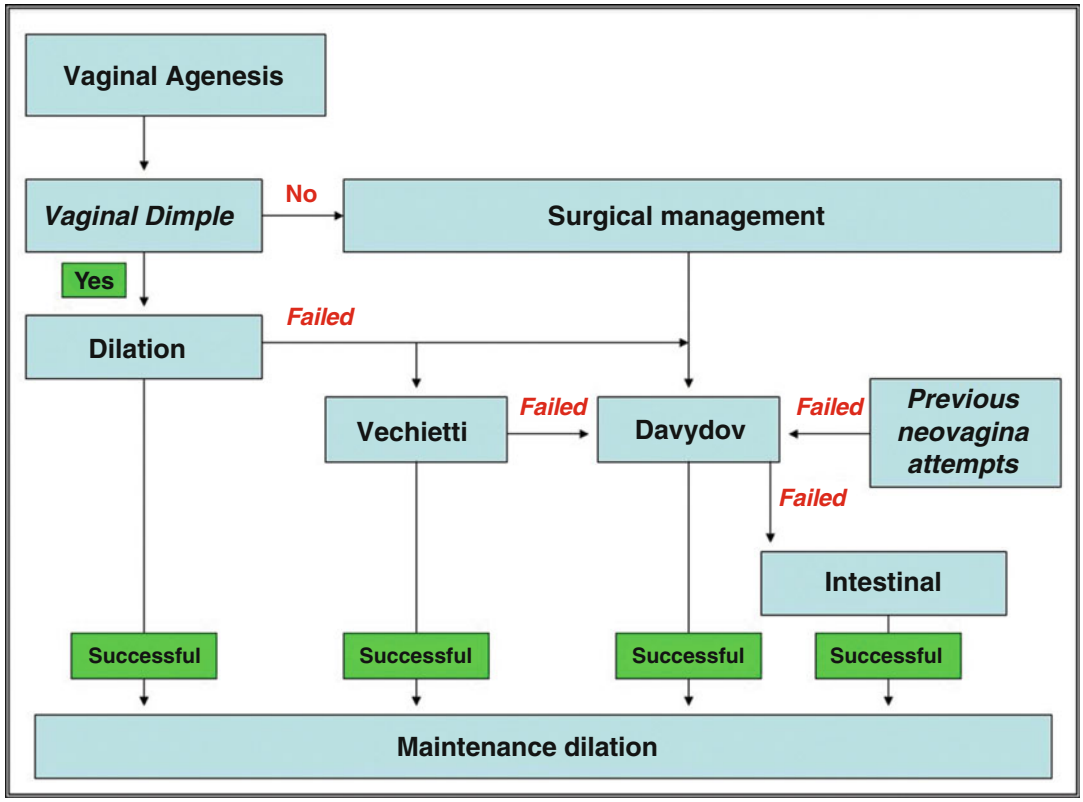

Fig. 21.1 Proposed algorithm based on the UCLH algorithm

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Part V

Treatment of Obstructive Anomalies

Vaginal Septae and Imperforate Hymen

22

Vasilios Tanos

Vaginal Septae

The incidence of obstructive Müllerian anomalies is 0.1 and 3.8 %. Vaginal septae anomalies may obstruct the outflow of menstruation and then blood accumulates in the uterus and the vagina. Retrograde menstruation via tubes ends in the abdominal cavity, causes severe dysmenorrhea and increases the risk of endometriosis. Correct and early diagnosis depends highly on gynaecologists awareness and suspicion. Primary amenorrhoea and increasing dysmenorrhoea with subsequent menstruations are the main symptoms. The timing and extend of surgical treatment depends on the level of obstruction, menarche and severity of symptoms. The anatomical and functional post operative success and fertility potential are directly related to the location level in the vagina and existence time of haematocolpos. Pain relief, preservation of sexual and reproductive function should be the primary concerns [1–3].

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Formation of Vaginal Longitudinal Septae

During the 6th week of gestation Müllerian ducts identified in embryos of both sexes. By the 9th week of gestational age the ducts elongate and reach the urogenital sinus. The uterovaginal canal is formed and inserts into the urogenital sinus at Müller's tubercle. When the two lateral Müllerian ducts fail to fuse at their lower border, then uterine and vaginal defects arise, resulting in a double uterus, with two hemiuteri and two hemi-cervices. Each cervix shares a hemi-vagina. When the two vaginas fuse with the urogenital sinus a double vagina is developed. Fusion of the two ducts proceeds from the vaginal introitus up to the uterine fundus. Internal canalization and septum resorption occurs by approximately 20 weeks' gestation. The hymen is formed and becomes perforated during fetal life [4].

Longitudinal Vaginal Septum Without Obstruction

Once the lower parts of the Mullerian ducts forming the vagina failed to fuse result to longitudinal septum [5]. Two cervices and two vaginas are formed without any obstruction. Usually the right hemi-vagina is larger than the left one and coitus is able without difficulty. In a retrospective study

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among 202 patient reported 46 % to have a complete septum from the cervix to introitus, 36 % a high partial septum and 18 % a low partial septum [6]. Cases with longitudinal vaginal septa are associated with uterine malformations up to 88 %. Complete uterine septum is most frequently diagnosed in 60 % and partial septated uterus at 15 % of women with vaginal septum while bicorporated uterus in 24 % [6, 7]. Bicorporated uterus accompanied by longitudinal vaginal septum, usually present one uterine hemicorpus to be less developed that the other. Usually intercourse is feasible in the more developed vagina side, however if intercourse occurs on the vaginal side connected to the well developed uterine hemicorpus can be confirmed by transvaginal sonography. Under-developed hemi-uterus is at higher risk for recurrent miscarriages and infertility [8].

Symptomatology and Diagnosis and of Patients with Longitudinal Vaginal Septum

The clinical picture and symptomatology of patients with longitudinal vaginal septum varies according to the severity of the malformation and age. During prepubertal age there are no symptoms but after puberty and adolescence by the initiation of menstruation cyclic lower abdominal pain and abnormal bleeding are frequent while very rarely pelvic inflammatory disease may also be a diagnosis. Magnetic resonance imaging is considered the gold standard for diagnosis, but also offers excellent information about anatomy of adjacent organs including uterus, parametria and adnexae [9]. Diagnostic hysteroscope of 2.8 mm is possible to perform a diagnostic vaginoscopy even to virgo, without injury of the hymen in order to confirm the diagnosis. In patients that already had coitus usually complain for dyspareunia, penetration difficulties and difficulties for tampon application. Per speculum examination to patients that already have sexual intercourse diagnosis is easy, a long septum can be identified and usually one vaginal side is more developed than the other. Non obstructive septa do not require any intervention once menstruation, sexual activity, pelvic examination and labour process are not disturbed [10]. However the need of surgical intervention may arise once infertility is a problem because sperm enter only into one hemi-uterus. In addition excision of the vaginal septum can improve pregnancy outcome, vaginal delivery and may reduce labour complications.

Longitudinal Vaginal Septum and Surgical Approach

Vaginal septum excision is an easy operation however caution should be taken not to injure the urethra, bladder and rectum. Introduction of a metallic of silastic urine catheter assist to define the anatomical relation of the urethra to the vaginal septum prior to and during the operation. Uterine assessment with 2D, 3D ultrasound, contrast sonography, MRI, and hysteroscopy are helpful prior to operation in order to have a complete view of the uterine anatomy. Surgical repair involves excision of the vaginal septum, as completely as possible by scalpel or diathermy or laser in non obstructive septum. An effort should be made to excise and ligate the septum along all its length because if a remnant tissue is left behind might cause post–operative dyspareunia. Post operatively increased mucous discharge is evident until complete healing. In cases that two cervices exist pay attention that annual cervical smear test is recommended for each cervix. In general the pregnancy rate after longitudinal vaginal septum resection ranges from 37 to 40 % in cases with bicorporate and unicornuate uterus [11]. Low reproductive outcome can be also attributed to Endometriosis which is frequently found in these patients [12].

Longitudinal Vaginal Septum with an Obstructed Hemi-vagina

Under unknown and very rare circumstances simultaneous malfunction of mullerian and metanephric ducts around 8 weeks of gestational age lead to double uterus, unilateral vaginal obstruction and ipsilateral renal agenesis [4, 13, 14]. The right uterus and vagina are affected in 63.5 % of the cases. The great majority of these patients

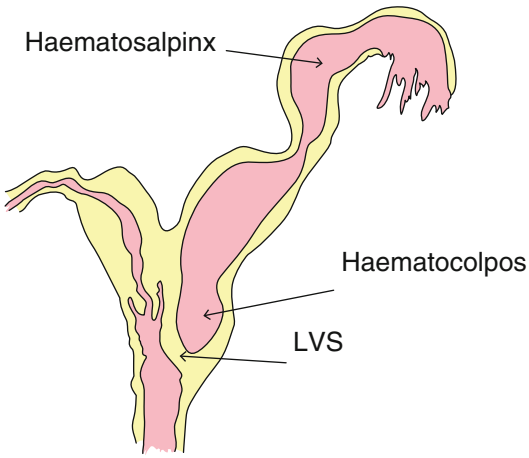

Fig. 22.1 Obstructive longitudinal vaginal septum (LVS)

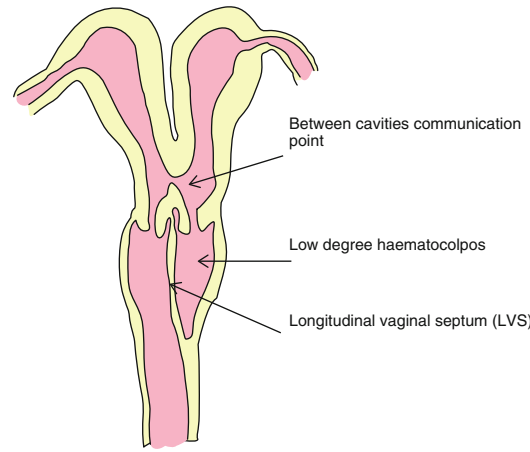

Fig. 22.2 Longitudinal vaginal septum (LVS) with communicating uterine cavities

have regular periods hence this syndrome may easily be overlooked. Imaging techniques such as 3D US and MRI can diagnose the obstructed vagina, double uterus and absent kidney. Clinical symptoms vary depending on the degree and level of the vaginal obstruction and if communication between uterine cavities exists or not. In case with double uterus most patients 71–73 %, have dysmenorrhoea and or pelvic vaginal mass [15]. Patients with incomplete vaginal obstruction and uterine communication, reliable and complete diagnosis and images interpretation might be very difficult. Large amounts of menstrual blood is absorbed between periods and vagina is quite distensible so large volume of accumulated blood is needed to cause pain and make a woman to seek medical advice. Retrograde bleeding will eventually cause endometriosis [5].

Three variations of longitudinal vaginal septae with an obstructed henivagina are classified as:

Type 1 with a complete unilateral vaginal obstruction without uterine communication.

Type 2 with an incomplete unilateral vaginal obstruction without uterine communication (Fig. 22.1).

Type 3 with a complete vaginal obstruction but with a laterally communicating double uterus (Fig. 22.2).

Types 1 and 3 have similar clinical symptoms with regular menses, dysmenorrhoea, lower pelvic pain, paravaginal mass. Type 2 patients characterized by occasional intermenstual bleedings, dysmenorrhoea and lower pelvic pain, and excessive foul mucopurulent vaginal discharge [16].

Operation of the Obstructed Hemi-vagina

The treatment of choice is surgery and by vaginal approach. Resection of the septum and opening of the hemi–vagina can treat successfully 84–87 % of the patients [5, 7]. The target should be one curative operation rather than a sequence of operations. Usually the results of the surgery are excellent and retraction of the septal pedicles is almost complete. Prophylactic antibiotics administrated before initiation of the operation. Once the vaginal pouch is excised and open, suction and lavage evacuate the entrapped blood and mucous. About 10 % of the patients will need a second operation due to reclosure of the hemivagina or due to vaginal stricture. When the septum is thick the operation can be difficult with unsatisfactory results. Complications such as post-operative haemorrhage and a partially successful or unsuccessful operation may occur. Small incision or inadequate opening of the blind septum may result in ascending infection and hemi-vagina abscess and septicaemia hence skilful surgeons should operate these cases.

Attention to leave a generous vaginal pedicle during resection and avoid unnecessary suturing.

Sutures are placed only to secure slippage of the tissue. Keep in mind that remained pedicles retract during healing, decreasing the risk of post operative vaginal stenosis. Post operative vaginal mould is not always necessary but frequent follow ups are helpful to control post operative results. In cases of pyocolpos or severe haematocolpos distention and stretching of the septal tissue increases the risk of inadequate resection and possible post operative vaginal stenosis. Haddad et al. recommended for difficult cases, two step surgery small septum resection of 3 cm to allow adequate drainage and after 1 month to remove any remaining septum [7]. Behind the obstruction is mucous-lined vaginal epithelium and cervical type glandular crypts that progressively transform to mature squamous epithelium, hence increased vaginal secretions will continue until cell maturation [17]. Uterine reconstruction is not indicated for cases with type 3, lateral communication of the uterine horns. Some authors have reported the use of hemi-hysterectomy in patients with a high thick walled obstruction, severe forms of pelvic endometriosis or adenomyosis however this approach is not recommended for young patients.

Formation of Transverse Vaginal Septae (TVS)

Incomplete vertical fusion between the Müllerian duct component of the vagina and the urogenital sinus component forms a transverse vaginal septum that varies in both the level and thickness. The incidence estimated to be 1 in 2,100 to 1 in 72,000, while this phenomenon is unclear. Probably is one of the rarest anomalies of the female genital tract but it is much less common than congenital absence of the vagina and uterus [13]. Like imperforate hymen the transverse vaginal septum is not associated with Müllerian malformations [1]. The TVS is associated with imperforate anus and bicornuate uterus and very few urologic anomalies [18]. Most cases are suspected to have a genetic background indicating a female sex-limited autosomal recessive transmission [14] and associated with other congenital anomalies such as coarctation of the aorta, atrial septal defect and malformations of the lumbar spine. Scrutinized family history and physical examination of each patient are mandatory [4]. Transverse vaginal septa (TVS) may be complete or incomplete and found 46 % in upper vagina, 40 % in midvagina and 14 % in lower vagina [19–21] (Table 22.1) (Fig. 22.3). Septa found in the upper vagina and closer to the cervix are usually thicker and most of the times are over 1 cm in thickness [2, 15]. Patients with mid and lower vaginal septa, perineal bulging and a pelvic mass along with a cervix and uterus might be detected during gynaecological examination [1]. Higher the position of the septum in the vagina higher is the risk of presence and extension of pelvic endometriosis, infertility and miscarriage rates. These results probably are explained by the fact that patients with high TVS experience retrograde menstrual blood flow via endometrial cavity and fallopian tubes in much younger age and for a long time [17] (Table 22.1).

Table 22.1 Frequency of TVS according to vaginal height

Position of the TVS	Lower vagina (%)	Mid vagina (%)	Upper vagina (%)
Lodi et al. [20]	14	40	46
Rock Zakur [21]	19	35	46

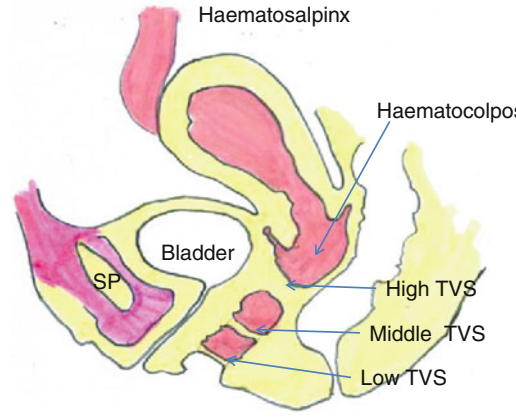

Fig. 22.3 Present the locations of the transverse vaginal septa (TVS)

TVS in Infancy

Neonates with TVS are at risk due to higher morbidity and mortality since formation of a large mucocelle above the septum may compress the ureters, rectum and vena cava. The lower surface of the septum is covered with glandular epithelium which under the influence of the maternal estrogens secretes mucous. The fluid collected might be enormous but the flexibility of the vagina may allow its asymptomatic distention upto a year after birth [22]. When the septum is formed higher in the vagina and closer to the cervix, perineum bulging is absent and hydrocolpos develops towards the upper vagina and beyond. Long standing compression may lead to urethrovaginal and other urinary tract system fistulas [2]. Clinical examination, image and endoscopic investigation usually demonstrate a large pelvic and lower abdominal mass as a result of the distended vaginal septum. The bladder is displaced anteriorly while hydroureters and hydronephrosis are prominent. Severe compression to the gastrointestinal tract and indirectly to the diaphragms respiratory movements, inevitably lead to respiratory distress and to an emergency operation to save the life of the neonate. The septum should be operated trans perineally and close post operative follow up for short and long term sequellae is advised [22]. Surgery under these difficult and complex conditions endanger high recurrence rate of vaginal stenosis and urinary tract obstruction while vaginal reconstruction might be required later in life [5]. In general TVS excision prior to puberty is associated with a high rate of vaginal stenosis, demanding another operation in adolescence to improve coitus and ease menstruation flow [5, 14].

TVS in Puberty and Adolescence

History at the time of puberty with increasing cyclical abdominal pain in the absence of menstruation is highly suspicious for TVS and diagnosis may be missed for several months. In adolescent girls already by their first few menstruations blood is collected above the septum and haematocolpos is formed. Usually adolescents with TVS present in the emergency room with acute abdominal pain and/or urinary retention. Clinical symptoms are cyclic pelvic pains, development of a central abdominal or pelvic mass and primary amenorrhoea while the incidence of endometriosis is high. The mass is tender to palpation and sonography confirms the presence of a haematocolpos and a haematometra. A haematosalpinx may be detected and even more rarely an endometrioma. Clinical examination of a low and middle TVS will probably reveal a 'pink' bulging membrane while in case of an imperorated hymen the bulging membrane is dark bluish. Occasionally a small spontaneous crack of the septum allows menstrual blood partial evacuation and symptoms are then variable [23]. Patients that already tried to have intercourse complain of very short vagina, difficult coitus and place a tampon. In case of a fistula between bladder and upper vagina cyclic haematuria might be observed. Non obstructing transverse septa that will eventually allow a pregnancy, severe dystocia is expected during labour. Gynaecological examination when is possible, vaginoscopy, rectal and abdominal sonography can help to obtain the correct diagnosis. Magnetic resonance image can measure the thickness of the septum and detect pelvic mass and other associated malformations [9, 22].

Surgical Treatment of the TVS

Once the diagnosis of TVS is established both in asymptomatic and symptomatic pubertal girls, vaginoplasty is indicated. Surgery will allow natural menarche and alleviate dysmenorrhoea, will prevent pelvic mass formation and endometriosis. It has been reported that many patients psychologically may feel better to delay definitive surgical therapy once diagnosis has been established however, this is possible only in asyptomatic children below age of 10 [14, 19, 24]. Vaginoplasty for TVS demonstrated high rate of post operative vaginal strictures because of the absence of large vaginal segment and poor motivation of the pubertal patients to perform frequent vaginal dilatation after the operation.

Surgery is the only treatment for a TVS and is relatively easy when the septum is thin and found in lower vagina. The principle of the TVS surgery is to excise the septum and reconnect the vagina by end-to-end anastomosis between the upper and lower vaginal parts. A transverse incision in the centre of the vault of the lower short vagina leads into the upper vagina and haematocolpos is exposed. Using a vaginal speculum will facilitate progress within the vaginal space while presence of areolar tissue may create some uncertainty to anatomical structures and disorientation. Simultaneous bi-digital vaginal and rectal examination, palpating the urine catheter on the anterior vaginal wall will guide the direction of dissection. Lateral dissection permits complete excision of the septum. When the septum is low then the upper vaginal wall is brought easily to oppose the lower vaginal segment and leaving a neo-vagina with normal calibre. Some surgeons at the site of the anastomosis place a firm vaginal mould for 10 days after the operation to reduce the risk of ring stenosis. In addition, cases with lower and middle transverse septal defects and the use of vaginal dilators for 2–3 months subsequent to the removal of the mould, increase the chances for excellent functional vagina in the future [25]. The post operative satisfactory sexual function success rate after TVS obstruction vaginoplasty has been reported as 100 % (27/27) for the lower TVS, 45 % (12/27) for the mid TVS and 41 % (11/27) for high TVS [25]. The major post operative problems of these patients remain vaginal stenosis, dyspareunia and infertility. The pregnancy success rate reported, after septectomy of a low TVS was 100 %, mid TVS 40 % and for the high TVS was only 20 % [23]. Most probably the high incidence of endometriosis especially found in patients with the high TVS explains the high dyspareunia and infertility rates.

Depending on the height of the septum, dissection continues until palpation and view of the cervix. A thin membrane like a pocket might be in front of the cervical os and should be excised too. The exposed cervical os is reddish, covered with a columnar epithelium that will convert to squamus, once the normal anatomy of the vagina is reestablished [2, 14, 19]. The pedicles created by incising the septum will be used to cover the new formed single lumen vagina. The edges of the upper and lower vaginal mucosa are sutured by interrupted delayed – absorbable sutures [26]. Upper transverse and thick vaginal septa require extensive dissection, undermining and mobilization of the vaginal mucosa to permit end-to-end anastomosis. In order to prevent stenosis vaginal mould is used for 4–6 weeks until complete healing [14] while not sexually active patients should continue vaginal dilation after the operation. Some cases of high transverse vaginal septum during excision and repair a split-thickness skin graft may be needed to cover the vagina area from the excised septum [26, 27]. A vaginal mould should be used to hold the graft but also postoperative frequent vaginal dilations are necessary to maintain a functional vagina. Sometimes high vaginal septum is very thick, the anatomy is disturbed and orientation towards the cervix is misleading thus vaginal anastomosis is impossible. In addition TVS location closer to the cervix, endangers more defective and less normal vaginal tissue. The defect after excision of the septum is large in size and mobilization of the remaining vagina is very difficult, impose a combined vaginal and abdominal intervention. The upper vaginal portion may be very short and there is a risk to damage the bladder and/or the rectum during dissection through the vagina. Using laparoscopy or laparotomy a uterine sound or probe may be placed through the uterine fundus and cervix to push and distend the septum in order to recognize it and dissect it [14]. Another challenging situation is the mass formed above the septum to be so large, that exploratory laparotomy may be required [10].

When anastomosis between the upper and lower vaginal segments is impossible because a large part of the vagina is missing drainage of haematocolpos with a needle under US guidance and continuous oral contraceptives to suppress menstruation has been recommended. Vaginal dilation for several weeks will give the opportunity to increase the vaginal surface below the septum in order to facilitate re-anastomosis and vaginal repair at a later time [24]. Patients at age 12 or 13 with a high TVS, is almost impossible to encourage them to perform pre and/or postoperative

vaginal dilatations. Menstruation suppression for 2–3 years by continuous administration of oral contraception pill is the best option. Aging allows them to become mature and there is higher chance to use the vaginal dilators before and after surgery. Only cases that expectant management is unsuccessful or impossible there is an indication to perform surgery in advance [10, 25].

Patients pregnancy rate after re-anastomosis of a transverse vaginal septum and vaginal reconstruction varies between 37 and 47 % among those attempted to get pregnant. The high incidence of endometriosis especially in cases of high transverse vaginal septum probably explains this low pregnancy rate [2, 14].

Imperforate Hymen

During embryogenesis a thin membrane is formed at the junction of the sinovaginal bulbs and the urogenital sinus forming the hymen. Normally perforation of the hymen is accomplished as the fetus develops in utero but the mechanism is still unknown. Failure of the perforation process will result to imperforated hymen [25]. It is postulated that incomplete canalization of the urogenital sinus with the Müllerian system can lead to imperforate hymen. A variety of hymenal abnormalities exist and this abnormality may present at different stages of life. An imperforate hymen and occasionally a microperforate hymen may present as an obstructive anomaly. The imperforate hymen is usually an isolated finding, its incidence is about 0.1 %, and is not associated with any other Müllerian abnormalities [2, 19, 27]. Occasionally family history indicates a familial predisposition [2, 19]. Imperforated hymen can be diagnosed even during infancy although most of the infants are asymptomatic. Maternal estrogens stimulate vaginal mucous secretion, accumulated in the vagina and bulge the introitus. In rare cases the formed mucocolpos cause urinary tract infection or bladder obstruction and incision and drainage of the imperforated hymen under anaesthesia is indicated.

In prepubertal girls the perineum is not fully formed and defined due to low or lack of estrogens. Hence, it's difficult to differentiate the absent vagina syndrome from imperforate hymen solely by inspection. Sonography and rectal examination assist to diagnose the existence of the uterus. Occasionally just applying the vaginal US probe superficially to the perineum good view of the uterus is obtained. In case the uterus is present then patient is invited to come between age of 10-11 before breast development and the presumed time of menarche for further treatment [2, 18]. The differential diagnosis between imperforate hymen and a low transverse vaginal septum is made mainly by magnetic resonance imaging and sonography.

Symptomatology of Patients with Imperforated Hymen

Imperforate hymen like other obstructive anomalies prevent normal menstruation, allow collection of blood in the uterus and the vagina, increasing the incidence of retrograde menstruation. Once menstruation initiates repeated menstrual bleeding accumulated behind the imperforated hymen, vagina distends and large haematocolpos is formed. Several months might be needed until profound pain and other symptoms appear, due to the great distensibility of the vagina. Once haematocolpos is large enough may cause problems with micturition, defecation and overflow incontinence. The characteristic symptoms of the imperforate hymen are the cyclic pelvic pain, primary amenorrhea and occasionally painful urination, back pain and painful defecation [5, 27]. Usually the large haematocolpos formed in the pelvis can be even palpated abdominally. Gynaecological examination by opening the labia reveals a bulging hymen with a bluish colouration. Often appears as a dark blue mass and menstrual blood may be seen [25].

Imperforated Hymen Surgery

Abdominal ultrasonography reveals a hypoechogenic mass beneath the bladder and anterior to the uterus. A urine catheter in the bladder assists to orientation and defined anatomy. Simple drainage by needle or a small incision of imperforate

hymen are inadequate and increase the risk of infection and recurrence. Some authors propose hymen incision and drainage to be performed once estrogen levels are high. Tissues under the influence of estrogens become stronger and thicker and facilitate surgery and introitus vagina reconstruction. A needle can be placed into the bulging mass in order to confirm hematocolpos. A symmetrical "X" incision (2 to 8 o'clock and 10 to 4 o'clock) by scalpel or by diathermy needle on the bulging mass will release vaginal content. Spontaneous drainage is completed within 3–5 days. Some surgeons avoid hematocolpos evacuation with instruments and suction at the time of surgery in order to reduce the risk of perforation of the vagina and ascending infection. Others use suction canulla for faster evacuation of the accumulated vaginal content. The old blood and mucous within the vagina becomes viscous and sometimes suction blocks. Frequent irrigation of the tubing with normal saline will save unnecessary delays, facilitating the evacuation of the vagina. The accumulated amount is sometimes huge and shows the enormous distensibility of the vaginal walls. Vaginal digital dissection can further brake and release intravaginal pockets from collected mucous higher up in the vagina.

The hymen pedicles created after incision are left or excised according to the appearance of the new vaginal introitus. Once the vaginal entry satisfies good menstrual flow and unobstructed coitus, the remnant hymen pedicles may be left in situ. In case that further excision of the remnant hymen tissue should be followed, then Allis clamps are placed along the cut edges of the incision and reduction of the excess tissue is performed. Absorbable vicryl 2.0 sutures are used to re-approximate the vaginal mucosa, stop bleeding and keep the hymenal ring open in order to prevent re-closure. In general there are no sequelae following imperforate hymen and surgery. Long-term follow-up of patients with imperforate hymen present normal fertility rates and their reproductive performance compares equally with that of the normal population [21].

Summary

Vaginal Longitudinal and Transverse Septae are the result of late fusion defects of the Müllerian duct. Vertical fusion defect lead to TVS and lateral fusion defect lead to LVS. Imperforated hymen is the failure of perforation process of the hymen that takes place during fetal life. These rare vaginal obstructive anomalies diagnosis and surgical treatment present in childhood and adolescence. TVS usually becomes symptomatic by menarche once menstrual flow is obstructed while LVS may not be found until initiation of coitus. Magnetic resonance imaging and sonography are currently the most efficient to define the complex and abnormal anatomy and differentiate among other pathologies. Occasionally the distensibility of the vagina delays the appearance of the symptoms due to Müllerian anomalies. A high index of suspicion is necessary for proper diagnosis and resection of the septa and hymen are the sole treatments. Timing of vaginal reconstruction is crucial and highly depends on the age of the patient, menarche and symptoms. Although these obstructive anomalies are very rare, the high incidence of endometriosis at early puberty and infertility problems in adulthood may propose the need of a screening for Müllerian anomalies to all female infants, at least those with positive family history for urogenital tract anomalies.

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Treatment of Obstructing Anomalies: Cervical Aplasia

23

Carla Roberts, Heather Hipp, and John A. Rock

Introduction

One of the more uncommon congenital anomalies is cervical agenesis, or the absence of the cervix. These patients present with primary amenorrhea, cyclic chronic pelvic pain and a palpable pelvic mass resulting from a hematometra, due to the obstructed outflow of menstrual blood [13]. Reviews of the literature emphasize its rarity, with an estimated incidence of 1 in 80,000–100,000 births [16]. A 2004 review reported 116 cases since 1900 [8].

The cervix typically forms as a result of condensation of stromal cells around the fused müllerian ducts, which is in contact with the urogenital sinus. Embryologically, cervical agenesis is thought to result from a failure of canalization of the fusion of the ascending sinovaginal bulb with the descending Müllerian system. An adequate vagina and formation of the cervix also depends upon elongation of the müllerian ducts. The co-occurrence of cervical and vaginal agenesis could result from a failure of the elongation of the mullieran ducts [7].

Cervical agenesis or dysgenesis is often present with other genital or urogenital tract anomalies. Vaginal asplasia often occurs with cervical agenesis (60 out of 83 reported cases of cervical agenesis), but is much less commonly associated with cervical dysgenesis [8]. Cervical agenesis has also been found to be associated with renal anomalies, with an approximated incidence of 20 % (from a case review of 20 patients) [7]. Rock et al. found associated anomalies in 10 of their reported 30 cases: ovarian malposition (n = 4), tubal abnormalities (n = 4), endometrial hypoplasia (n = 5), and a solitary kidney (n = 2) [15].

Diagnosis

The diagnosis of cervical agenesis or dysgenesis can be facilitated with radiologic studies, including ultrasound and MRI. Valdes et al. first reported the diagnosis of cervical or vaginal atresia via ultrasound in 1984 [18]. Some have advocated the use of trans-rectal ultrasound, especially in

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associated cases of vaginal canalization defects [6]. Other reports have found MRI to be extremely useful for pre-operative diagnosis [11, 12, 15]. MRI also has the advantage of imaging of the upper genito-urinary tract. All radiologic studies should be corroborated by pelvic examinations under anesthesia for a conclusive diagnosis. Pre-surgical diagnosis is helpful, however, for appropriate surgical preparation [13]. It is also crucial to differentiate these patients from those with an atretic segment of the vagina and those with a high transverse vaginal septum.

There are two broad categories of cervical anomalies: cervical agenesis and cervical dysgenesis. Patients with cervical agenesis have no uterine cervix and the lower uterine segment ends in a peritoneal sleeve [13]. Patients with cervical dysgenesis can be divided into four subtypes:

1. A cervical body consisting of a fibrous band extending towards the vagina that may have endocervical glands
2. Intact cervical body with obstruction of cervical os
3. Stricture of the midportion of the cervix, which is hypoplastic, with a bulbous tip
4. Fragmentation of the cervix with no portions connected to lower uterine segment [14] (Fig. 23.1).

Management

Current management recommendations are based on case reports and literature reviews; there have been no randomized trials to elucidate best surgical practice. This chapter summarizes surgical recommendations from several different reviews of the surgical literature with specific recommendations dependent on each patient's specific cervical anatomy.

Traditionally, hysterectomy was advocated as the treatment of choice for these patients. Early attempts to create uterovaginal anastomosis resulted in a variety of serious surgical complications, including endometritis, pelvic inflammatory disease, sepsis, and injury to other pelvic organs including bowel and bladder. Even if a passage is created through fibrous tissue between the uterine cavity and the vagina, there are not typically functioning endocervical glands. The resulting absence of cervical mucus creates a difficult environment for sperm transport for patients desiring fertility.

Furthermore, patients are also subjected to long-term post-operative complications. Endometriosis can develop along the fistulous tract and these patients are also at higher risk for retrograde menstruation, increasing the likelihood of endometriosis in the pelvis [14]. The tract can re-stenose, requiring the need for repeat operations for further scar tissue [2, 14]. Recurrent pelvic infections after attempted fistulous tract formation can also eventually result in a hysterectomy and, if the infections are severe enough, bilateral oophorectomy [14].

Since the 1990s, however, there has been a shift towards attempting anastomosis of the utero-vaginal tract for reconstruction. This shift parallels advancement in surgical techniques and the availability of broad-spectrum antibiotics. There are, however, a few peri-operative considerations for patient selection to obtain higher rates of a successful surgical outcome, typically defined as long-term patency of the cervical canal, with subsequent cyclical menstruation and the possibility of pregnancy. Ideal surgical patients have a larger amount of cervical stroma and the presence of rudimentary endocervical glands. Rock et al. defines sufficient amount of cervical stroma as being at least 2 cm in diameter [15]. In addition, there should be a small discrepancy between the size of the uterine muscularis and vaginal stroma for ideal juxtaposition of the anastomotic site to decrease scarring [13]. Patients with vaginal agenesis tend to have more complicated surgeries due to the requirement of additional grafting of the neovagina.

As data for reconstructive surgery comes from smaller case reports, it is important to have an honest discussion pre-operatively with the patient disclosing the risks of surgery. In addition, it is helpful to obtain thorough imaging to attempt a pre-surgical diagnosis as noted above.

Once surgery is begun, the pelvic anatomy is carefully defined and the vesicouterine and recto-uterine space are fully developed. It is imperative

that the surgeon develop these spaces to determine whether there is sufficient cervical tissue for possible coring or anastomosis of cervical fragments. If reconstruction is not deemed feasible or if the uterine cavity is hypoplastic, a hysterectomy is performed [15].

If reconstruction is undertaken, surgical techniques vary depending on the amount of cervical

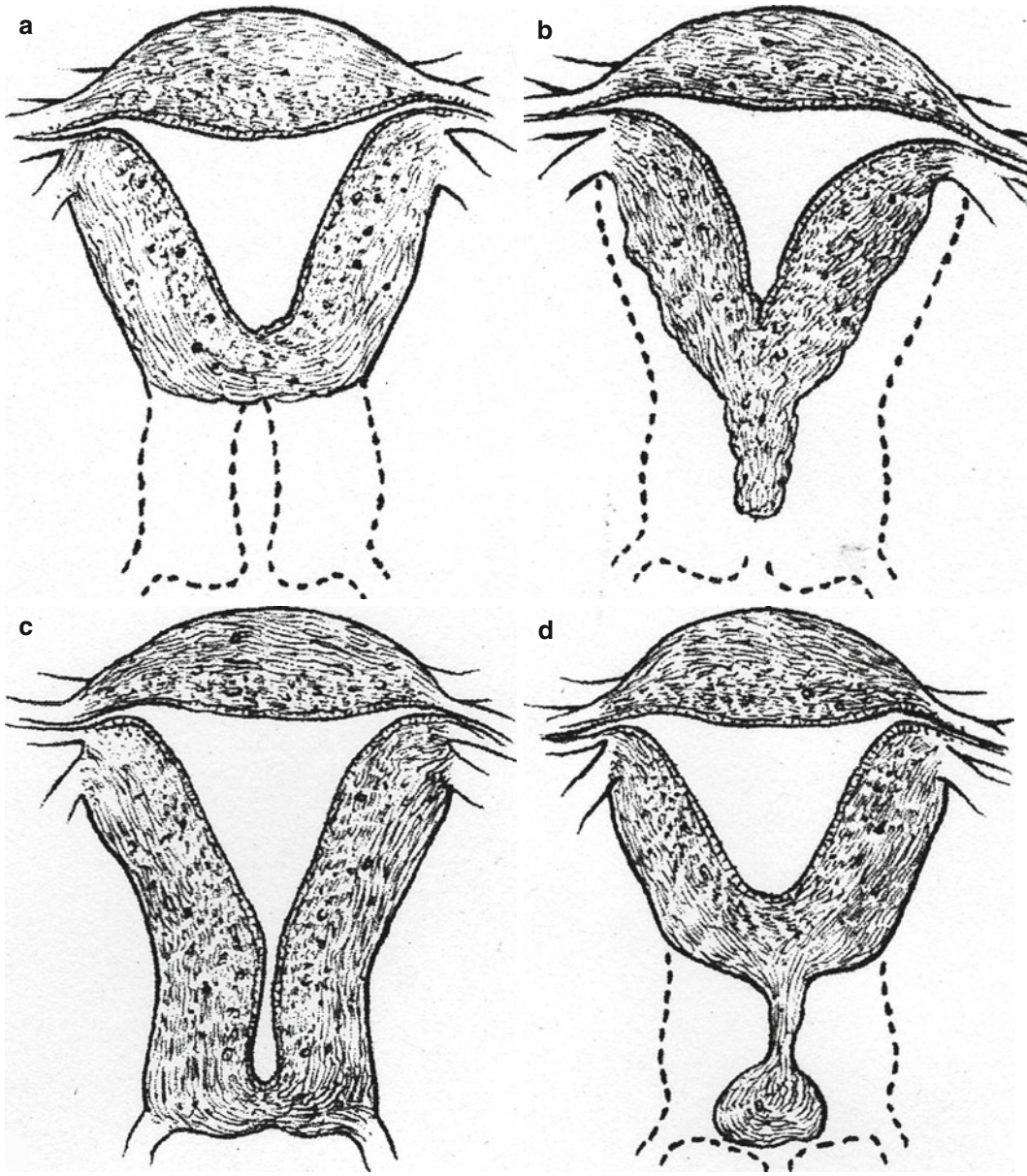

Fig. 23.1 Depictions of cervical agenesis and cervical dysgenesis (With permission from Rock and Jones [14]). (**a**) Cervical aplasia. (**b**) Cervical body consisting of a fibrous band of variable length and diameter that can contain endocervical glands. (**c**) The cervical body is intact with obstruction at the cervical os. Variable portions of the cervical lumen are obliterated. (**d**) Stricture of the midportion of the cervix, which is hypoplastic with a bulbous tip. No cervical lumen is identified. (**e**) Cervical fragmentation in which portions of the cervix are noted with no connection to the uterine body

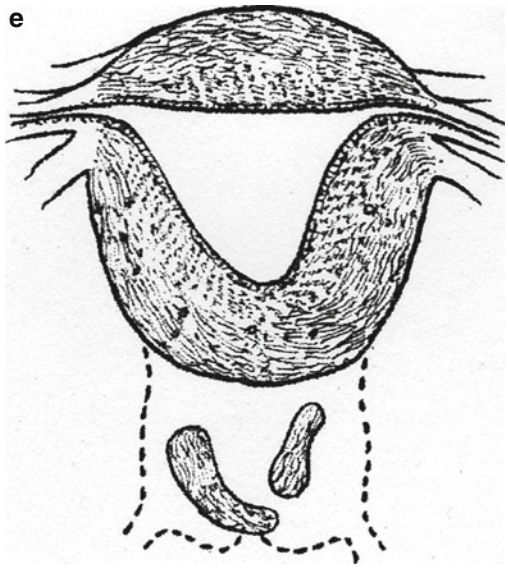

Fig. 23.1 (continued)

tissue present. If there is a small amount of cervical obstruction or a small atretic segment of the endocervical canal with a normal vagina, the surgeon can perform a coring or drilling procedure. During this procedure, the cervix is cored to remove the obstruction. A catheter is left in place, optimally with a full- thickness skin graft around the catheter to allow the tract to epithelialize more rapidly [15]. If there is accompanying vaginal aplasia, the surgeon can perform a vaginoplasty using the McIndoe technique [15].

In the presence of cervical agenesis or dysgenesis with cervical fragments or a fibrous cord, a more extensive surgery, such as an uterovaginal anastomosis, is advocated.

A large case series published by Deffarges et al. in 2000 described the surgical technique of uterovaginal anastomosis in 18 patients with cervical atresia. The patients underwent laparotomies with dissection of the vesicouterine and rectouterine space. An incision on the most superior portion of vaginal tissue was made and a channel formed between the bladder and the rectum until the abdominal anterior and posterior dissections were reached. A 10-mm dilator was inserted through an incision on the uterine fundus and placed at the most inferior portion of the uterus. The atretic vaginal tissue was resected in a similar technique as with a cervical conization until the uterine cavity was entered. The uterus was then sutured in a circumferential manner with 3-0 polyglactine. A 16 French Foley catheter was placed in the canal to maintain patency for 15 days and patients were given Ampicilin for the duration [4].

A similar technique was described by Creighton et al. however the authors incorporated the use of laparoscopy. Laparoscopically, sutures were placed on the uterus for uterine suspension. An incision was made in the uterine fundus with a harmonic scalpel and a probe placed in the uterus to identify the lowermost portion of the uterus, which was incised horizontally. A second probe was placed in the vagina and a laparoscopic incision made over the most superior portion of the vagina. A Foley catheter was passed between the vagina and the uterus and the uterus closed with 2-0 polydioxanone suture circumferentially at 12, 3, 6, and 9 o'clock. In this case, the Foley was left in place for 4 weeks and the anastomotic site remained patent [3].

Other case reports have discussed the need for accompanying the cervical reconstruction with a graft of the neocervical canal to allow for improved healing and decreased stenosis. Possible graft tissue includes full thickness skin grafts [15], bladder mucosa graft, or amniotic membrane (from a case describing reconstruction after cesarean section) [10].

Another surgical technique involves the use of end-to–end anastomosis for the cases of cervical dysgenesis with cervical fragmentation. Grimbizis et al. describes a patient with cervical fragmentation in a symmetrical transverse fashion. They created an end-to-end anastomosis during a laparotomy, connecting the central and distal portions of the cervix and then using a Foley catheter as a stent in the endocervical canal [8] (Table 23.1).

Outcomes of Surgical Management

Reports of outcomes have differed between case series. In a retrospective 2010 review from Rock et al. describing surgical experience from 1940 to 2008, 30 patients with cervical agenesis and dysgenesis were described. Nineteen of the 30 patients underwent hysterectomy and

Table 23.1 Description of suggestive reconstructive surgical treatment

Anatomic findings	Suggested reconstructive surgical treatment
Cervical agenesis	
Present vagina	Anastomosis of lower uterine segment to vagina epithelium
Absent vagina	Suture uterine muscularis to stroma and graft material used to create neovagina
Cervical dysgenesis with cervical fragmentation	
Present vagina	Creation of a lumen by coring out center of cervical fragments or drilling a new lumen with insertion of a stent and optional grafting of neocervical canal. Sew fragments together or remove fragments and create a uterovaginal anastomosis
Absent vagina	Create neovagina using a graft
Cervical dysgenesis with fibrous cord	
Present vagina	Remove cord and perform uterovaginal anastomosis or create a neocervical canal with drilling or coring technique with insertion of a stent (if sufficient diameter cord)
Absent vagina	Removal of cord and uterus and create a vaginoplasty
Cervical dysgenesis with cervical obstruction	
Present vagina	Create a neocervical canal using a drilling/coring technique. Optional grafting of endocervical canal or remove cervix and perform uterovaginal anastomosis Create a neocervical canal using a drilling/coring technique. Optional grafting of endocervical canal.
Absent vagina	Vaginoplasty if required

Adapted from Rock et al. [15]

11 of the 30 had attempted uterovaginal anastomosis. Six of the 11 patients who underwent surgical reconstruction (55 %) eventually underwent a follow-up hysterectomy due to subsequent re-obstruction at the surgical site. The patients with the best outcomes were those with an intact cervical body and an obstructed cervical os; all of those patients (n = 4) had successful menstruation and one of the patients had two viable live births. Of those with cervical dysplasia consisting of a fibrous cord or cervical fragments, nine out of the ten patients ultimately required a hysterectomy [15].

In the case series from Deffarges, all 18 patients with cervical atresia (100 %) had restoration of menses though five (33 %) suffered from postoperative dysmenorrhea. Two of their patients had a low vaginal stenosis and one had secondary cervical stenosis, requiring multiple attempts at recanalization. Four of the patients (22 %) became pregnant spontaneously for a total of six spontaneous pregnancies. All required cesarean sections for delivery [4].

In 2008, Fedele et al. described uterovestibular anastomosis in 12 consecutive patients with cervical and vaginal aplasia. In their case series, all women (100 %) attained regular menstruation and had patency of the neovagina. Interestingly, all 12 of their patients were found to be producing mucus at the uterovaginal anastomosis despite complete cervical atresia on a pre-operative MRI in ten of the patients. The authors hypothesized the most caudal endometrial glands could undergo a "mucinous- secretive metaplasia." None of their patients had attempted pregnancy at the time of publication, so fertility and pregnancy outcomes were not reported [5].

Pregnancy outcomes have been incompletely reported. There have been some reports of pregnancy after reconstruction [4, 9, 15] and after IVF with laparoscopic zygote intra-Fallopian transfer (ZIFT) [17]. There have been two case reports of transmyometrial embryo transfer after in-vitro fertilization in patients with cervical agenesis that had not undergone surgical reconstruction [1, 10]. Most reports describe delivery by cesarean section [4, 9, 17].

Conclusion

Cervical agenesis and dysgenesis are rare Müllerian anomalies for which the management has been based upon small case series. Although hysterectomy has traditionally been the primary mode of surgical management, surgical reconstruction is a possibility for well- selected patients in the form of canalization, uterovaginal anastomosis or the creation of an end-to-end anastomosis depending on the anatomy observed. The majority of well- selected patients have good surgical outcomes with the attainment of cyclical menstruation and a few with subsequent live births.

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Treatment of Patients with Non-communicating Horns with Cavity

24

Theodoros D. Theodoridis and Grigoris F. Grimbizis

Introduction

Rudimentary horns are rare congenital female malformations resulting from embryologic maldevelopment of the müllerian or paramesonephric ducts during the first weeks of fetal life. Uterus is formed from the fusion of the bilateral paramesonephric ducts that first appear at approximately the sixth week of gestation as a finger-shaped invagination of the coelomic epithelium at the upper pole of the mesonephros. These tubular structures are met and fused in the midline to form the unified uterine body by the tenth week of gestation. Thus, the sequence of events during normal müllerian development is: formation, canalization and fusion of the ducts followed by septal resorption.

Failure of one or both müllerian ducts to form and canalize, results in the formation of ***hemi-uterus*** (former unicornuate uterus) ***or uterine aplasia***. Partial development of one or both of the paramesonephric ducts results in formation of rudimentary uterine horn with or without functional cavity, depending on the canalization of that partially developed duct. The embryologic tendency of dominance of the right-side unicornuate uterus remains unexplained. Moreover, in some cases of ***uterine aplasia***, characterized by the absence of any fully or unilaterally developed uterine cavity, bi or unilateral rudimentary horns with cavity can be found, while in others, only uterine remnants without cavity.

The aim of this chapter is to present the clinical manifestations and the various alternatives for the treatment of rudimentary horns with cavity in cases of vaginal aplasia and hemi-uterus, by reviewing all the available data from case series and case reports. Complications and questions raised for the proper management are also addressed.

Rudimentary Horns with Cavity: Anatomic Variants and Classification

The recently introduced European's Society of Human Reproduction and Embryology (ESHRE) and European's Society for Gynaecological Endoscopy (ESGE) Classification of female genital anomalies aims to provide a more suitable classification system for the accurate, clear, and simple categorization of female genital anomalies, that is correlated with clinical management [31, 32]. It was generally accepted that the previous American's Fertility Society (AFS) Classification

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ESHRE/ESGE Classification

Classification of rudimentary horns with cavity

	Uterine anomaly		Cervical/Vaginal anomaly	
	Main class	***Sub-class***	***Co-existent class***	
U0	Normal uterus		***C0***	*Normal cervix*
U1	Dysmorphic uterus	**a.** T-shaped **b.** Infantilis **c.** Others	***C1***	*Septate cervix*
U2	Septate uterus	**a.** Partial **b.** Complete	***C2***	*Double "normal" cervix*
U3	Bicorporeal uterus	**a.** Partial **b.** Complete **c.** Bicorporeal septate	***C3***	*Unilateral cervical aplasia*
U4	**Hemi-uterus**	**a. With rudimentary cavity (communicating or not horn)** **b.** Without rudimentary cavity (horn without cavity/no horn)	***C4***	*Cervical aplasia*
U5	**Aplastic**	**a. With rudimentary cavity (bi- or unilateral horn)** **b.** Without rudimentary cavity (bi-or unilateral uterine remnants/Aplasia)	***V0***	*Normal vagina*
			V1	*Longitudinal non-obstructing vaginal septum*
			V2	*Longitudinal obstructing vaginal septum*
			V3	*Transverse vaginal septum and/or imperforate hymen*
			V4	*Vaginal aplasia*
U6	Unclassified malformations			
U			***C***	***V***

Fig. 24.1 ESHRE/ESGE classification of uterine horns with cavity: hemi-uterus with rudimentary cavity (Class U4a) and aplastic uterus with rudimentary cavity (Class U5a)

System [4] as well as the other proposals for the categorization of the anomalies [1, 51] were associated with several disadvantages [33].

Thus, ***hemi-uterus*** is classified as ***ESHRE/ESGE Class U4*** [31, 32]; a rudimentary horn, cavitated or not (depending on the presence or absence of an endometrial cavity), could be also present. Cases of ***hemi-uterus with rudimentary horn having cavity*** are classified as ***ESHRE/ESGE Class U4a*** (Fig. 24.1); they are clinically important and rudimentary cavity might or might not communicate with the main uterine cavity of the hemi-uterus. There are two anatomical variations concerning the attachment of the rudimentary horn to the unicornuate uterus. The former can either be attached by a band of tissue, or attached firmly to the latter [22].

On the other hand, ***uterine aplasia*** is classified as ***ESHRE/ESGE Class U5***. Cavitated or non-cavitated rudimentary horns could be also present in those women; cases of ***uterine aplasia with uni- or bilateral rudimentary cavity*** are clinically significant variants and they are sub-classified as ***ESHRE/ESGE Class U5a*** (Fig. 24.1) [31, 32].

Incidence of Rudimentary Horns

The true incidence of female congenital malformations is unknown. The use of diagnostic methods with different accuracy, the subjectivity in the criteria used for diagnosis and classification of the anomalies and the drawbacks of the existing classification systems represent the main biases for that [33, 64]. Moreover, in some studies the population was not representative whereas the existence of undiagnosed cases is another potential bias, as many of the patients with malformations may be asymptomatic without ever reporting any gynaecological or reproductive problem.

Reports in the literature estimate that the incidence of female genital anomalies in general population varies between 4.3 and 6.7 %, while in women with fertility problems between 3.4 and 10.8 %. In patients that suffer from recurrent miscarriages, congenital anomalies are reported to range between 12.6 and 18.2 % [34, 64]. In a more recent review of 94 observational studies comprising 89.861 women, the prevalence of uterine anomalies diagnosed by optimal tests (investigations that are capable of accurately identifying and classifying congenital uterine anomalies accurately) was found to be 5.5 % [95 % confidence interval (CI), 3.5–8.5] in the general/unselected population, 8.0 % (95 % CI, 5.3–12) in infertile women, 13.3 % (95 % CI, 8.9–20.0) in those with a history of miscarriage and 24.5 % (95 % CI, 18.3–32.8) in those with miscarriage and infertility [9].

In a systematic review of studies using high-accuracy diagnostic methods, the mean ***prevalence of unicornuate uterus (currently ESHRE/ESGE hemi-uterus)*** was found to be 0.4 % in general population; in infertile patients it was 6.1 % and in recurrent miscarriage patients 2.3 % respectively [64]. In another more recent review overall 0.1 % (95 % CI, 0.1–0.3) of the unselected population had a unicornuate uterus diagnosed by an optimal test. It is important to note that unicornuate uterus was found to be significantly more common in women with a history of miscarriage (0.5 %; 95 % CI, 0.3–1.1; $P=0.025$), miscarriage in association with infertility (3.1 %; 95 % CI, 2–4.7; $P<0.001$) and infertility (0.5 %; 95 % CI, 0.3–0.8, $P<0.01$) when compared with the unselected population [9]. ***Rudimentary horns with cavity*** are found in 74 % of unicornuate uteri. The prevalence of non-communicating horns is 70–90 % [39].

Patients with aplastic uterus usually have co-existent defects and mainly vaginal aplasia, the well-known Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome ***(ESHRE/ESGE Class U5/C4/V4)***. The reported incidence of MRKH syndrome is 1/4,000 [3]. The presence of uterine remnants is not rare; in a cohort of 284 patients with MRKH syndrome 84.2 % had bilateral and 9.5 % had unilateral rudimentary or aplastic horns [52]. However, only a minority of them are rudimentary horns with functional cavity; in a cohort of patients with MRKH syndrome, 7.5 % of them had rudimentary cavity >4 cm ***(ESHRE/ESGE Class U5a)*** [23].

Diagnosis

The diagnosis of these anatomical malformations is not an easy task. Bimanual examination can miss the presence of a small non-communicating horn and possible luck of symptoms may disorient the clinicians from the correct diagnosis. The extensive use of transvaginal ultrasound proved an effective diagnostic tool to evaluate the presence of a rudimentary horn. Traditionally, Magnetic Resonance Imaging (MRI) has been considered the best noninvasive method for diagnosing those Müllerian anomalies (Fig. 24.2). MRI provides excellent delineation of both the internal and external uterine contours and enables measurement of the intercornual diameter, visualization of the endometrial contour, and identification of a uterine horn should one be present [17]. MRI has been quoted as having an accuracy of up to 100 % in correctly identifying müllerian anomalies [58].

Like MRI, three-dimensional ultrasound (3D US) allows the assessment of both the internal and external uterine contours. The addition of the coronal plane enables visualization of the cavity and fundus; 3D US and Doppler studies further enable the study of vascularization and the calculation of the uterine cavity volume. The accuracy

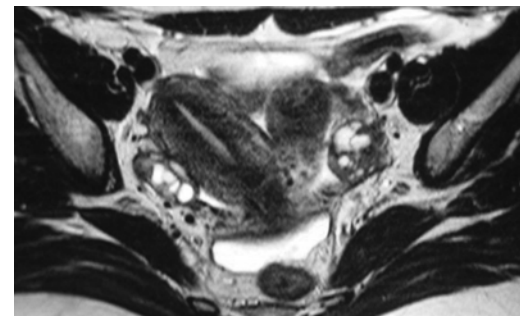

Fig. 24.2 Right hemi-uterus with a left non-communicating rudimentary horn with cavity: magnetic resonance imaging (MRI) findings

of 3D US in the diagnosis of uterine malformations has been reported to be very high with a sensitivity of 98 % and specificity of 100 % [18]. In another study comparing MRI with 3D US for the diagnosis and classification of uterine anomalies, images obtained from each modality were practically equivalent. The authors argued that 3D ultrasound was a valid alternative to MRI, considering its lower cost and that it improves patient tolerability [7].

As there is an association between obstructive müllerian anomalies with renal abnormalities and endometriosis, pre-operative assessment for renal anomalies by renal ultrasonography or intravenous pyelography should be performed routinely. MRI may also aid in the diagnosis. Once the diagnosis is made, other useful information includes the type of attachment and communication between the rudimentary horn and unicornuate uterus, the presence of a cavity in the horn, and the size of the hematometra.

Hemi-uterus with Rudimentary Cavity (ESHRE/ESGE Class U4a)

Clinical Presentation

Hemi-uteri with rudimentary cavity are susceptible to many gynecologic and obstetric complications; endometriosis, primary infertility, hematometra, and urinary tract anomalies are common in those women [25, 36]. However, *non-communicating* cavitated rudimentary horns are the most clinically significant as they are more likely to be associated with pelvic pain from hematometra or from endometriosis due to retrograde menstruation from the existing functional endometrium. It seems that, the prevalence of endometriosis in patients with hemi-uterus was significantly greater than that in patients with other non-obstructive Mullerian anomalies [24, 36]. Such horns often require surgical resection for symptoms relief. The symptoms associated with functional non-communicating horns result mainly from cryptomenorrhea. The presentation varies from progressive or chronic pelvic pain following menarche, to a more acute-onset abdominal pain or a more delayed-onset of dysmenorrhea [39].

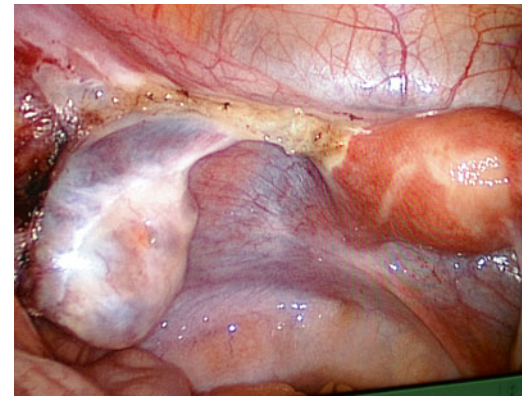

Fig. 24.3 Laparoscopic view after removal of a left non-communicating rudimentary horn with cavity together with the ipsilateral tube

Treatment

Excision of the Rudimentary Cavity

The excision of the rudimentary horn is the proposed treatment; since its first documentation [8], laparoscopic management of unicornuate uterus with rudimentary horn is the preferred alternative method to laparotomy. The ipsilateral fallopian tube should be removed to prevent tubal pregnancy in the future [26, 70] (Fig. 24.3). If the contralateral tube is damaged then microsurgical Fallopian tube transposition can be considered [28].

Laparoscopy offers the advantage of a shorter hospital stay, quick recovery, less postoperative pain and fewer short- and long-term complications such as infections and adhesions. In addition, smaller incisions are made leading to minimal abdominal scar formation. The shift to laparoscopic surgery for uterine rudimentary horns excision follows a similar trend in the introduction of minimally invasive surgical approaches for hysterectomy and myomectomy.

Preoperative treatment with a GnRH-analogue or danazol has been suggested aiming to reduce the size of hematometra before surgery [44, 50]. Other authors reported excellent laparoscopic results without application of any medical treatment prior to surgical laparoscopic management [26, 70].

The laparoscopic procedure is greatly influenced by the extent of the anatomical connection

between the rudimentary horn and the unicornuate uterus. When the attachment is very broad, the endoscopic procedure tends to be tougher. In fact, the cleavage plane between the unicornuate uterus and the rudimentary horn is not well defined. The firmly attached rudimentary horn is likely to receive its blood supply not only from the ipsilateral uterine artery, but also from the myometrial arcuate arteries of the contralateral uterine artery, which need to be carefully occluded during dissection [22, 59].

A key aspect during laparoscopic surgery is avoidance of damage to the remaining hemi uterus so as to preserve fertility. Surgical removal of the attached horn may leave a myometrial defect that has to be repaired. Application of sutures requires good laparoscopic skills, and experience in intra-corporeal or extra-corporeal suturing is essential. If such intervention occurs, Caesarean section should be the mode of delivery in future pregnancies, due to increased risk of rupture of the repaired hemi-uterus. The use of both scissors and electrosurgery for the dissection has been reported [22, 26, 70]. However, with the recent advances in laparoscopic equipments, an ultracision energy scalpel has been also used for more accurate and easier dissection [12]. The simultaneous use of hysteroscopy to separate the two horns and the use of automatic endoscopic staplers instead of diathermy have also been reported [44, 50, 59]. The procedure can also be assisted by robotic technology [66].

In cases that the non-communicating rudimentary horn is firmly attached to the hemi uterus laparoscopic surgery becomes more complex. Cautious surgery to avoid damage to the remaining uterus can result in retention of functional tissue from the contralateral side and later recurrence with further menstrual obstruction [48].

In all cases identification of the ureter is essential and in some cases anatomical dissection might be necessary to prevent their injury [22, 26, 48, 70]. The excised rudimentary horns can be removed through an enlargement of the suprapubic trocar site [70]. This procedure is easy to perform and also ensures an excellent cosmetic result. Colpotomy or morcellation may be alternative methods, especially in cases where the specimen is large or solid and malignancy is not suspected [26].

Restoration of Continuity

In cases of a cavitated rudimentary horn that is firmly attached to the hemi-uterus, an alternative and more conservative surgical procedure can be applied. Dilatation of the cervix is performed followed by insertion of resectoscope. Preferably under ultrasonograhic guidance, incision is made at the uterine cavity surface that is in contact with the rudimentary cavity, till the continuity of the cavities is restored. As soon as the rudimentary cavity is identified, the incision is extended up to the rudimentary cavity margins.

This technique most likely eliminates the clinical symptoms from haematometra and allows functionality of the cavity. On the other hand, if such interventions are applied attention should be given in the possibility of a future pregnancy in the restored rudimentary horn cavity and its consequenses.

Rudimentary Horn Pregnancy and its Management

Pregnancy in the rudimentary horn is a rare complication and can become possible when sperm migration occurs through the peritoneal cavity. The natural course of a rudimentary horn pregnancy is rupture during the first or mid-second trimester; in the majority of cases, horn rupture occurs before 20 weeks resulting in a life threatening heavy intra-peritoneal bleeding associated with high maternal mortality rates [14]. Reports of rupture in the third trimester of pregnancy have been also described. The term “ectopic” is adopted for horn pregnancies due to their dramatic natural course. Rupture is attributed to the compromised thickness of the poorly developed horn musculature and impaired distensibility of the myometrium [14, 41, 54].

Fetal survival could not be excluded, but even then the prognosis is poor, with an increased risk of miscarriage, fetal growth restriction, oligohydramnios, preterm labor and fetal malpresentation. Intrauterine growth restriction and

intrauterine fetal death are presumed to be secondary to the poor vasculature of the horn and, placenta accreta secondary to the poorly formed endometrium [27, 36, 38, 49].

Its estimated prevalence is one out of 76,000–150,000 pregnancies; 5.3 % of them are twins [49]. The mortality rate has been reduced from 23 % at the turn of the twentieth century to 0.5 % nowadays. Fetal survival was only 6 % [49]. The dramatic improvement in maternal mortality rates is likely to be related to an increase in pre-rupture diagnosis and prompt intervention. However, sensitivity of ultrasound for the diagnosis of rudimentary horn pregnancies remains poor and is less than 30 % [10, 39, 40].

Delay in diagnosis and hemorrhage may result in an adverse pregnancy outcome in such cases. Prompt intervention is necessary to remove the horn and its tube when a diagnosis of pregnancy is made. Because in most cases of uterine horn rupture occurs in the second trimester, early diagnosis in the first trimester provides time to take measures that can minimize surgical risks. Laparotomy in these cases is always mandatory. However, early diagnosis of pregnancy has recently facilitated management of rudimentary horn pregnancy by laparoscopic means [20].

Most cases of rudimentary horn pregnancies provide a diagnostic challenge and are diagnosed after rupture, leading to emergency surgery, blood transfusion, and increased morbidity [68]. Three-dimensional ultrasound imaging and MRI are useful tools with improved diagnostic accuracy, guiding both counseling and surgical planning. It is important to emphasize that, although cases of neonatal survival have been reported, life-threatening uterine rupture and hemorrhage at early gestational weeks remain the most likely outcomes, and neonatal survival is still rare [5, 41, 54].

Differential diagnosis of rudimentary horn pregnancy includes ectopic pregnancy, appendicitis, intestinal perforation, and even peptic ulcer disease. The common misdiagnoses on ultrasound includes bicornuate uterus with pregnancy in one horn, uterus didelphys, abdominal pregnancy, or even normal intrauterine pregnancy with an adnexal mass undergoing torsion [11, 21, 38, 62, 68].

The contour of the uterine cavity, the number of interstitial tubes, communication between the gestational sac and uterine cavity, continuity of the myometrium surrounding the sac with the uterus, the presence of a connecting vascular pedicle, and the mobility of the gestational sac could help in distinguishing intrauterine pregnancy in an anomalous uterus, from tubal, interstitial, abdominal, and cornual pregnancies [46]. Pseudo pattern of asymmetrical bicornuate uterus, absent visual continuity between cervical canal and lumen of pregnant horn, and the presence of myometrium surrounding the gestational sac can be also criteria for the antenatal diagnosis of rudimentary horn pregnancy [71]. Other criteria that can help in ultrasonographic diagnosis include greater distance between the horns, US with the use of intrauterine Foleys, hyper-vascularity of the placenta, the presence of very thin surrounding myometrium, the presence of placenta accreta, intraperitoneal free fluid, and the presence of an empty uterus and an ectopic gestational sac [68].

Three-dimensional ultrasound imaging and MRI have proved useful for a detailed evaluation of the fetus and the placenta and they both characterize more accurately the pregnant and non-pregnant uterine malformations [60, 63, 71]. MRI, though many times is limited by expense and availability, is a better diagnostic tool as it provides better differentiation of the anatomical structures inside and outside the uterus in both axial and coronal sagittal planes. It can be used for diagnosing uterine anomalies, communication of the uterine cavity and horn, and for planning surgery by localizing the position of its attachment [53].

Prompt intervention is necessary to remove the horn and its tube when a diagnosis of pregnancy is made. Surgical excision of the rudimentary horn and ipsilateral fallopian tube is the gold standard of management. Traditionally, such surgical resection has been accomplished via laparotomy, but with increasing expertise in laparoscopic surgery there have been several reports of endoscopic management of the pregnant rudimentary horn. Removal of the ipsilateral fallopian tube is essential [13, 19, 20, 37, 56, 65, 73].

The principles of surgery are similar to that in the non-pregnant state. However, in the pregnant

woman the pedicles are likely to be more vascular. Medical management with methotrexate and potassium chloride followed by gonadotrophin-releasing hormone injections have also been used pre-operatively to reduce the blood loss from the associated placenta accreta. This enables a delayed laparoscopic excision of the uterine horn in a safe and less invasive manner [13, 21, 56, 69].

Aplastic Uterus with Rudimentary Cavity (ESHRE/ESGE Class U5a)

Clinical Presentation

Women with aplastic uterus, associated usually with cervical and vaginal aplasia in the context of MRKH syndrome, present with primary amenorrhea. The presence of a rudimentary cavity is an important factor as it can be responsible for symptoms in the clinical presentation of women with such malformations, mainly cyclic recurrent lower abdominal pain. The escalating pain inevitably leads to the need of surgical intervention; removal of the remnant hematometra and in some cases of the coexisting hematosalpinx as well is an established treatment alternative [6, 29].

Treatment

Excision of the Rudimentary Cavity

Treatment strategy for these patients is not well defined. Removal of the remnants of the müllerian ducts by laparoscopic means in patients with MRKH has been described in the literature [45, 57, 72]. Prophylactic removal of uterine rudiments in women with MRKH is still controversial. The pain is clearly not dependent on the presence of endometrium within the uterine rudiments. In a recent study of women with MRKH only 46.2 % of patients reported cyclic lower abdominal pain and 41.4 % of asymptomatic patients had evidence of endometrium in the rudimentary horn [61]. Cyclically recurrent lower abdominal pain resulting from endometrial proliferation within uterine rudiments, from endometriosis and myomas has been described in 6–10 % of patients with MRKH syndrome [47, 30, 55, 15, 16, 42, 43]. The incidence of pelvic endometriosis resulting from retrograde menstruation in patients with MRKH having rudimentary cavity is high and laparoscopic excision has been proposed as the preferred procedure when the uterine remnants and pelvic endometriosis cause cyclic pelvic pain [2].

It is generally accepted that the presence of such malformations does not necessitate treatment unless the patient is symptomatic. Removal of such rudiments should be individualized and may be an alternative option in symptomatic patients in whom other underlying causes of pain have been excluded [61].

Restoration of Continuity (Isthmo-Vaginal Anastomosis)

In cases of MRKH patients with rudimentary functional uterine horns an alternative surgical approach can be offered and that is the utero-vaginal anastomosis and restoration of menstrual function.

Neovagina creation, metroplasty (incision of the uterine bulbs, surgical consolidation of the uterine horns and creation of a large uterine cavity) and utero-neovaginal anastomosis can lead not only in the function of the horn but in successful pregnancy as well [67].

The successful laparoscopic Davidov's vaginoplasty and abdominal isthmo-neovagina anastomosis in a two-step surgical procedure resulting in adequate menstruation has been also recently documented [35] (Fig. 24.4). The anatomic restoration of the genital tract in these patients appears to have good outcomes and leads to functional menstruation and restitution of the sexual life. Therefore, the strategy of removing uterine tissue in MRKH patients is strongly challenged and should be individualized. Proper patient selection and careful preoperative workout with detailed information regarding the procedure steps are key points in the management of these patients.

Conclusions and Issues Open for Further Research

Rudimentary horns are rare female congenital anomalies with a wide spectrum of clinical symptoms and complications; they are found either with hemi-uterus, classified as ESHRE/

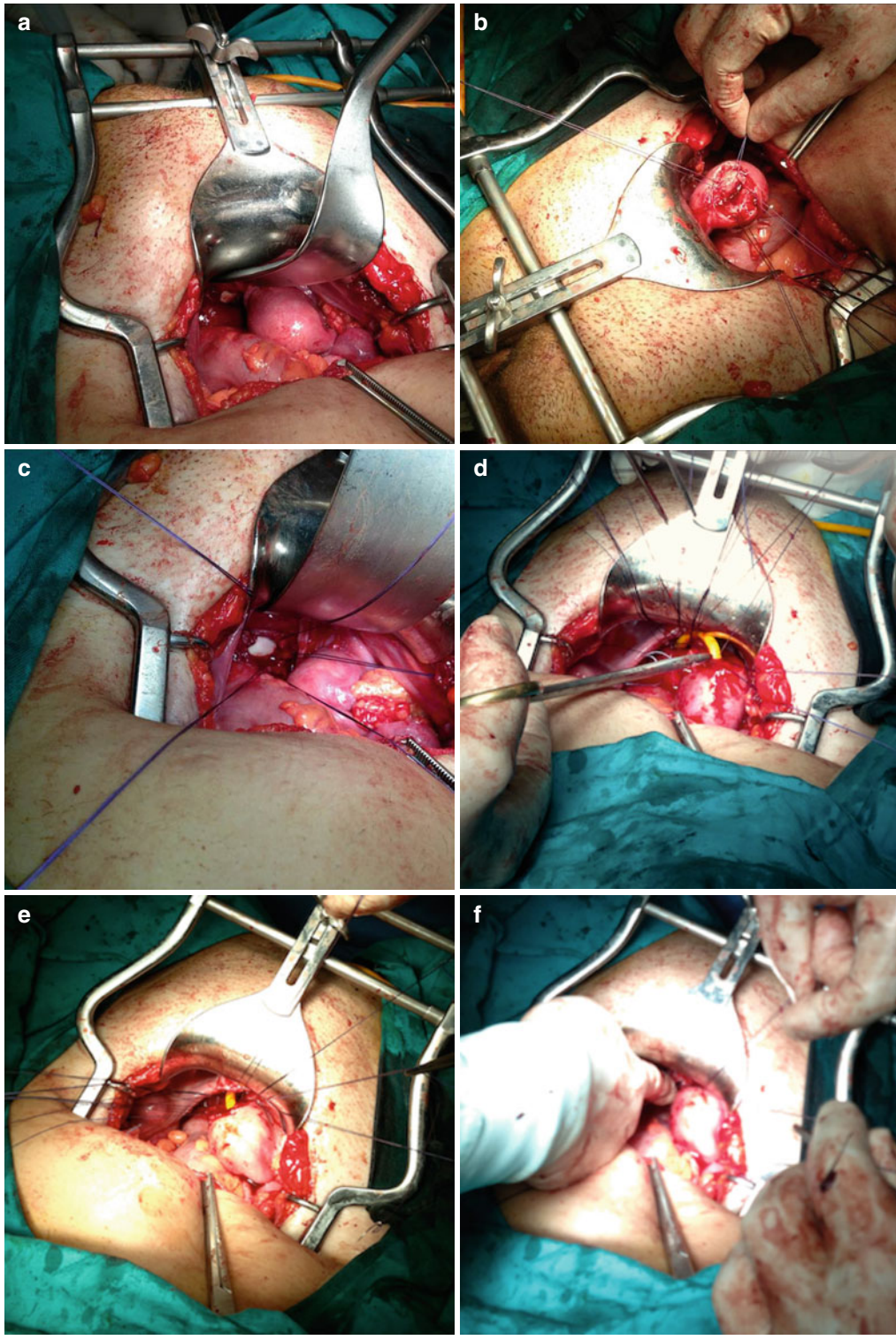

Fig. 24.4 Horn-neovagina anastomosis in a MRKH patient with RT rudimentary horn with cavity: (**a**) rudimentary (RT) horn with cavity in a MRKH patient (uterine and vaginal aplasia) previously who underwent neovagina formation with Davydov's technique (peritoneal vaginoplasty), (**b**) opening of the uterine's horn isthmus, (**c**) opening of the neovagina, (**d**) insertion of a folley catheter through the neovagina and fixation into the uterine's horn cavity, (**e**) isthmo-neovagina anastomosis using the inserted folley catheter as a stent and, (**f**) final result

ESGE Class U4a, or uterine aplasia classified as ESHRE/ESGE Class U5a. Although various diagnostic methods have been used for their diagnosis, 3D US and MRI have the highest accuracy and objectivity. Surgical removal of the cavitated horns appears to be the established method of treatment of rudimentary horns for symptoms relief and avoidance of complications. Laparoscopy has advantages over classical surgery. Another surgical treatment alternative in highly selected cases is restoration of continuity.

However, it seems that there are still some open issues in the management of patients with rudimentary cavities. Is surgery of rudimentary horns really indicated for all patients or only for symptomatic ones? Is the removal of the rudimentary horns the indicated method of treatment in all cases? Is the alternative surgical option of continuity restoration a safe options, which are the benefits and what are the criteria for choosing that kind of treatment? At what age is surgical approach most convenient? It seems that larger number of patients is essential to withdraw valuable conclusions.

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Part VI

Treatment of Uterine Malformations

T-Shaped Uterus

25

Rose Meier and Rudi Campo

Introduction

The dysmorphic uterus or class U1 according to the new ESHRE/ESGE classification, differentiates from the normal uterus by only a subtle deformation of the uterine cavity. The T-shaped uterus (U1a) is a subset of the dysmorphic group, characterized by a narrow cavity due to thickened lateral walls, with a normal cervix-corpus ratio and normal thickness of the fundal myometrium [20, 21]. A combination of T shape with a fundal increased myometrial thickness can be allocated to the U1c to provide the clear differential diagnosis between T shaped (U1a), infantilis (U1b) and the mixed forms (U1c). During the last decades, the T-shaped uterus (TsU) has received special attention due to its association with in-utero exposure to diethylstilbestrol (DES). During the late 70' and early 80', several reports associated DES with congenital uterine malformation, particularly TsU [22, 28]. Nevertheless other factors can be implicated in the development of this condition and the TsU can be found in DES non-exposed patients [32].

This malformation is considered an infrequent condition, although its real prevalence is difficult to estimate. The lack of appropriate classification systems in the past to uniformly and unbiasedly allocate this malformation to a group has probably contributed to an under-reporting of this subtle uterine malformation. Also, the lack of awareness of the condition by health providers and the possibility of an asymptomatic presentation reduced even more the accuracy of the registry. In the infertile patient, the possible importance of a TsU was described in a prospective registration of 530 consecutive infertility women, in whom 13 % congenital malformations were diagnosed. Within this group 66 % was uterine septum, 33 % T-shaped uterus and 1 % others [8].

Due to the administration of DES hormone during early pregnancy from the 50s until the late 60s, we have a significant iatrogenic increase in the incidence of TsU [37], and this specific population has been studied extensively [28]. Kaufman has reported the risk for infertility increased by 1.49 in the presence of a T-shaped configuration, by 2.26 in the presence of mid constriction, and by 2.63 when both anomalies were present [30]. Even the pregnancy outcome appears often compromised, with higher rates of ectopic pregnancies, abortions and premature deliveries [7, 29, 30, 37, 39], while the rate of implantation after in vitro fertilization is decreased [26, 31,

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36]. Although this group of patient has now left the reproductive age and will not contribute to the prevalence anymore, an important question is if the observations made with the DES uterus can be translated to the non-DES exposed T uterus.

The first description of the hysteroscopic surgical treatment in patients with TsU and impaired fertility was done by Nagel and Malo in [34]. They proved the feasibility to enlarge the uterine cavity through incisions in the lateral walls. Also the clinical outcome was successful. Further reports, using electrosurgical needles or the resectoscope reported similar surgical results and clinical outcome [2, 3, 15, 16, 27]. Unfortunately most of the studies do not reach the scientific level to draw firm recommendations.

Surgical Management

Diagnosis

Accurate diagnosis of the uterine malformation is the corner stone of a correct treatment. In ideal conditions, the complete evaluation of the uterus can be done in a one-stop procedure. The "one stop uterine diagnosis" (Fig. 25.1) performs in one session, without any form of analgesia or anaesthesia, a transvaginal ultrasound, a Trophy or mini hysteroscopy, a contrast sonography and if necessary a tissue sampling. For the tissue sampling, the new Trophy hysteroscope provides the possibility to do this in a one-stop action by replacing the optic of the Trophy by a special suction curette (Karl Storz endoscope, Tuttlingen). After the endometrial curettage, the optic is reintroduced and the exact anatomical area of tissue sampling can be visualized (Fig. 25.2). This can be of interest if we want to document the presence of endometrial cells along the long arm of the T and correctly differentiate the pure T shape and the mixed forms from the uterus infantilis. Through this approach, we will define which kind of surgery has to be performed. In case of an unclear situation or more complex anomalies, the evaluation should be enlarged with an expert 3D ultrasound, visualising the uterus in the coronal plane for correct judgement [5, 25]. We refer to the appropriate chapters for more discussion on this topic.

Indication and Contraindication for TsU Correction

There are no standardized criteria for reconstructive surgery of a TsU, because many of these patients do not have obvious symptoms and can carry a pregnancy to term [13]. The published results support that the surgery could be beneficial in patients with long term primary infertility, history of implantation failure, repeated miscarriage and preterm delivery [15, 17, 33]. Patients before start of an in-vitro fertilization (IVF) treatment may also benefit from surgery, but prospective randomized controlled trials are lacking to give a firm recommendation.

Patients with a dysmorphic uterus U1b, also referred to as an infantile uterus, we currently do not see an indication for reconstructive surgery.

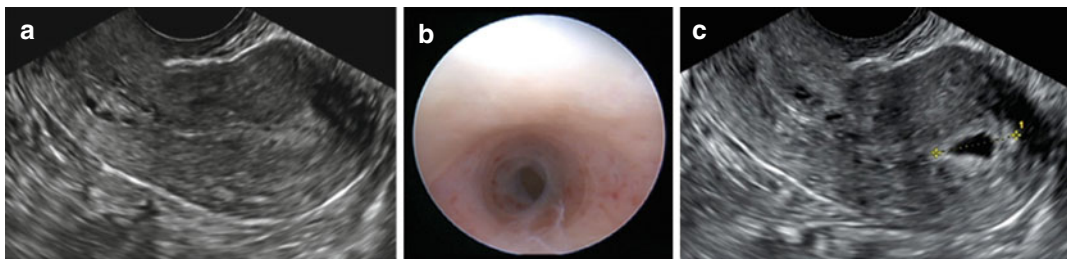

Fig. 25.1 "One stop uterine diagnosis". (**a**) 2D ultrasound; (**b**) Hysteroscopy with the Trophy hysteroscope; (**c**) Contrast sonography showing cavity of less than 2 cm in sagital plane

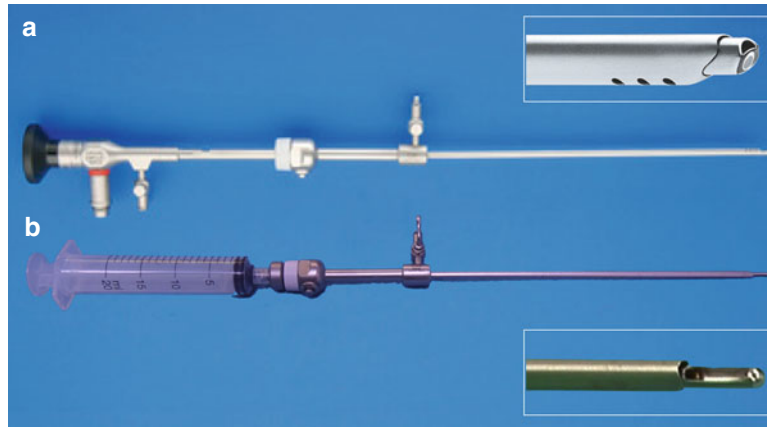

Fig. 25.2 Trophy hysteroscope. (**a**) Trophy hysteroscope with the diagnostic sheath in active position; (**b**) Replacement of the scope by the Trophy suction curette

Ambulatory Setting

In general, the surgery should be performed in an outpatient hysteroscopy service by an experienced surgeon. The surgery is performed under conscious sedation and the patient can leave the facilities after one hour. Surgery is facilitated in case of a thin endometrium and for this reason most of the authors agree to perform the procedure during the early follicular phase of the menstrual cycle or under oral contraception treatment [11].

No cervical preparation is needed before the metroplasty as it is advised to use a small diameter operative hysteroscope. In contrast, dilation of the cervix to allow the insertion of larger instruments, like the 26 Fr resectoscope, increases the risk of cervical lacerations, perforations and the risk of subsequent cervical incompetence [10, 14].

Special cases, as patient with decompensated disease (American Society of Anesthesiologists class III-IV) or coagulation disorders, should be planned in the conventional operating room, due to the higher risk of complication secondary to their base pathology [12].

Different modalities of sedation/anaesthesia have been proposed to perform the surgery. Our group combines propofol with alfetanil to achieve a grade 3 sedation, according to the Observer's Assessment of Alertness/Sedation scale [12]. The scheme is safe and the recovery time is short with low side effect [24]. Other authors perform the surgery under general, regional or local-regional anaesthesia, but here the patient compliance is lower and the recovery time longer [40].

Surgical Strategy

The aim of the surgery is to create the normal pear shape anatomy of the uterine cavity through incisions in the redundant myometrium of the lateral wall and if necessary of the fundus (Fig. 25.3).

The first description of the technique used the hysteroscopic scissors, but since then different reports have been published on the use of the mono or bipolar resectoscope, mini-hysteroscopes with 5 Fr needles or micro-scissors to enlarge the uterine cavity. Mini-Hysteroscopy has brought diagnostic and therapeutic hysteroscopy as a mainstay of modern gynaecological practice. Nowadays, both procedures can be performed in a one-stop sessions at optimal patient comfort. Furthermore, the use of a small diameter hysteroscope and the vaginoscopic approach that follows the anatomical pathway avoids blind cervical dilatation and therefore reduces the risk of cervical trauma, uterine perforations, and postoperative analgesia requirements [9, 19]. It also facilitates working in very small cavities like the dysmorphic uterus.

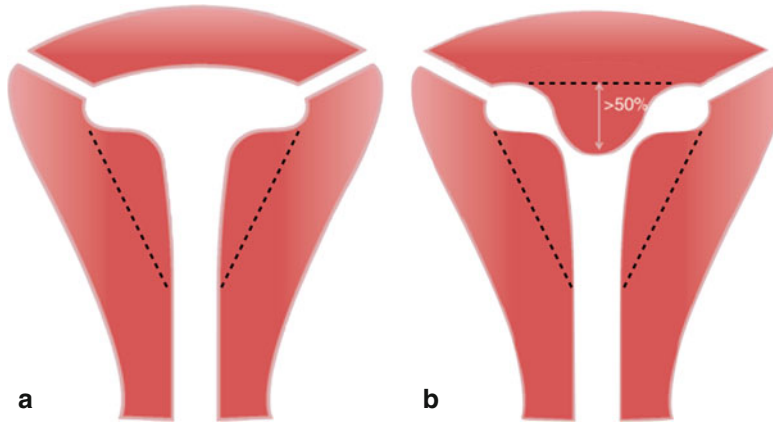

Fig. 25.3 Diagram of the incisions in dysmorphic uterus surgery. (**a**) Lateral incision in subtype U1a; (**b**) Lateral and fundal incisions in subtype U1c

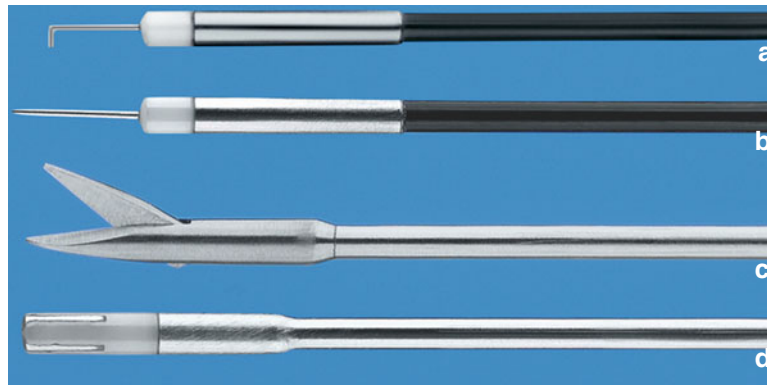

Fig. 25.4 5 Fr instruments possible to use in TsU surgery. (**a**) Bipolar dissection electrode, angled 90°; (**b**) Bipolar needle; (**c**) Sharp scissors; (**d**) Gordts-Campo Bipolar ball electrode

Instruments

Every hysteroscope with a total diameter less than 5 mm, double flow function and an operative channel for 5 Fr instruments is advised for this kind of surgery.

Especially the new Trophy hysteroscope is appropriate for this kind of minimal invasive surgery. It is a new compact 30° rigid 2.9 mm scope with a special designed instrument tip for atraumatic passage through the cervical canal. The innovative feature is that it can be loaded with accessory sheaths in an active and passive position providing a visually controlled dilatation to a maximal diameter of 4.4 mm.

Preferentially the surgery is performed with the 5 Fr sharp scissors, but also bipolar or unipolar needles are used (Fig. 25.4). If a resectoscope is used, the smaller 22 Fr is loaded with the needle to perform the sidewall incisions.

In an ambulatory setting we recommend only to work with bipolar energy and ionic fluid as distension medium, using a flow and pressure controlled pump unit at the lowest required pressure.

Surgical Technique

The surgery starts with a transvaginal ultrasound to measure the fundal myometrium thickness, in order to confirm the diagnosis and evaluate possible additional fundal incision. If the thickness of the fundus is more than 11 mm, the surgery should include an incision of the fundal

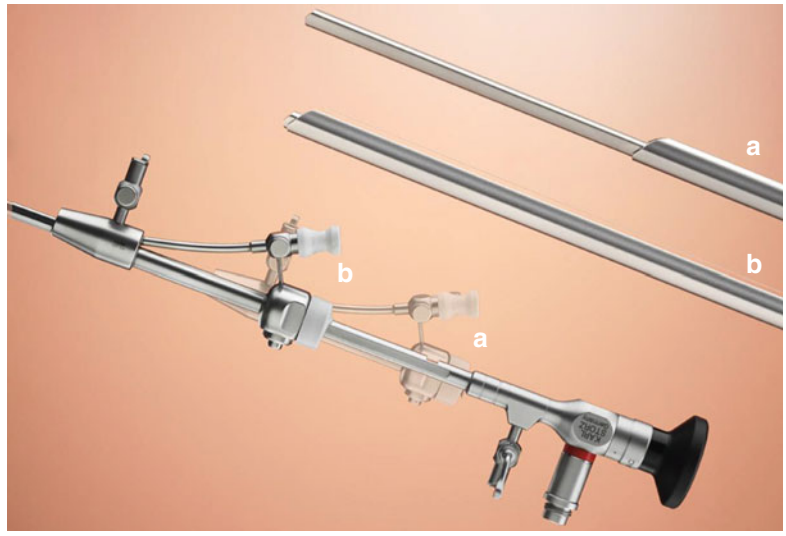

Fig. 25.5 Trophy hysteroscope with the operative sheath. (**a**) Operative sheath in passive position; (**b**) Operative sheath in active position

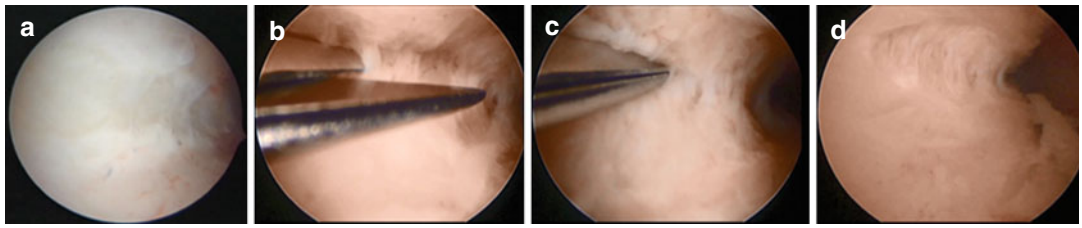

Fig. 25.6 Metroplasty with Trophy hysteroscope and 5 Fr scissors in TsU. (**a**) Demarcation line from the tubal ostium towards the isthmus; (**b**) and (**c**) Lateral incisions with the sharp scissors; (**d**) Alignment of the two referential marks

myometrium as is done in the surgery for a uterine septum.

The hysteroscope is introduced in the uterine cavity and the T shaped form is confirmed. In case of using the Trophy hysteroscope, gentle activation of the operative sheath is performed and a progressive visual dilatation of the cervical canal up to a diameter of 4.4 cm is performed (Fig. 25.5). Using the 5 Fr sharp scissors, an incision line is made from the tubal ostium to the isthmus uteri. Then successive incisions along the line are made from the isthmus to the cornua, keeping the scissors in parallel with the anterior and posterior wall (Fig. 25.6). The incisions are performed to align the internal tubal ostium with the isthmic point of reference achieving a normal pear shape like cavity (Fig. 25.7). The depth of incision is like for the septum incision determined by the anatomical reference, the myometrial vascularisation and a security zone of approx. 10 mm of myometrium measured by transvaginal ultrasound. Myometrial bleeding can be controlled with the use of the bipolar needle or coagulation probe.

In case the surgeon makes the incision with the bipolar needle, the rules of bipolar surgery for good cutting should be met, firm tissue contact before activating the cutting modus. For this reason, we recommend to insert the needle in the uterine sidewall mechanically only then activate the cutting current with a medial movement, taking care to minimize the thermal injury to the sidewall myometrium (Fig. 25.8).

For unipolar surgery and vaporizing electrodes, like the Versapoint® (Gynaecare), the sidewall incision is performed in the conventional way

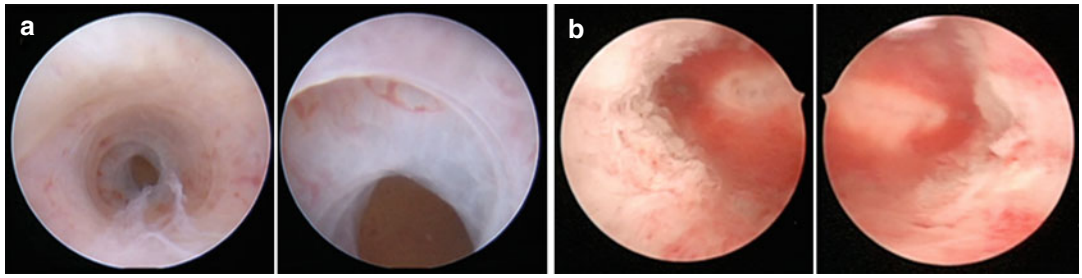

Fig. 25.7 Hysteroscopic view before and after the surgery in U1c malformation. (**a**) Cylindrical cavity of the TsU during the diagnostic phase; (**b**) Normal pear shape like cavity after incisions in the fundus and lateral walls

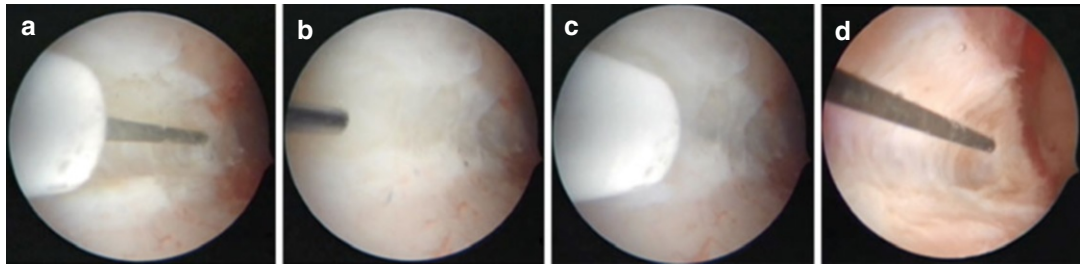

Fig. 25.8 Metroplasty with Trophy hysteroscope and bipolar needle. (**a**) Line from the ostium to the isthmus; and (**b**) start mechanical perforation (**c**) position of bipolar needle before activating power. (**d**) Incision after activating cutting power

with gentle tissue contact in which no mechanical force may be used.

At the end of the surgery, careful control for arterial bleeding is given by lowering the preinstalled pressure by closing the inflow channel. Anti-adhesion gel barrier (Hyalobarrier®, Nordic Pharma), is inserted in the cavity to prevent post-operative adhesions. The use of this modified derivative of hyaluronic acid is based on the principle of keeping the adjacent wound surfaces mechanically separated and by its natural role in modulation the inflammatory phase of wound healing. Its effectiveness in the prevention of intrauterine adhesions after hysteroscopic adhesiolysis was demonstrated by prospective, randomized, controlled studies [1, 18]. Additionally, a recent systematic review and meta-analysis of the literature concludes that the use of APC gel or polyethylene oxide–sodium carboxymethylcellulose gel following operative hysteroscopy decreases the incidence of de novo adhesions at second-look hysteroscopy at 1–3 months [6].

After inserting the barrier a transvaginal ultrasound is performed taking advantage of the contrast to evaluate the results of the surgery with exact measurements of the cavity and myometrial thickness (Fig. 25.9).

Postoperative Care

The main postoperative concern is the possible intrauterine adhesion (IUA) formation and it is questioned if any post-operative measurement can contribute to reduce the risk of adhesion formation.

Oestrogen: Use of oestrogen as perioperative adjuvant therapy has been suggested for preventing recurrent adhesions, based on its critical role in stimulating and enhancing endometrial growth via angiogenesis. A recent systematic review concludes that in patient with IUA, hormone therapy is beneficial, however oestrogen therapy needs to be combined with an ancillary treatment to obtain maximal outcomes [23]. Most of the studies used a sequential oestro-progestative combination for 2 months. We recommend to restrict the indication to patient

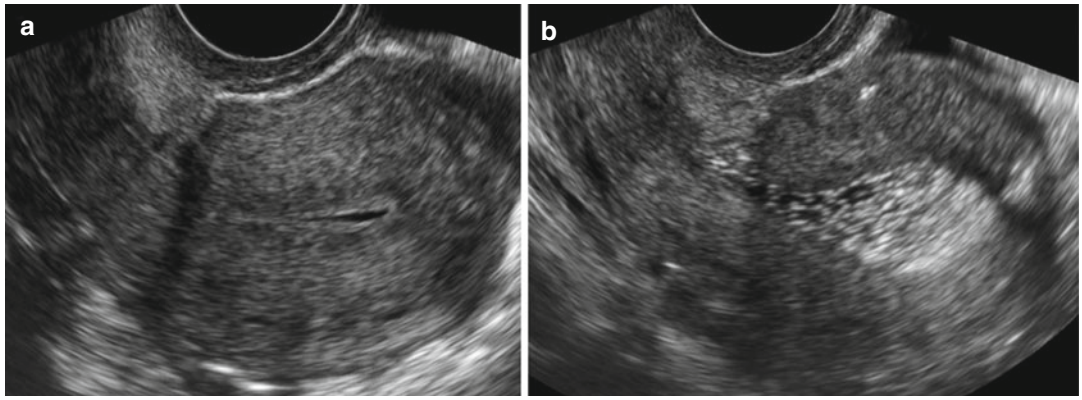

Fig. 25.9 2D Ultrasound in a dysmorphic uterus U1c. (**a**) Pre-surgery, cavity length 18 mm and fundal thickness 13 mm; (**b**) Post-surgery US, cavity length 25 mm and fundal thickness 9.8 mm. contrast is due to hyalobarrier®

with anovulatory or irregular cycles. In case of normal endocrinological profile with regular menstrual cycles no adjuvant oestrogen therapy is recommended.

Antibiotics: The prevalence of infection following an operative hysteroscopy is low, 1 %. Although antibiotic is still used widely after hysteroscopic surgery recent randomised trials do not find any evidence of benefit and recommend not to implement Antibioprophylaxis routinely as it does not reduce the risk of infection [11, 35].

Second-look Hysteroscopy: Most published series report the use of an early hysteroscopy in order to diagnose and remove the adhesions during the same hysteroscopy [11]. In general we perform after two menstrual bleedings, a one-stop uterine diagnosis session as previously described to evaluate the result of the surgery.

Complication

The complication rate during and after TsU hysteroscopic correction is low and can be classified in intraoperative and postoperative complications. The main intraoperative risks are the uterine perforation and haemorrhage. This complication is higher when cervical dilatation is performed and resectoscope is used. In the literature there is only one case of uterine perforation and one case of haemorrhage after T-uterus surgery, reported by [15]. In our data of 100 women operated with the mini-hysteroscope and mechanical energy, no perforations nor haemorrhages were recorded.

Other possible complications like fluid overload, gas embolism, electrosurgical hazards or complications related to the anaesthesia are not reported until now.

The postoperative complications, which should receive attention, are the intra uterine adhesion (IUA) formation, cervical insufficiency and abnormal placentation.

IUA is seen as the most frequent complication after hysteroscopic metroplasty. Aubriot et al. reported in a series of 51 patients operated with the monopolar resectoscope up to 33 % of moderate adhesions [2]. Fernandez using different approaches reports an incidence of 5 % [15]. In our own series of 100 surgeries, using the scissors only, we found one case of moderate adhesion formation and three cases with minimal adhesions.

Abnormal placentation has also been described as complication after surgical correction of TsU. Two cases of placenta accreta published by Aubriot et al. and three cases of placental retention described by our group, where one of them was followed by a severe postpartum haemorrhage. The depth of the myometrial incisions and altered vascularization in patients with TsU could play a role in the pathophysiology.

Cervical insufficiency, Fernandez et al. reported ten cases of cerclage after surgery for TsU in 97 women, from which five cases had a

previous history of cervical incompetence. Confounding factors are the use of cervical dilatation and the antecedent to DES-exposure that can be associated with cervical insufficiency [4]. None of our 100 patients was complicated with postoperative cervical insufficiency.

Clinical Outcome

The results of surgical correction are encouraging in terms of feasibility and reproductive outcome [2, 3, 15, 17, 27, 33, 34]. Today we have two reports on large series evaluating the postoperative outcome after TsU surgery. Both studies are retrospective, but very interesting is that 63 % of the patient collective of Fernandez were DES-exposed, whereas our series of 100 surgeries no DES patient was included.

Fernandez et al. reported on 48/96 women (49.5 %) who became pregnant after the metroplasty, with a mean time until the first conception of 10.5 months (range: 2–36 months). Nine women were pregnant twice, therefore he analysed 57 pregnancies.

They resulted in early pregnancy losses of 36.8 % (21) and from the remaining 36 pregnancies 8 had a delivery before 30 weeks of gestation. Remarkable is that 53 % (19) of the patients delivered by caesarean section.

Regarding the women with secondary infertility, the first trimester miscarriage rate, with or without detection of fetal heart beat, decreased from 78.2 to 26.9 % ($P < 0.05$), and the live birth rate increased from 0 % before to 73 % after the metroplasty. Five cases of ectopic pregnancy were described in the group with primary infertility.

In our data of 100 women without DES-exposure, the intermediate analysis shows that 57 women (57 %) became pregnant with a median time to the first pregnant of 4 months (range: 0–52 months). The pregnancy ended in a miscarriage in 9 cases (16 %) and no ectopic pregnancy was recorded. In the remaining women, the register showed 11 ongoing pregnancies, one preterm delivery for a twin pregnancy at 32 weeks and 36 deliveries at term with a normal mean birth weight.

Conclusion

The TsU described as a rare uterine malformation seems to be a common finding in infertile patients and patients suffering from recurrent abortion. Due to the limited publications and confounding factors like confusing classification systems with inappropriate group allocation and the possible bias of DES exposure, every statement made is of limited scientific value. The new ESHRE/ESGE Classification provides the possibility of correct and unbiased group allocation; this is seen as an obligatory condition for correct prevalence studies.

It seems that the surgery improves or normalizes the reproductive results, although this evidence is mainly based on retrospective studies. At present, patients with dysmorphic uterus and history of recurrent pregnancy loss, preterm delivery or prior to entering an assisted reproductive programme could benefit from a hysteroscopic correction. For an experienced surgeon, using a small diameter hysteroscope and the micro scissors, excellent anatomical results are obtained in a simple ambulatory procedure with low complication rate.

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Septum Resection: Techniques and Post-treatment Reproductive Performance

26

Marco Gergolet

Introduction

Uterine septa, are commonly considered as one of the most important factors causing pregnancy loss or premature delivery with the poorest infant viability [1]. Septate uterus is described as a common cause of spontaneous miscarriage in the first trimester, but also as a possible cause of preterm delivery and malpresentations. Hysteroscopic metroplasty dramatically improves the pregnancy outcome with a concomitant decrease of the miscarriage rate and an increase in term of live birth rate [18, 28, 50, 61]. Until the development of hysteroscopic operative techniques, the treatment of septate uterus was considered only in very selected cases, due to the laparotomic approach and numerous postoperative complications such as adhesions or risk for uterine rupture during pregnancy and labor. Termination of pregnancy by caesarean section was mandatory. It is comprehensible how metroplasty was taken into consideration only in patients who suffered numerous first and second trimester miscarriages, and in those women who presented complete or almost complete septations. Until vaginal ultrasound probes have not been developed also the diagnosis of septate uterus was less accurate especially in the detection of small uterine indentation. The most accurate diagnostic tool at that time was hysterosalpingography (HSG), and gas hysteroscopy soon after.

In the early 1980s of last century several Authors reported series of patients successfully operated by hysteroscopic approach and soon became evident that transcervical approach should be preferred to Tompkins's (laparotomic) metroplasty [15, 16, 19, 20, 22, 23, 34]. In fact, the relative simplicity of the operation, the low complication rate and the possibility to vaginal delivery were strong arguments in favour of transcervical approach. Hysteroscopic approach, according to Israel and March "allowed liberalization of operative indications" [17, 34, 48]. The development of hystero-resectoscopes determined an incredible turnaround in the philosophy of the treatment of such malformations. Since metroplasty become less invasive and the compliance of the patients increased, the cases in which decision of clinicians to propose metroplasty begun more easy to take, nevertheless because of the short healing process and the possibility to undergo pregnancy few months after surgery [6, 34]. The new diagnostic procedure broadened the rate of patients candidates to surgery because of a more precise diagnosis even of small malformations.

The Tools and the Techniques

Metroplasties were performed at the beginning mostly with two different tools. Hystero resectoscopes with monopolar electrodes, similar to

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those used in prostatic surgery so called small diameter or "office" hysteroscopes, with the possibility insert into a 5 Fr operative channel micro scissors or micro electrodes either monopolar or bipolar. Other methods have been proposed during the years, became available soon after, such as those utilizing laser energy or hysteroscopic morcelators, but the rate of patients operated with those systems is minimal [11].

Resectoscope

The tool is still widely used. The energy source is either monopolar or bipolar. It consists in an external double sheet with an inflow and an outflow channel and a working element covering usually a 0° or a 12° fore-oblique angle telescope. Resectoscopes are nowadays thinner than in the past, and need cervical dilatation to 6 or 7 mm. The so called Gubbini micro resectoscope by Tontarra (Germany) is 5.4 mm thin and usually doesn't need cervical dilatation [30]. According to the energy source, the distension medium may be isotonic – saline solution- in case of bipolar electrode or a non ionic low viscosity fluid such as Dextran or Glycin in case monopolar energy is used. The latest requires more attention since fluid overload may represent a threat for pulmonary oedema and coagulopathy [14, 54, 59, 60]. The cutting electrode more widely used is the 90° angled "Collins" electrode but other Authors prefer and find faster and more manageable the semicircular equatorial electrode [45]. The technique is uniformed and requires the incision of the septum equidistantly from the anterior and the posterior wall after obtaining a good visualization of the whole uterine cavity and keeping the tubal ostia as landmarks. After distension of the uterine cavity, the resection is performed perpendicularly to the septum. The operation is stopped when the muscular layer is reached (Fig. 26.1). It is important to pay attention to not cut too deep into the muscular layer and to leave a safety thickness of 10 mm of the fundal wall, in order to avoid possible future uterine ruptures.

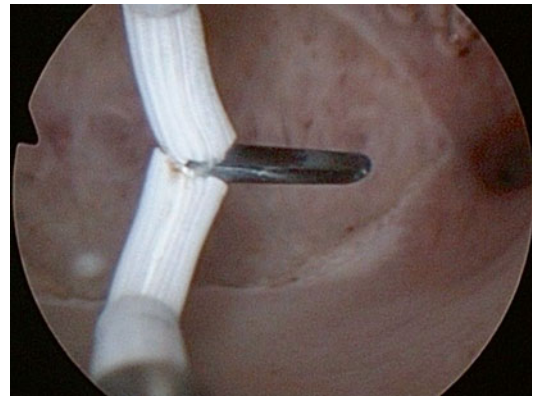

Fig. 26.1 The operation is stopped when the muscular layer is reached. It is important to pay attention to not cut too deep into the muscular layer and to leave a safety thickness of 10 mm of the fundal wall, in order to avoid possible future uterine ruptures

Small Diameter Hysteroscopes and "Office Procedures"

Usually do not need general anaesthesia and most of the times neither local application of anaesthetics. The scope, complete with operative sheet is 5.5 mm thin or below. Different office operative hysteroscopes are available in the market, the most diffused are the Bettocchi scope and recently the TROPHY Campo scope. Several Authors prefer this method because of the facility to entry the uterus without cervical dilatation, use of saline solution as distension medium and, according to the Authors, reduced possibility of uterine perforation and thermal trauma. Authors, who prefer this technique, stress particularly the fact that, according to their opinion, office technique is safer and carrier of a lower incidence of complications. As will be reported below the adverse events during metroplasty and the clinical results are independent from the used techniques. Litta compared the results of resectoscopic metroplasty versus the same procedure using office hysteroscope with 5 Fr bipolar electrode, called Versapoint. The results were comparable but the rate of a residual septum of more than 1 cm was almost double higher in the Versapoint group [38]. A higher necessity for second surgery

for incomplete septum resection by Versapoint was reported also by other authors [13].

The technique is called also "vaginoscopic". The scope is introduced in vagina and, once visualized the external cervical ostium, the uterine cavity is reached without using specula and tenacula. The distension medium (warm saline solution) is used to facilitate the trespassing of the cervical canal. Since the visualization of the cavity is not as broad as in the resectoscopic technique, two incisions, as landmarks, must be done at both sides of the septum before starting the incision. The incision can be done by cold scissors or electric devices.

Fibre Optic Laser

Soon after first hysteroscopic metroplasties were successfully performed, Fiberoptic Nd:YAG laser, argon laser or KTP-532 lasers were introduced on the market and several studies were published reporting the feasibility, patients compliance, complications and clinical results of those tools [57]. In a series of 21 patients Candiani e co-workers report on a comparison between resectoscopy by argon laser versus the same procedure performed by micro scissors. Authors did not find significant differences in clinical outcome between the two groups. Nevertheless laser technique was more time consuming, complicated and more expensive than the micro scissors technique [7]. Similar results were reported by Fedele, comparing laser, micro scissors and resectoscope techniques [21]. In front of higher costs laser surgery did not evidenced better reproductive performances. More, thermal injuries may cause small uterine wall weakness or misdiagnosed perforations with subsequent risk of ruptures during pregnancy or labor [31, 39].

Outcomes and Clinical Results

Complications

Several original papers and reviews refer of a series of complications during surgical procedure or during subsequent pregnancy and labor. In a extensive review, Valle and Ekpo report different complications, mostly uterine perforations, during surgery. Such complications occurred either in case of use of resectoscopes or of small diameter hysteroscopes. Argumentations about the higher incidence of surgical complications by using resectoscope instead of small diameter scope with micro scissors or Versapoint seem more subjective impressions of some authors than facts proved by evidences [13, 38, 42].

Distension media may cause fluid overload due to intravasation into the vascular system. The overload may cause hyponatriemia, pulmonary and disseminated intravascular coagulation. It must be clear that each used distension medium may cause intravasation, either low viscosity fluids such Dextran and Glycin, or saline solution but the safety limit of saline solution is much higher than the others media. A consequence of this fact is that bipolar resectoscopes and small diameter hysteroscopes using bipolar energy such as Versapoint devices or even micro scissors which are, from this point of view, much more safe than monopolar devices. On the other hand metropasties are, in experienced hands, not time consuming procedures and the amount of fluid intravasation is minimal, non comparable to longer procedures such as hysteroscopic myomectomies.

In case of total uterine septum and the presence of a septate or double cervix, U2C1or U2C2, according to the ESHRE/ESGE Classification on female genital tract congenital malformations [29], persist the dilemma if the cervix should be resected together with the septum, or left in order to avoid cervical weakness during subsequent pregnancy. The anomaly is very rare and unclassified by most recognized international classifications [9, 47, 53].

Clinical Results

Septate uterus may cause, according to numerous authors, infertility (often classified as unexplained), miscarriage and preterm delivery and

malpresentations. Clinical results of hysteroscopic metroplasties are generally good and seem to be independent from the tools, the type of energy and the techniques used. Improvement in fertility and pregnancy outcomes in patients operated with resectoscopes are as good as in those operated by micro scissors or Versapoint [4, 8, 13, 25–27, 33, 35, 38, 56].

Infertility

Almost 40 % of women with so-called idiopathic infertility have a septate uterus and up to 60 % of these patients spontaneously conceive after metroplasty of septa larger than 1 cm [18, 28, 61]. In a series of forty patients, Pace reports a 75 % of spontaneous pregnancy rate after surgery for septate uterus. Uterine artery pulsatility index after metroplasty was find to be significantly lower than before on Doppler velocimetry [43, 44]. According to Mollo, metroplasty improved the spontaneous pregnancy rate after surgery in a population with septum and no other cause of infertility. The life birth rate was significantly higher, comparing to a similar population of idiopathic infertility but without a septum [41]. In a review by Homer, a general improvement of spontaneous pregnancy rate is reported after surgery in a population of patients with primary infertility [32]. In their meta-analysis of studies published from 1986 to 2011, Valle and Ekpo report an overall pregnancy rate of 63.5 % and a live-birth rate of 50.2 % [58].

On the other hand, Daly published in 1989 a series of 70 patients treated for uterine septum. He recorded a significant improvement in first and second trimester miscarriage rate, but did not find a reduced incidence of preterm labor neither an improvement of fecundity in patients with primary infertility [15]. Homer [32] compared the reproductive outcome before and after hysteroscopic metroplasty resulting in a decrease in miscarriage rate from 88 % before to 14 % after metroplasty and an increase in live birth rate from 3 % before to 80 % after. Although the role of metroplasty in unexplained infertility still remains controversial, he reported an overall crude pregnancy rate of 48 % after metroplasty. According to Porcu, the spontaneous pregnancy rate in women who underwent metroplasty for septate uterus is similar to the pregnancy rate obtained with Assisted reproductive techniques (ART) [49].

ART may represent a model in order to study uterine factor of infertility, since tubal and male factor have been by-passed by the ART procedures. In a retrospective study done on patients undergoing ART in a period of 10 years, pregnancy rate (PR) and live birth rate (LBR) were significantly lower in patients with septate uterus, comparing to other patients. On contrary, PR and LBR were similar in patients who underwent metroplasty before ART comparing to the controls [56].

Recurrent Miscarriage

In a retrospective study the presence of chromosomal anomalies in aborted concepti was significantly lower in a group of patients with septate or disfused uterus versus those with a normal uterus (15.4 % versus 57.5 %). The same authors found a higher probability to a repeated miscarriage in cases with a higher ratio between the length of the indentation and the remaining uterine cavity, according to Salim and co-workers [52, 55]. Other studies did not find a significant correlation in the miscarriage rate between the grade of distortion of the cavity and the dimension of the uterine septation either before or after metroplasty [4, 25, 26, 46]

In a series of 70 patients either with primary infertility, repeated miscarriage, second trimester pregnancy loss or preterm delivery, Doridot reports a significant improvement of pregnancy outcomes in the population of women suffering for repeated miscarriage or in those who experienced second trimester pregnancy loss or preterm delivery after metroplasty for septate uterus. The paper evidences also a reduced risk for miscarriage in primary infertility patients who conceived after metroplasty. The author concludes that an expecting policy in patients with a septate uterus who suffered for a miscarriage or other obstetric complication is not a wise management [18]. Patients with two ore more consecutive miscarriage who never gave birth are more likely to

have a septate uterus, comparing to those who gave birth at least once. On contrary, the presence of acquired uterine anomalies are not influenced, according to Jaslow and Kutteh, from previous deliveries [36]. Miscarriage rate is lower after metroplasty independently from the obstetric history before surgery and is independent from the dimension of the septum [5]. After stratifying 288 patients according the deepness of the uterine septation (less than 1.5 cm and 1.5 cm or more), the outcomes of spontaneous pregnancies were analyzed. The miscarriage rate did not differ between the two groups either before metroplasty (75 % vs. 75.2 %) or after metroplasty (13.6 % vs. 16.7 %). According to the results it seems that the dimension of the septum is not influencing the severity of the obstetric complication of septate uterus [25].

Preterm Delivery

In 1994 a French study concluded that resecting the septum is the only way to increase the pregnancy outcome and should be preferable to cervical cerclage [24]. In a review of the literature, Homer reports an overall incidence of preterm delivery of 9 % in patients before metroplasty and a reduction to 6 % of preterm delivery after surgery.

In a systematic review of a British group the paper reports a 2.3-fold risk for preterm delivery in patients with septate uterus [10]. According to Zlopasa, small uterine septa and bicornuate uteri are mostly implicated in the aetiology of preterm delivery [63]. Zhang reports a 19.8 % of preterm delivery in women with septate uterus [62]. In a population of women undergoing hysteroscopy due to abnormal uterine bleeding, Maneschi reports that women with uterine malformations showed a significantly lower term delivery rate [40]. Hua reports an adjusted Odds ratio (aOR) of 7.4 for preterm delivery before 34th week of pregnancy and a 5.9 aOR for delivery before 37th week. On the other hand Agostini worries about increased risk for fetal malpresentations at term, low birth weight infants, and delivery by caesarean section after metroplasty for septate uterus [3].

Conclusions

The estimated prevalence of congenital uterine anomalies, and septate uterus in particularly, varies from author to author. Even using same or similar diagnostic tools, the lack of uniformity between papers seems to indicate a different interpretation of examination results, more than to real differences in the studied populations [2, 12, 37, 51].

According to most of the related papers, septate uterus is cause of repeated miscarriage, second trimester pregnancy loss and malpresentations. Septate uterus is not generally admitted to be a cause of infertility, even if several papers report a longer time to conceive in patients with septate uterus before metroplasty. Similarly, septum may impair the results of assisted reproductive techniques.

Randomized controlled trials are needed to confirm the beneficial effects of metroplasty reported by numerous publications. Such trials are difficult to carry on, not only because of a relative difficulty to randomize the patients, but also because of an objective difficulty to design an appropriate study.

In the era of internet, women candidate to enter the randomization who are aware of dozens of non randomized publication which confirm the improvement of pregnancy and live birth rates after metroplasty would decline to enter the study. More, a multicentre randomized trial would be difficult also because of a lack of uniformity in the distinction between a normal uterine cavity and a small septate uterus. The new ESHRE-ESGE classification on congenital uterine anomalies may result a helpful tool to reach a greater homogeneity of studies or almost of the interpretation of uterine imaging procedures, since the terminology “arcuate” uterus has been abandoned by this classification. Waiting for the highest level of evidence, according to prospective and retrospective epidemiological studies, is seem that hysteroscopic resection of uterine septum may improve the pregnancy outcome, the outcome of ART techniques and may shorten the pregnancy seeking time in couples with prolonged primary or secondary infertility.

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Bicorporeal Uterus: Treatment Options

27

Theodoros D. Theodoridis, Leonidas Zepiridis, and Grigoris F. Grimbizis

Introduction

Uterus is formed from the fusion of the bilateral paramesonephric ducts that first appear at approximately the sixth week of gestation as a finger-shaped invagination of the coelomic epithelium at the upper pole of the mesonephros. These tubular structures are met and fused in the midline to form the unified uterine body by the tenth week of gestation. Thus the sequence of events during normal müllerian development is: formation, canalization and fusion of the ducts followed by septal resorption.

The previously reported bicornuate uterus, nowadays, classified as bicorporeal according to the recently introduced European's Society of Human Reproduction and Embryology (ESHRE) and European's Society for Gynaecological Endoscopy (ESGE) Classification, represents one of the most common uterine malformations [10, 19, 21, 22, 41]. This involves the incomplete fusion of the two müllerian ducts at the level of uterus creating a single cervix with varying degrees of separation and/or communication between the two resulting uterine cavities. Complete failure of fusion of the two müllerian ducts results in duplication of the uterine corpus and cervix, previously called uterus didelphys or double uterus. This malformation usually is characterized by two endometrial cavities, two cervices fused or not in the lower uterine segment and, usually, a longitudinal vaginal septum situated between the two cervices.

Patients with uterine didelphys do not always have symmetric anatomy and, often, present quite early for clinical evaluation due to problems such as obstructed hemivagina, which usually occurs on the side of a renal anomaly and is referred as OHVIRA (Obstructed Hemi-Vagina with Ipsilateral Renal Anomaly) syndrome [43, 46].

Classification and Definition

Until recently, three classification systems have been devised for the classification of female genital tract anomalies: the American Fertility Society's (AFS) currently American Society of Reproductive Medicine system [6, 9], the embryological-clinical classification system of genito-urinary malformations [2, 3] and the Vagina, Cervix, Uterus, Adnexae and associated Malformations system based on the tumor nodes metastases (TNM) principle in oncology [33].

However, those classification systems have been criticized for their confusion, incompleteness,

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ESHRE/ESGE Classification
Bicorporeal uterus and its variants

	Uterine anomaly		Cervical/Vaginal anomaly	
	Main class	***Sub-class***	**Co-existent class**	
U0	Normal uterus		***C0***	*Normal cervix*
U1	Dysmorphic uterus	**a.** T-shaped **b.** Infantilis **c.** Others	***C1***	***Septate cervix***
U2	Septate uterus	**a.** Partial **b.** Complete	***C2***	***Double "normal" cervix***
U3	**Bicorporeal uterus**	**a.** Partial **b.** Complete **c.** Bicorporeal septate	***C3***	***Unilateral cervical aplasia***
U4	Hemi-uterus	a. With rudimentary cavity (communicating or nor horn) b. Without rudimentary cavity (horn with out cavity/no horn)	***C4***	*Cervical aplasia*
U5	Aplastic	a. With rudimentary cavity (bi-or unilateral horn) b. Without rudimentary cavity (bi- or unilateral uterine remnants/aplasia)	***V0***	*Normal vagina*
			V1	***Longitudional non-obstructing vaginal septum***
			V2	***Longitudional obstructing vaginal septum***
			V3	*Transverse vaginal septum and/or imperforate hymen*
			V4	*Vaginal aplasia*
U6	Unclassified malformations			
U			***C***	***V***

Fig. 27.1 ESHRE/ESGE classification of bicorporeal uterus and its variants: partial (*Class U3a*), complete (*Class U3b*), bicorporeal septate (*Class U3c*), complete bicorporeal with septate cervix (*Class U3bC1*), complete bicorporeal with double cervix (*Class U3bC2*, *former AFS didelphys*), complete bicorporeal with unilateral cervical aplasia (*Class U3bC3*) and complete bicorporeal with double cervix and longitudinal obstructing vaginal septum (*Class U3bC2V2*)

or irrelevant detail. Although the AFS classification received wide acceptance and it is still the most broadly used system, it is associated with various limitations in effective categorization of the anomalies. It is also interesting that until now none of the other available options was able to effectively replace the AFS system.

The recently introduced ESHRE/ESGE Classification of female genital anomalies aims to provide a more suitable classification system for the accurate, clear, and simple categorization of female genital anomalies, that is correlated with clinical management [21, 22].

According to the ESHRE/ESGE classification all fusion defects are placed in the third class of the system characterized as bicorporeal uterus (U3). Thus, bicorporeal uterus is defined as any uterus having an abnormal fundal outline: it is characterized by the presence of an external indentation at the fundal midline exceeding 50 % of the uterine wall thickness. This indentation could divide partly or completely the uterine corpus including in some cases the cervix and/or the vagina. As it could easily be imagined it is also associated with an inner indentation at the midline level that divides the cavity as happens also in the case of septate uterus.

Depending on the degree of uterine deformity bicorporeal uterus (ESHRE/ESGE Class U3) is further divided into three sub-classes (Fig. 27.1):

(a) Class U3a or partial bicorporeal uterus, which is characterized by an external fundal indentation partially dividing the uterine corpus above the level of the cervix.
(b) Class U3b or complete bicorporeal uterus, which is characterized by an external fundal indentation completely dividing the uterine corpus up to the level of the cervix; patients with complete bicorporeal uterus (Class U3b) could have or not coexistent cervical (e.g. double cervix formerly didelphys

uterus-U3bC2) and/or vaginal defects (e.g. obstructing or not vaginal septum).

(c) Class U3c or bicorporeal septate uterus, which is characterized by the presence of an absorption defect in addition to the main fusion defect. In patients with bicorporeal septate uterus (Class U3c) the width of the midline fundal indentation exceeds >150 % the uterine wall thickness.

The true incidence of female congenital malformations is unknown. The use of diagnostic methods with different accuracy, the subjectivity in the criteria used for diagnosis and classification of the anomalies and the drawbacks of the existing classification systems represent the main biases for that [20, 41]. Moreover, in some studies the population was not representative whereas the existence of undiagnosed cases is another potential bias, as many of the patients with malformations may be asymptomatic without ever reporting any gynaecological or reproductive problem.

Reports in the literature estimate that the incidence of female genital anomalies in general population varies between 4.3 and 6.7 %, while in women with fertility problems between 3.4 and 10.8 %. In patients that suffer from recurrent miscarriages, congenital anomalies are reported to range between 12.6 and 18.2 % [19, 41]. In a more recent review of 94 observational studies comprising 89.861 women, the prevalence of uterine anomalies diagnosed by optimal tests (investigations that are capable of accurately identifying and classifying congenital uterine anomalies accurately) was found to be 5.5 % [95 % confidence interval (CI), 3.5–8.5] in the general/unselected population, 8.0 % (95 % CI, 5.3–12) in infertile women, 13.3 % (95 % CI, 8.9–20.0) in those with a history of miscarriage and 24.5 % (95 % CI, 18.3–32.8) in those with miscarriage and infertility [10].

Bicornuate uteri, which are uncommon in the unselected population (0.4 %; 95 % CI, 0.2–0.6), are significantly more prevalent in women with infertility (1.1 %; 95 % CI, 0.6–2.0, P = 0.032) and those with miscarriage (2.1 %; 95 % CI, 1.4–3, P < 0.001), particularly if these coexist (4.7 %; 95 % CI, 2.9–7.6, P < 0.001) [10]. The prevalence of uterus didelphys was 0.3 % (95 % CI, 0.1–0.6) in the unselected population. This anomaly is no more prevalent in women with infertility (0.3 %; 95 % CI, 0.2–0.5), or in women with a history of miscarriage (0.6 %; 95 % CI, 0.3–1.4), but is significantly more common in infertile women with miscarriage (2.1 %; 95 % CI, 1.4–3.2, P < 0.001) [10].

Obstetric Outcome in Bicorporeal Uterus

Class U3 and U3bC2 (bicornuate and didelphys uterus), do not appear to reduce fertility but are associated with aberrant outcomes throughout the course of pregnancy, that depend on the type of the congenital anomaly. Generally women with bicornuate uterus have an increased risk of miscarriage (both first and second trimester), preterm birth and fetal malpresentation at birth, while women with uterus didelphys seem to have only a modestly increased risk of preterm labor and malpresentation at delivery [11, 19]. Uterine anomalies have been also associated with an increased incidence of placental abruption, intrauterine growth restriction (IUGR), prematurity, operative delivery, retained placenta and fetal mortality [37]. Obstetrical outcomes are generally reported to be better in cases of bicornuate uterus than in unicornuate uterus, perhaps given the significant variation in bicornuate uterine anatomy, subtypes of which involve a partially fused central uterine cavity [36, 38].

The cause of adverse obstetrical outcomes may be secondary to abnormal uterine vasculature, decreased cervical connective tissue and decreased uterine musculature [38]. Disturbance in the uterine blood flow, caused by absent or abnormal uterine or ovarian vessels, could potentially explain the IUGR and increased rates of spontaneous abortions [8]. Abnormal ratio of muscle fibres to connective tissue in uterine cervices is associated with abnormal müllerian development [7, 40]. Also decreased uterine musculature gestational capacity is said to be jeopardised by the presence of only half the full complement of uterine Musculature. Usually the myometrium of

congenitally abnormal uteri are thinner than normal and mural thickness diminishes as gestation advances, causing inconsistencies over different aspects of the uterus [30, 31, 38]

Surgical Management of Bicorporeal Uterus

Whether surgical correction for a bicornuate uterus is necessary is controversial although it may be indicated for patients with repeatedly poor fertility outcomes in who other causes have been excluded [26]. Prerequisites are the proper classification, the clear surgical indications and the feasibility and safety features of the procedure.

The Strassman metroplasty is the traditional surgical correction for both bicornuate and didelphic uteri, currently bicorporeal uterus (Fig. 27.2a–e). The Strassman procedure essentially involves the unification of two endometrial cavities of an otherwise divided uterus. A single longitudinal incision from one cornua to the other is made into the endometrial cavity. Retracting the cornua laterally with right angle clamps, each horn of the uterus will evert and a single layer of interrupted figure-of-eight sutures beginning on the anterior uterine wall are placed transversely to form a single uterine cavity. Serosal stitches are placed in a fashion similar to a myomectomy [26, 44]. Resection of a vaginal septum associated with uterine didelphys should be undertaken if associated with obstruction, dyspareunia or infertility. The Strassman procedure has been used to reconstruct the bicornuate uterus [39]. In an uncontrolled study of 289 women with bicornuate uteri and history of previous preterm loss, the fetal loss rate was approximately 70 %. After surgery, the live birth rate significantly improved to 85 % [45]. Further studies concluded that abdominal metroplasty serves as a viable treatment modality to improve obstetric outcomes [27, 34]. In a total of 22 patients after abdominal metroplasty, 88 % of pregnancies ended with the birth of a viable infant [27]. In another study after metroplasty the fetal survival rate was 81 % in the recurrent miscarriage group and 92.8 % in the infertile group of patients [34].

Recently, laparoscopic unification in cases of ESHRE/ESGE U3bC2 (complete bicorporeal with double cervix, formerly AFS didelphys) and U3bC0 (complete bicorporeal with normal cervix) uteri has been reported in the literature [4, 29, 35, 42]. The first laparoscopic metroplasty was reported to be a safe and successful surgical option [42]. It was followed by other case reports and case series showing good restoration of the uterine anatomy, minimal peritoneal adhesions, less blood loss, creation of a spacious uniform uterine cavity, shorter hospital stay and good scar integrity [4, 29, 35].

Strassmann metroplasty is technically quite challenging when performed by endoscopic means and good surgical skills are needed. The same surgical principles as abdominal metroplasty apply. The surgeons must be experienced laparoscopists to perform such procedures [4, 42]. The pregnancy outcomes after endoscopic metroplasty should be evaluated in large prospective trials to prove the obstetric benefit of the procedure.

Metroplasty at the time of diagnosis for patients with primary infertility is not recommended, given that fertility rates are not significantly reduced from the norm and successful pregnancies without intervention are common [11, 19, 38]. Patients should be counseled regarding the need for subsequent cesarean section, given the significant risk of uterine rupture during labour after such procedures [38].

The necessity to perform cervical cerclage is addressed. Cervical incompetence is an issue with uterine malformations, especially with the bicornuate uterus [18]. Because of this potential association, a study was performed using limited prophylactic cervical cerclage in patients with bicornuate uteri (*ESHRE/ESGE class U3C0*) and comparing fetal survival rate before cerclage to that after cerclage in the same subjects. Fetal survival improved from 21 to 62 % [1]. Further trials are needed to evaluate whether the cerclage is beneficial after metroplasty. It is also not clear at which week of pregnancy it should be performed.

In many cases major congenital uterine anomalies present a management dilemma in women

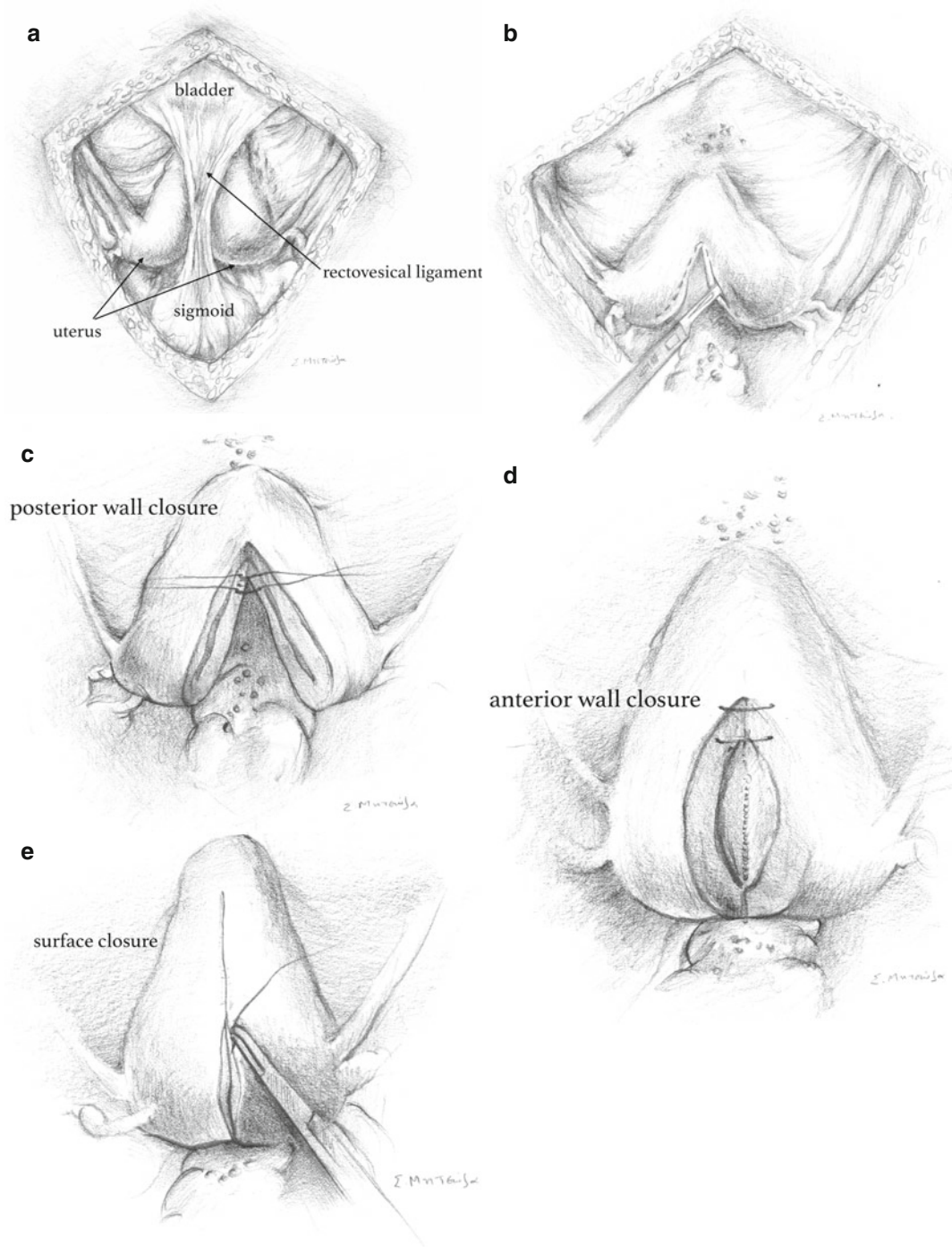

Fig. 27.2 Strassmann procedure: surgical steps. (**a**) bicorporeal uterus (**b**) incision from one cornua to the other (**c**) posterior uterine wall closure (**d**) anterior uterine wall closure (e) serosal closure

who are symptomatic due to menorrhagia and not responsive to medical therapy. It was reported that the incidence of uterine malformations in women presenting with abnormal uterine bleeding was 19/322 (5.9 %) [28]. In these cases surgical management appears to be the best option and given the established safety of laparoscopic procedure for removal of morphologically normal uteri, it was considered to be a suitable alternative treatment option in a case of didelphys uterus (*ESHRE/ESGE class U3bC2*). Erian et al. [16] performed a day-case laparoscopic subtotal hysterectomy in a woman with U3bC2 uterus and menorrhagia [16]. Technically, the procedure was similar to laparoscopic subtotal hysterectomy performed in morphologically normal uteri [15]. The most significant difference was the separate removal of the two uterine corpora using two lap loop systems sequentially [16]. It should be noted that surgical identification of the ureters is essential part of the surgery as urinary tract anomalies are frequent in women with uterine congenital malformations [16, 23].

Surgical Management of Bicorporeal Uterus Variants

Depending on the anatomical status of cervix and/or vagina, bicorporeal uterus could be presented in some not very common variants (Fig. 27.1); Fedele et al. [17] in an interesting epidemiological study of 87 patients with bicorporeal or septate ("double") uterus, unilateral cervico-vaginal obstruction and ipsilateral renal anomalies have examined all the anatomic variants and their relative frequency. In 67 out of 87 cases a didelphys uterus was found; in 63 cases with a concomitant longitudinal obstructing vaginal septum (*complete bicorporeal uterus with double cervix and longitudinal obstructing vaginal septum – ESHRE/ESGE Class U3bC2V2*) and in 4 patients with unilateral cervical aplasia (*complete bicorporeal uterus with unilateral cervical aplasia – ESHRE/ESGE Class U3bC3V0*). Furthermore, in 10 cases a bicornuate uterus was diagnosed; in 9 patients with double cervix and longitudinal obstructing vaginal septum (*partial bicorporeal uterus with double cervix and longitudinal obstructing vaginal septum – ESHRE/ESGE Class U3aC2V2*) and in 1 patient with septate cervix and longitudinal obstructing vaginal septum (*partial bicorporeal uterus with septate cervix and longitudinal obstructing vaginal septum – ESHRE/ESGE Class U3aC1V2*). Didelphys uterus with longitudinal obstructing vaginal septum and ipsilateral renal agenesis is known also as Herlyn-Werner-Wunderlich or OHVIRA syndrome [12, 24, 43, 47]. In all these variants the existing obstruction is the main indication for surgical treatment.

Bicorporeal Uterus with Unilateral Cervical Aplasia (ESHRE/ESGE Class U3bC3)

Surgical treatment is necessary and laparoscopic management feasible in these rare subclasses of bicorporeal uterus, which present with obstructing symptoms other than fertility (Fig. 27.3). Removal of the obstructed side of the uterus is the indicated treatment; successful laparoscopic removal followed by morcellation of the obstructed part of a didelphys uterus with unilateral cervical and renal aplasia (ESHRE/ESGE Class U3bC3) has been already reported [5].

It should be noted that in such cases the hemi-uterus might act clinically as rudimentary horn and the risk for a pregnancy is possible; the only difference between a rudimentary horn and a hemi-uterus with cervical aplasia is the presence of uterine isthmus in cases of hemi-uterus. Pregnancy in an obstructed part of a didelphys uterus must be treated, as one would do with any other ectopic pregnancy and this could be done by minimal access surgery [32]. Furthermore, it seems reasonable that an obstructed hemi-uterus should be removed in symptom-free patients as soon as diagnosis is made to avoid potential complications and surgical removal during pregnancy [32].

Restoration of utero-vagina continuity of the obstructed hemi-uterus has been also proposed as an alternative either by laparoscopically assisted cervicoplasty in cases of cervical atresia or by isthmo-vagina anastomosis [17]. However, it should be offered in patients after proper counseling and understanding of its potential compli-

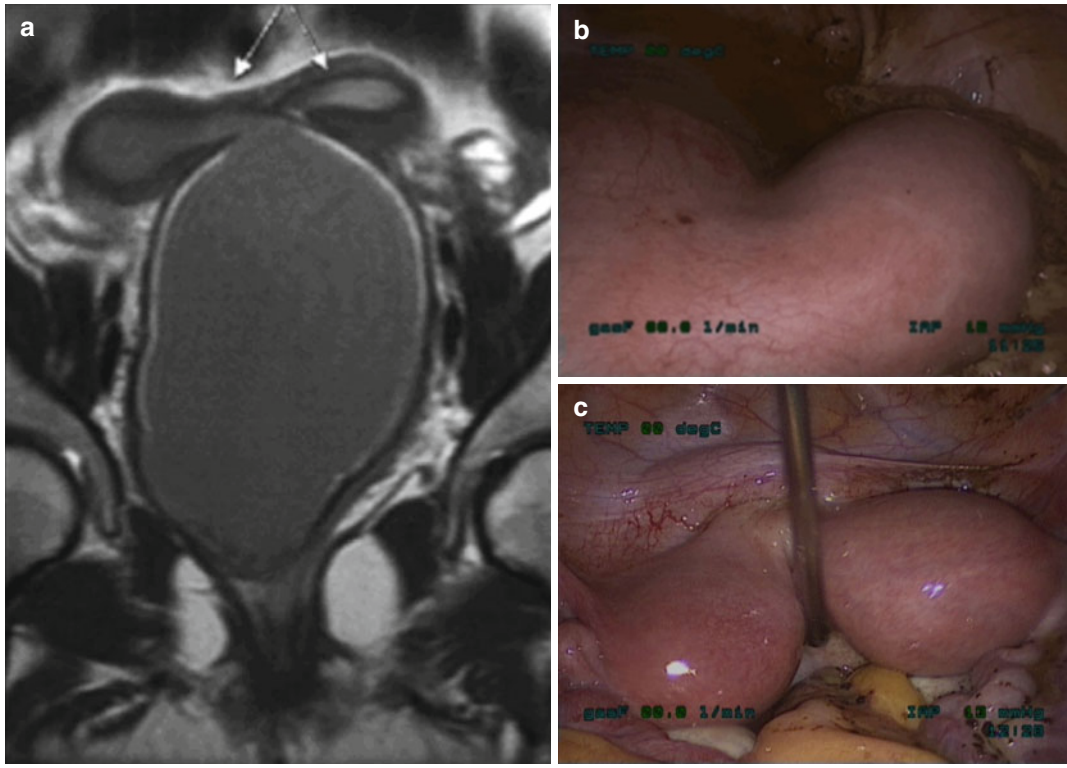

Fig. 27.3 Complete bicorporeal uterus with double cervix and longitudinal obstructing vaginal septum (ESHRE/ESGE Class U3bC2V2): (**a**) MRI image showing the presence of RT hemi-hematometra, RT hemi-hematocolpos and LT side normal, (**b**) Laparoscopic view showing the RT obstructed hemi-uterus and the RT hemi-hematocolpos and (**c**) Laparoscopic view after incision of the vaginal septum showing the two sides of the uterus

cations, especially ectopic pregnancy. Written consent is essential prior to these procedures.

Bicorporeal Uterus, Double Cervix and Longitudinal Obstructing Vaginal Septum (ESHRE/ESGE Class U3bC2V2)

In cases of longitudinal obstructing vaginal septa (Fig. 27.4), excision or incision of the septum until the cervical level is the indicated treatment to relief from obstruction and to restore continuity [17]. The excision of the obstructed hemi-uterus is not necessary and this could be an option only in very rare cases where a concomitant cervical anomaly is present; in 1999, there was a report of a 17-year-old adolescent with a uterus didelphys, right hematometra, hypoplastic cervix, right obstructed upper hemivagina, and ipsilateral renal agenesis. In this case, the right hemi-uterus was removed by laparoscopy using endoscopic staplers rather than attempting to make a fistula for fear of infection [25].

Surgical Management of Bicorporeal Septate Uterus

Cases of class U3c in ESHRE/ESGE classification represent a very interesting clinical entity and their proper management is a challenge; the co-existence of absorption and fusion defects permits the partial correction of the anomaly by cutting the septate element of the indentation.

The largest series of patients with coexistence of a uterine septum in cases diagnosed as bicornuate uterus and their management was

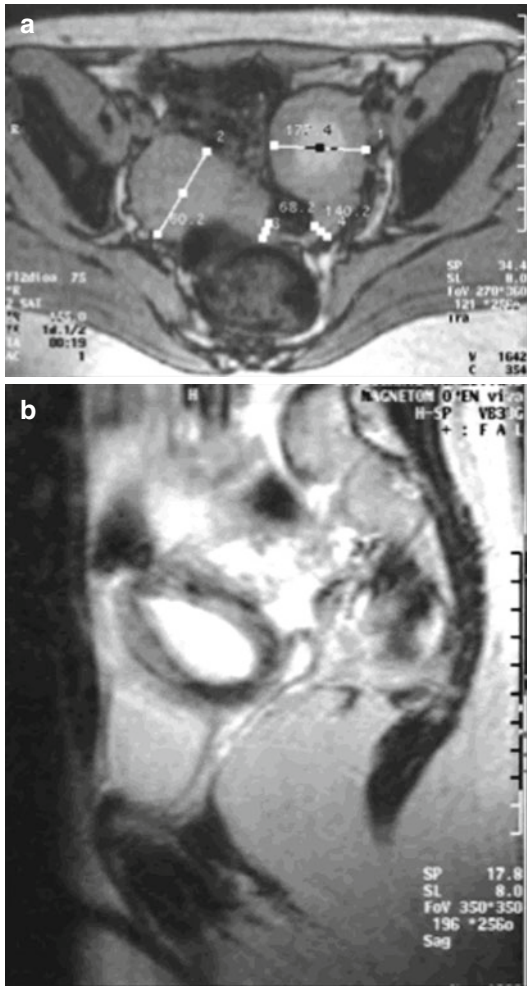

Fig. 27.4 Complete bicorporeal uterus with LT unilateral cervical aplasia (ESHRE/ESGE Class U3bC3): (**a**) MRI image showing in the transverse plane the complete bicorporeal uterus with LT hematometra, (**b**) MRI image showing the LT cervical aplasia in the coronal plane

reported recently [14]. The authors report this malformation as uterus of hybrid septate variety (HSV). Thus, in a total of 357 bicorporeal uteri, they found 17 bicorporeal septate (U3c) and they treated them with hysteroscopic metroplasty under laparoscopic guidance and inspection. Successful reproductive outcomes were reported in 12 out of 15 (80.0 %) patients [14]. The use of laparoscopic control does not seems to be necessary; in these cases a pre-operative 3D ultrasound mapping of the uterus is a prerequisite and the hysteroscopic procedure could be done under ultrasound control.

In the same series of cases there was a unique case of a patient with a septate uterus with a fundal depression and hemi-uterine obstruction. She underwent hysteroscopic resection under laparoscopic monitoring. Laparoscopy was beneficial in diagnosis and treatment of associated pathology and monitoring the hysteroscopic procedure. Hysteroscopic metroplasty was performed and resulted in unification of the lower two thirds of the uterus. Dysmenorrhea was dramatically improved after the procedure. Subsequent office hysteroscopy confirmed restoration of a unified lower uterine corpus anatomy mimic to the original bicornuate state [13, 14].

Conclusions and Issues Open for Further Research

The Strassman metroplasty is the traditional surgical correction for bicorporeal (*ESHRE/ESGE Classes U3bC0 & U3bC2*, former bicornuate and didelphys) uterus (Table 27.1). It is based on the surgical unification of "two" endometrial cavities of an otherwise divided uterus. Laparoscopic metroplasty is also, nowadays, feasible. Transabdominal metroplasty significantly improves the reproductive outcome in women with bicorporeal uteri (class U3b and U3bC2 in ESHRE/ESGE classification) who experience poor reproductive outcome. However, whether surgical correction of bicorporeal uterus with Strassman metroplasty is necessary is highly controversial given that fertility rates are not significantly reduced from the norm and successful pregnancies without surgical correction intervention are common.

Thus, it should be avoided as a prophylactic procedure especially in infertile patients and, it might be indicated only for selected patients with extremely poor reproductive outcome or history of recurrent miscarriages and/or preterm labor, in whom other causes have been excluded. Patients should be counseled for the need of a subsequent caesarean section.

Table 27.1 Variants of bicorporeal uterus and their surgical treatment

Anatomical variant	ESHRE/ESGE Class	Surgical treatment	Comments
Partial bicorporeal *Septate or double cervix* *Longitudinal obstructing vaginal septum*	**U3aC1or2V2**	*Cervical septum incision* (*in cases of septate cervix*) Vaginal septum incision	*Not necessary* Recommended
Complete bicorporeal *Normal cervix* *Double cervix*	**U3bC0** **U3bC2**	Strassmann metroplasty (open or laparoscopic)	Not recommended as a prophylactic procedure
Complete bicorporeal *Septate cervix* *Longitudinal obstructing vaginal septum*	**U3bC1V2**	Vaginal septum incision	Recommended
Complete bicorporeal *Double cervix* *Longitudinal obstructing vaginal septum*	**U3bC2V2**	Vaginal septum incision	Recommended
Complete bicorporeal *Unilateral cervical aplasia*	**U3bC3V0**	Removal of the obstructed hemi-uterus Restoration of continuity (cervicoplasty or isthmo-vaginal anastomosis)	Recommended Unclear place
Bicorporeal septate	**U3c**	Hysteroscopic incision of the septate element	Recommended

In cases of bicorporeal uterus with unilateral cervical aplasia (*ESHRE/ESGE Class U3bC3*), removal of the obstructed hemi-uterus is indicated in order to relieve from obstructing symptoms and avoid a pregnancy in the obstructed part of the uterus (Table 27.1). Restoration of continuity with cervicoplasty or isthmo-vaginal anastomosis has been also reported as surgical alternatives. Although these options offer, also, a relief from obstructing symptoms (cyclic pelvic pain, hemi-hematometra), their safety in cases of a future pregnancy in this part of the uterus is not yet proven.

Patients with bicorporeal uterus, double cervix and longitudinal obstructing vaginal septum (*ESHRE/ESGE Class U3bC2V2*) should be treated surgically by cutting or resecting the vaginal septum (Table 27.1). This is necessary to alleviate vaginal and hemi-uterine obstruction by restoring continuity.

Finally patients with bicorporeal septate uterus (*ESHRE/ESGE Class U3c*) should be treated hysteroscopically by incising the septate part of the indentation offering to the patient a better uterine cavity (Table 27.1). This could improve prognosis of future pregnancies reducing miscarriage and preterm delivery rates.

Although several surgical options are nowadays available for the treatment of patients with bicorporeal uterus and its clinically significant variants, their exact place in the management of these patients is not yet clear. Larger number of patients and well-designed studies are essential to withdraw valuable conclusions. RCT's comparing the pregnancy outcomes between cases treated and not treated by metroplasty among patients with poor obstetric history are needed because it is not established whether surgery alone could improve live birth rate.

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Bicorporeal Uterus: Laparoscopic Metroplasty

28

Bruno J. van Herendael, Benedikt Tas, Sanket Pisat, Anne Mie De Boodt, and Patricia Duvivier

Introduction

The prevalence of uterine malformations in the general population is estimated to be ~3.4 % whilst in patients with recurrent pregnancy loss reaches up to 13 %. Bicorporeal, former bicornuate, uterus represent 25 % of the Müllerian malformations. The pregnancy outcome in untreated bicornuate uterus is rather poor with only 62.5 % term delivery rates [1]. The rationale to treat bicorporeal uterus surgically is two second trimester (>16 weeks of gestation) pregnancy losses.

Laparotomy was traditionally applied as the access of choice to unify the two horns using the Strassmann's technique. However, the open way of access (laparotomy) represented a problem for the patient. If the same operation could be done laparoscopically, the patient could benefit from the classical advantages of the laparoscopic entry (less bleeding, less discomfort, shorter hospital stay, faster return to work and faster restart of sexual activity) and, in a long-term basis, the technique could be more acceptable.

The first report on the feasibility of the laparoscopic approach emerged in the late 2005 – early 2006 [2] followed by two additional reports in 2009 [3, 4]. The aim of this chapter is to describe the technique and the results of laparoscopic unification in cases of bicorporeal uterus as it is applied by our team; joining of the two horns is the most challenging part of the technique.

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Technique

The different steps of the laparoscopic operation as it is applied at Ziekenhuis Netwerk Antwerpen (ZNA) Stuivenberg by our team are presented (Figs. 28.1, 28.2, 28.3, 28.4, 28.5, 28.6, 28.7 and 28.8) [5].

Step 1: Establishment of Laparoscopy

A 20 cm Veress needle is inserted through an 1 cm incision as deep as possible in the umbilicus. The abdominal wall is elevated so that the needle penetrates perpendicular the fascia and the peritoneum. A pneumoperitoneum of 20 mmHg is installed. The CO_2 gas is brought

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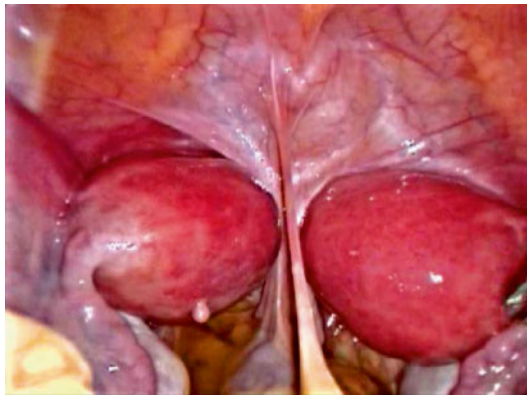

Fig. 28.1 Typical appearance of a uterus didelphus with the septum running from the bladder cephalad to the Douglas. Dividing the Douglas cavity up to the anterior wall of the rectum

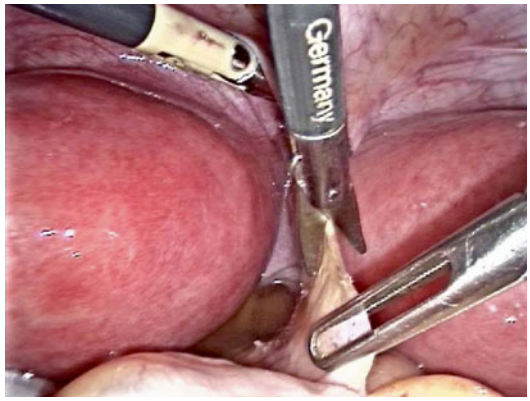

Fig. 28.2 The operation starts by dividing the septum anteriorly bur as extensive as possible posteriorly as to make a unique cavity of Douglas

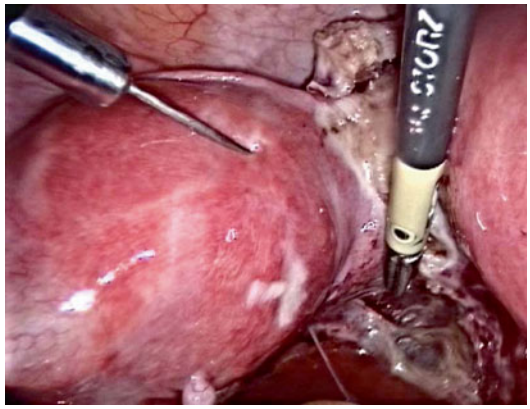

Fig. 28.3 The walls are infiltrated on the medial side with Ornitocine diluted 1:200 using a laparoscopic needle armed with a Luer lock syringe of 50 ml

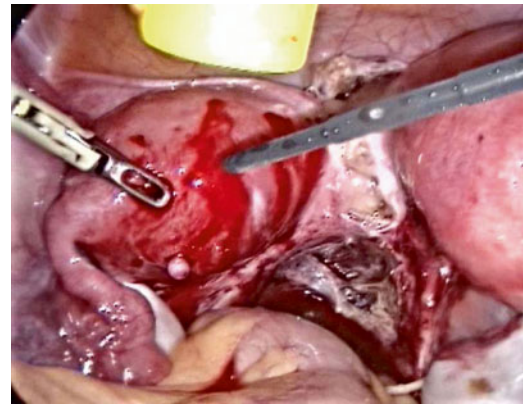

Fig. 28.4 A Manhez needle (Karl Storz Gmbh & Co Tuttlingen Germany) is used to delineate the first incision in the superficial layers of the myometrium

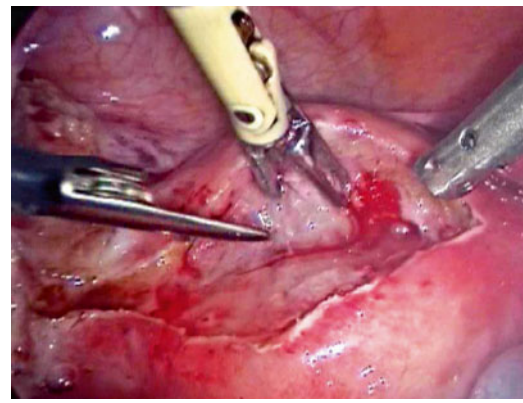

Fig. 28.5 For the deeper layers of the myometrium and for opening the endometrial cavity scissors are used to reduce the thermal spread on the tissues to zero by only using the crush effect of the scissors. Short burst of bipolar electrical energy, delivered through a Robi fenestrated forceps (Karl Storz Gmbh & Co Tuttlingen Germany), are used to clear the vision of the surgeon whilst lavage and aspiration are performed to clear the surgical field of blood

through a water bottle at 37 °C and is heated 20 cm from its entry into the abdomen. Allowing the gas to pass from 32 °C at the wall inlet to be heated up to 35 °C at its entry in the abdominal cavity. The humidity reaches up to 95 %. A pyramidal trocar of 12 mm is introduced after enlarging the umbilical incision and is brought into contact with the fascia. The fascia is hooked and the trocar is pushed into the abdominal cavity at an angle of 45° or less with the pressure of the

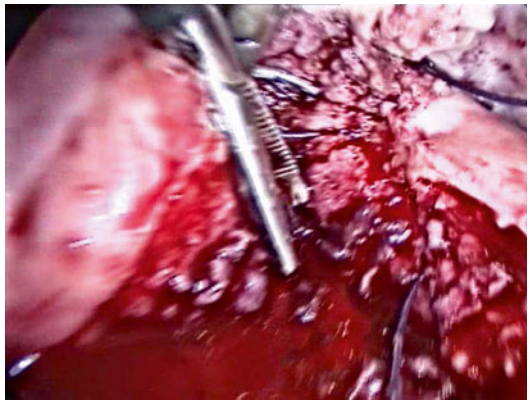

Fig. 28.6 The deeper muscle layers, to close the endometrial cavity, are united by Polyglactin 0 (Vicryl Ethicon)

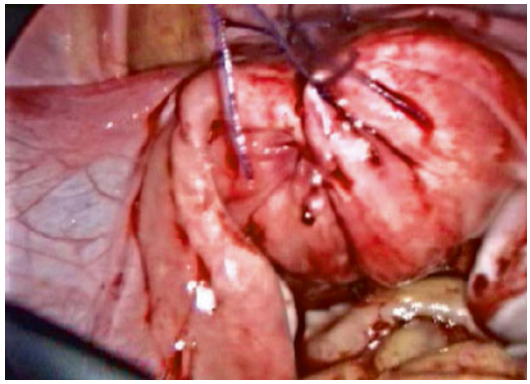

Fig. 28.7 The superficial muscle layer at the level of the serosa are closed by a hemostatic inverted suture of Polyglactin 1 according to the technique of Michel Degueldre

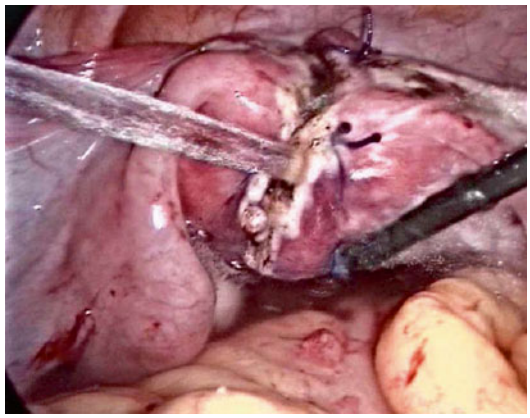

Fig. 28.8 At the end of the procedure Icodextrin 4 % (Adept Baxter healthcare SA) is used to float the uterus in the small pelvis as to minimise adhesion formation

bodyweight, the dominant hand guiding the trocar in the direction of the small pelvis. The non-dominant hand is wrapped around the trocar and has a brake function. This maneuver is comparable with the direct entry method. The intra-abdominal pressure is reduced to 16 mmHg. The patient is tilted into maximal Trendelenburg to let the bowels slip into the upper abdomen. The Trendelenburg is reduced to 15° and the operation is started.

Step 2: Opening of the Cavities

The two horns are brought into view. In most cases there is a septum between the two horns dividing the Douglas.

A damped monopolar electrical current is used at 18 W terminal power through a Manhez needle (Karl Storz & Co Gmbh Tuttlingen Germany) to cut the division. Both horns are infiltrated with a vasoconstrictant (Ornitocine) at a dilution of 1:200 through a laparoscopic needle inserted in the muscle at its median aspect using 250–400 ml in each horn. The anesthetist is present during the injection of the vasoconstrictant.

The Manhez needle is used again in the same power to open the median aspect of the horns in their outer 2/3 third. The final opening of the uterine cavity is performed with Metzenbaum type of scissors. Both uterine cavities have been filled with methylene blue as to direct the surgeon.

Finally the junction of the two open cavities is made at the level of the upper part of the cervix. A hysterometer is pushed up from below through the cervical canal as to form a reference point for the scissors of the lead surgeon. It is mandatory that the hysterometer is manipulated by an expert gynecological surgeon as to present the part to be cut directly to the lead surgeon. The upper part of the cervix is opened with scissors creating a transversal cut.

Step 3: Unification of the Cavities

The open cavities are now joined using a first layer of interrupted sutures avoiding the

endometrium with a 0/0 braided suture (Vicryl J&J) and a half circle needle round bodied taper pointed. The muscle layer is joined using a stronger braided suture 1/0 with a TP 2 cutting needle (Vicryl). The suture is an adapted matrass suture according to Michel Degueldre. The needle enters the muscle far from the suture line at a right angle to emerge some mm from the suture line. The needle is then brought in at the opposite side of the suture line again perpendicular to the suture line to penetrate deep into the muscle to emerge far from the suture line. The suture is the passed over the visceral peritoneum on the uterus to be passed into the muscle some 2 cm from its exit point and the process is repeated now from the opposite site as at the start. Here an ischemic suture is obtained that approximates both the edges of the opened cavities. Two or three sutures are needed on the anterior and the same amount posterior. It is easer to start with the posterior side and to finish with the anterior side.

The result is a unified body over an opened cervix. If the surgeon is in doubt he or she can please additional sutures on the border of the now unified cavity and the cervix anterior and posterior. There is no need for a watertight result.

The operation is finished by bringing in an adhesion barrier as adhesions are to be expected because of the long operating time blowing a substantial amount of CO_2 gas over the peritoneum and because of the necessary suturing there has been repeated manipulation of the visceral peritoneum over the uterus.

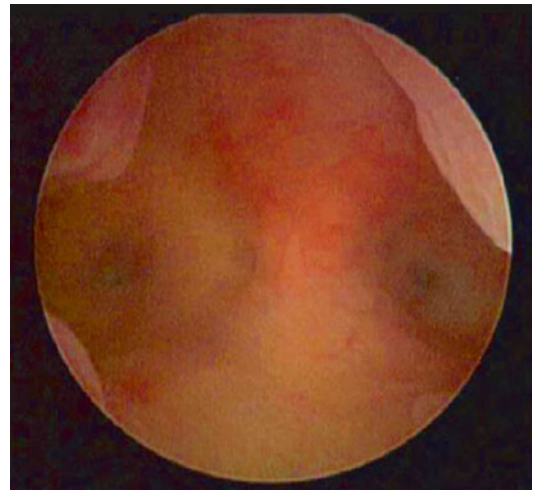

Fig. 28.9 Second look after 7 months reveals a unified fundus with an atypical anatomic positioning of both tubal ostia. The rest of the cavity is normal and there are no visible scars at the level of the cervix

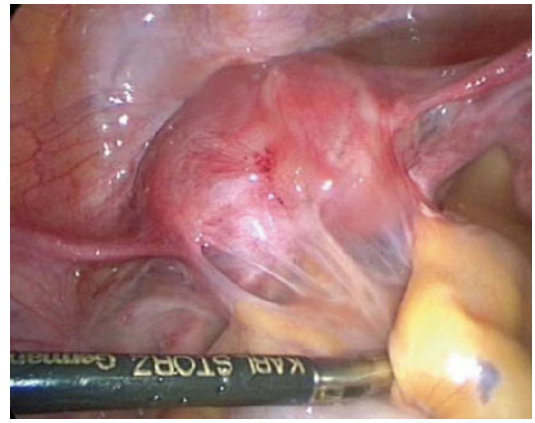

Fig. 28.10 At laparoscopy filmy adhesion at the level of the posterior fundus are visible. Typical for longer laparoscopic operations the adhesions are seen where the CO_2 gas has been blown over the operation field. The level of the scar itself seems less affected

Second Look Evaluation of the Uterine Cavity

A second look operation is ideally planned between 6 and 12 weeks after the original operation (Figs. 28.9, 28.10 and 28.11). However, in some of the cases we had to wait for the patient until she wanted to get pregnant again.

The second look operation started with a hysteroscopy, which is performed using the Bettocchi's vaginoscopic approach. A saline solution is used to distend the vagina as the first distention chamber with a 3.8 mm oval hysteroscope. The cervix is identified and cannulated and the cavity is observed.

Usually, following laparoscopic metroplasty, the cavity looks normal and the cavitary expansion is normal. The fundus however demonstrates like a stricture in the center so that both tubal ostia appear to lay on the fundal area itself and not at the cornual region lateral. Retracting the scope there is no visible scarring at the level of the isthmus.

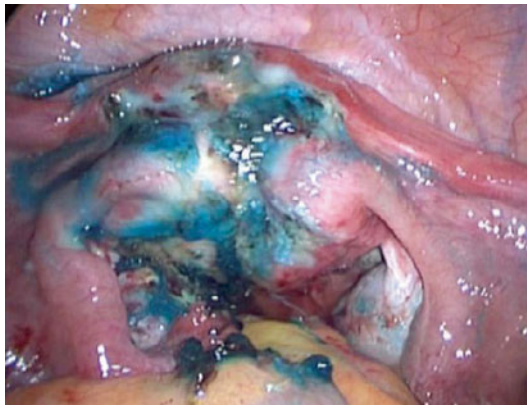

Fig. 28.11 After liberation of the adhesions a Poly Ethylen Glycol adhesion barrier (SparaySchield Covidien) is used to prevent further adehesion foemation

Follow-Up

There are several reports in the literature of spontaneous pregnancies after laparoscopic metroplasties. The attending physician has to take special care to avoid cervical dehiscence followed by spontaneous rupture of the membranes between 15th and 20th week of gestation. The patient described above conceived spontaneously but she had spontaneous rupture of membranes at 16th week of gestation thus losing her pregnancy. Thus, a preventive cervical cerclage (Shirodkar) could be placed in these patients using abdominal laparoscopic route in order to avoid contamination of the suture material by vaginal flora [6, 7].

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Part VII

Disorders of Sex Development

Disorders of Sex Development: Classification and Treatment

29

Stefanie Cardamone and Sarah M. Creighton

Introduction

Patients with Disorders of Sex Development (DSD) represent a heterogeneous group with unique and often multifaceted medical, surgical and psychological needs. For medical providers, caring for this subset of patients can often present exceptional challenges. Largely due to a scarcity of long-term outcome data, clear guidelines for management have not been established. What's more, intense debate continues, even amongst experts, in regards to controversial management issues including surgical interventions and disclosure.

In recent years, disapproval of the traditional approaches to patients with atypical sex development has grown amongst patients and medical professionals alike. Fueled largely by patient support groups, the prevalence of dissatisfaction with surgical outcomes and concerns regarding social stigmatization have been brought to the forefront. Simultaneously, advances in the identification of genetic and molecular causes of atypical sex development and improvements in surgical techniques are ongoing. In response, medical professionals are recognizing the need for a reexamination of these disorders and their management. Notably, there has been an increased awareness of the importance of psychological support in addition to surgical and medical care in this population at high risk of psychological morbidity. Traditional approaches, particularly related to surgical management, are being reevaluated.

This review will present the new terminologies and classifications of Disorders of Sex Development. Management options and controversies will be critically assessed and outcome data presented where available.

Classification

Historical Classification

Historically, words such as "intersex" and "hermaphroditism" were used in the description of patients with atypical sex development. Although used for some time, a growing dissatisfaction for these terms amongst families and patient support groups began to become apparent. Many felt them to be pejorative. Amongst health professionals, there was a recognition that these terms were often inaccurate, non- descript, and confusing. The imprecision of diagnoses precluded the accrual of sound scientific data on which to establish evidence-based guidelines for

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management. With improvements in molecular genetics and a better understanding of the etiologies of atypical sex development, it became increasingly clear that a revision of nomenclature was warranted.

New Classification

The Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology organized a meeting comprising 50 international experts in the field and patient advocacy group members alike. Following this meeting, a consensus statement incorporating a revised nomenclature was proposed in 2006. In it, the authors advocate the abandonment of terms such as "intersex," "pseudohermaphroditism," "hermaphroditism," and "sex reversal." Instead, the term "disorders of sex development" (DSD) was proposed to define "congenital conditions in which development of chromosomal, gonadal, or anatomic sex is atypical" [19].

The goals of this revised terminology were threefold. The authors aimed to integrate the molecular genetic etiologies of these disorders by creating genetically based diagnostic categories. This, they believed, would improve the organization and precision of diagnoses and therefore aid in accruing accurate and meaningful long-term outcome data. They hoped this data would subsequently provide evidence-based treatment guidelines for the care of patients with various disorders of sex development. Lastly, the authors aimed to remain sensitive to patient concerns regarding derogatory social stigmas surrounding the diagnoses of disorders of sex development and the previous terminologies.

Since its publication, the statement has been widely cited and endorsed in the literature as a model of patient care and incorporated into scientific literature. A follow up study of 60 DSD centers spanning 23 European countries indicated almost universal usage and acceptance of the new lexicon and a significant shift in terminology used in the medical literature [34].

Table 29.1 New nomenclature

Previous	Proposed
Intersex	Disorders of sex development
Male pseudohermaphrodite Undervirilization of an XY male Undermasculinization of an XY male	46, XY DSD
Female psuedohermaphrodite Overvirilization of an XX female Masculinization of an XX female	46, XX DSD
True hermaphrodite	Ovotesticular DSD
XX male or XX sex reversal	46, XX testicular DSD
XY sex reversal	46, XY complete gonadal dysgenesis

Reprinted with permission from Hughes et al. [19]

Table 29.1 outlines the former and proposed terminology that should be used in describing disorders of sexual ambiguity.

However, despite almost universal acceptance by clinicians, some patient groups remain uneasy with the new DSD terminology [39]. Reasons given include the application of the term "disorder" where "variation" might have been preferable and the lack of distinction in some languages between the terms sexual development and sex development. Finally, sufferers of Congenital Adrenal Hyperplasia (CAH) may regard their condition as a primarily endocrine disease rather than a disorder of sex organs. It is important that clinicians working within DSD remain sensitive to these differences in opinion.

The DSDs are broadly classified by their genetic etiologies as sex chromosome DSD, 46, XY DSD, and 46, XX DSD. Further identification of the source of the problem (for example gonad structure/function, androgen synthesis, androgen excess, receptor status) will lead to a specific diagnosis.

46, XY DSD

The most common XY DSDs involve disorders of androgen action or synthesis. In Complete Androgen Insensitivity Syndrome (CAIS), for example,

binding of testosterone and dihydrotestosterone (DHT) to the androgen receptor is impaired. The testes function normally, producing testosterone and anti-mullerian hormone (AMH) therefore preventing the formation of the internal müllerian system. However, androgen-dependant tissues are unresponsive to testosterone thus producing a female phenotype.

Defects in testosterone synthesis can be due to a number of enzyme deficiencies in the pathway of testosterone production. In 5α-reductase deficiency, the enzyme that converts testosterone to its more potent form, DHT, is defective. Since DHT is needed for masculinisation of the external genitalia, patients have undervirilised or phenotypically female external genitalia. In phenotypic females with 5α-reductase deficiency, virilisation may occur at puberty as testosterone production increases.

Other 46, XY DSDs include disorders of testicular development, including complete gonadal dysgenesis (Swyer syndrome), LH receptor defects and disorders of AMH (persistent müllerian duct syndrome). Isolated hypospadias and cryptorchidism are also considered forms of XY DSD.

46, XX DSD

46, XX DSDs result from defects in ovarian development or conditions leading to excess androgen exposure, of which CAH is the most common. In the female newborn, CAH is the leading cause of virilised genitalia. Inherited in an autosomal recessive manner, more than 95 % of cases are caused by a deficiency in 21-hydroxylase in the adrenal cortex. As a result, adrenal cortisol production is blocked, leading to a shunting of steroid precursors toward adrenal androgen production. In addition to virilisation, severe deficiencies can lead to critical electrolyte abnormalities and can be life threatening.

46, XX DSDs also include gonadal dysgenesis, androgen exposure due to placental aromatase and oxidoreductase deficiencies, as well as maternal virilising tumours. Abnormalities of the müllerian ducts, including vaginal atresia and cloacal anomalies, are also considered part of the spectrum of XX DSD.

Sex Chromosome DSD

Sex chromosome DSD include mosaic karyotypes including 45, X/46, XY mixed gonadal dysgenesis, Turner (45, X) and Klinefelter (47, XXY) Syndromes and their variants.

The Importance of the Multidisciplinary Team and Psychosocial Support

Patients with a DSD should be managed by a multidisciplinary team (MDT) with experience and expertise in the management of these complex disorders [19]. Although the exact composition of the team can vary from one centre to another, ideally the team would be composed of an endocrinologist, urologist/pediatric surgeon, gynaecologist, psychologist, ethicist, and geneticist. The collaboration of a variety of health professionals can facilitate timely assessment, ensure necessary and appropriate investigations are done, and abet decisions regarding sex assignment when necessary. It is increasingly clear that ongoing psychological care is essential to self-acceptance and social adjustment. Each case should be individualized and cooperation among specialists is crucial to ensure decisions are made in line with the best interests of each patient and family. In addition, parents should be intimately involved with the team immediately and their participation in decision-making should be encouraged.

The implementation of an MDT has been shown to be effective at improving medical and mental health services for patients with DSD. In the setting of structured multidisciplinary care, significantly more patients received appropriate indicated testing. Additionally, they benefited from more frequent mental health counseling, structured education, and peer support group participation [37].

Many European DSD centres have adopted an MDT approach to DSD care in accordance with the consensus recommendations. Encouragingly, nearly all centres surveyed (95 %) reported offering psychological support services. However, nearly half of European centres had not implemented a multidisciplinary approach to DSD care, highlighting that a need for improvement remains [35].

Presentation and General Management Considerations

Patients with a DSD may come to medical attention via two main clinical presentations. Some present with ambiguous genitalia at birth. In others, a diagnosis may come to attention around the time of puberty in the form of delayed pubertal development, primary amenorrhea, or virilisation at puberty. Gynaecologists managing DSD will therefore be involved in the care of adolescents with a known DSD transitioning to adult services as well as girls and women presenting for the first time with a new diagnosis of DSD.

Management of the Neonate

At birth, any atypical genital appearance should raise the possibility of an underlying DSD. Specifically, overt genital ambiguity, virilised female genitalia (clitoromegaly, labial fusion, inguinal or labial mass), and undervirilised male genitalia (bilateral cryptorchidism, unilateral cryptorchidism with incomplete scrotal fusion or hypospadias, and perineal hypospadias) require investigation. Such abnormalities, sufficient enough to warrant further investigation, are estimated to occur in 1/4,500 births [1].

A disorder of sex development at birth raises both medical and psychosocial issues that need to be immediately addressed. First and foremost, a life-threatening condition, namely salt-wasting CAH, must be excluded. Secondly, a specific diagnosis should be investigated and, whenever possible, be identified. Lastly, a viable sex of rearing needs to be determined. It is important however that the latter is done only after proper evaluation by an experienced multidisciplinary team.

Gender assignment recommendations are clear-cut in only a minority of patients. In all cases, it is imperative that decisions be made by a fully informed family along with the MDT. At the time of gender assignment, the primary goal is to avoid an assignment that is ultimately inconsistent with gender identity, leading to gender dysphoria and psychological morbidity. Multiple factors have been identified which may play a role in adult outcomes and can be used to guide gender assignment decisions. These include psychosocial factors (social/cultural circumstances), fetal CNS androgen exposure, anatomy of the external genitalia, options for functional surgical repair, anticipated quality of sexual function, and fertility potential. Outcome studies suggest that the best predictor of adult gender identity is, in fact, the initial gender assignment [16].

Once a sex of rearing has been determined, consideration is usually given to the need and desire for surgical reconstruction of gender concordant genitalia. As will be discussed, the indications, ideal timing, and methods for surgical management remain highly debated.

Management of the Adolescent

In the adolescent with either a known or newly diagnosed DSD, general considerations may include the need for gonadectomy, vaginal assessment and treatment for menstruation and future intercourse, and hormone replacement.

The Adolescent with a New Diagnosis

A significant proportion (10–20 %) of patients with a DSD present later in childhood or young adulthood. In these cases, ambiguity of the external genitalia is not present at birth. These patients most commonly seek gynaecologic care due to absent, delayed, or incomplete puberty, virilisation at puberty, or primary amenorrhea. An initial work up for delayed puberty including physical examination, FSH level and karyotype will provide clues to the diagnosis. More specific testing such as testosterone, androstenedione, DHT, AMH levels, HCG stimulation testing, specific gene sequencing, enzyme assays, and appropriate imaging can subsequently be performed. The majority of these patients will be diagnosed with CAIS, gonadal dysgenesis (XX or XY), or other XY DSD including testosterone biosynthesis defects.

The Adolescent with a Previous Diagnosis of DSD

At adolescence, patients diagnosed with a DSD in infancy will begin to transition to adult care. Adolescence can be a difficult time for all children, however this is particularly true in the setting of a DSD. Psychosocial support is of paramount importance during this transition period. The psychologist can address issues of gender identity, adjustment and transition through puberty, sexuality, sexual behavior and relationships.

In most cases, vaginal assessment will be required. Many patients will have had feminising surgery as infants and children. In those with a uterus, such as girls with CAH, examination should assess for patency for menstruation. Examination should also note whether there is sufficient vaginal caliber for future tampon use and vaginal intercourse. Given the high rates of vaginal stenosis in this setting, a thorough examination is important. In an adolescent, particularly in those with a history of multiple genital surgeries, examination can be difficult and is often performed under general anesthesia. Vaginal dilation and surgical vaginoplasty may be required depending on the examination findings.

Management Controversies in Disorders of Sex Development

Sex Steroid Replacement in DSD

Patients with DSD may require hormone replacement either due to gonadal failure or following gonadectomy. Hormonal supplementation is required to induce development of secondary sexual characteristics, acquire normal bone mineralization, and to initiate menses at the time of puberty. The gynaecologist should work along side an experienced endocrinologist to determine if and when hormonal replacement should be initiated. In general, puberty induction and maintenance is undertaken in three phases, simulating normal pubertal development. Estrogen replacement for the induction of breast development is most commonly followed by progestin and estrogen combination replacement for the establishment of normal menses if a uterus is present. Long-term maintenance of a normal estrogen state must be obtained for bone health. The selection of doses and method of cycling depends on individual needs. A progestin should be provided in girls with a uterus secondary to the established risk of endometrial hyperplasia with unopposed estrogen stimulation. However, there is no evidence that the addition of cyclic progestin is beneficial in those without a uterus.

Feminising Genitoplasty

Despite improving surgical techniques, controversy persists surrounding surgical care of patients with DSD. In patients assigned to a female sex of rearing, debate encompasses the type, timing, and indication for feminising genitoplasty. The controversy is fueled by a lack of long-term outcome studies in patients following genitoplasty. Most commonly, feminising genitoplasty is performed in virilised girls with CAH, but may also be performed in partially virilised patients with XY DSD assigned to a female sex of rearing (i.e. partial androgen insensitivity, mixed gonadal dygenesis). Feminising genitoplasty generally includes clitoroplasty, vaginoplasty, and labioplasty as needed.

Timing

Historically, sentiment surrounding feminising surgery in DSD patients was routed in the hypothesis of ‘psychosexual neutrality’ proposed by John Money in the 1950s. Inherent in this hypothesis, early reconstructive genital surgery was thought to be imperative to the acceptance of an assigned gender. The “optimal gender policy,” as it came to be known, encouraged early corrective surgery as this was thought to help the child, as well as their parents, to facilitate gender identity and appropriate gender role behavior [30, 31].

Supporters argue that early surgical management to create gender concordant genitalia will lead to better psychosocial outcomes and avoid ridicule from peers and social withdrawal in childhood. However, there have been no studies

to evaluate this hypothesis. There are currently no studies to show that early surgical feminisation improves psychosocial outcomes or gender acceptance. A study of a group of adult CAH women found no correlation between age of clitoroplasty or vaginoplasty and development of female gender identity [5].

Resistance to the paradigm of early feminising genitoplasty has arisen from accruing evidence of poor cosmetic and functional outcomes in adult women following surgery in infancy or childhood. The Intersex Society of North America has published recommendations that center on the avoidance of genital surgery unless medically necessary without the patient's informed consent, sighting the potential consequences of genital surgery [20]. Genitoplasty appears to be associated with impaired global sexual functioning including decreased arousal, sexual desire, lubrication, orgasm, as well as increased pain with intercourse. In addition, this population is less likely to be sexually active, and shows a lower frequency of intercourse when compared to the general population [12, 17, 18, 22].

Although these results may not be solely a result of surgical manipulation, recognizing the role of multifactorial psychological components in sexual satisfaction, there does appear to be sufficient data to suggest a detrimental effect of surgical genitoplasty on sexual function. DSD patients who have not undergone surgical intervention do not have the same discrepancies as those who have, with sexual function comparable to the general population [12].

Clitoroplasty

The clitoris is an organ with a sole function of providing sexual pleasure. The possibility of a disrupted sexual response due to reduced innervation of the clitoris after surgery must be considered before clitoroplasty is performed [29]. Crouch et al. objectively demonstrated decreased clitoral sensation amongst a group of CAH patients following clitoroplasty when compared to controls. There was a linear relationship between the amount of sensitivity impairment and severity of sexual difficulties [12].

Therefore, the main objectives of modern clitoroplasty are to reduce the size of the clitoris to achieve feminine appearing external genitalia while attempting to maintain clitoral sensitivity through preservation of the dorsal neurovascular bundle. Currently, a number of clitoral reduction techniques exist but there are no comparative studies of the outcomes of each. There continues to be much debate surrounding optimal techniques. As more has been learned about the functional outcomes of clitoral surgery, historical excisional procedures have been abandoned for nerve sparing reduction procedures. It does appear that procedures that preserve dorsal nerve function offer some functional benefit over total excision [12, 33].

Vaginoplasty

Vaginoplasty is considered to reconstruct or create a vagina in cases where little or no vagina is present. This can be in the setting of a primary procedure, or in cases with a history of previous vaginal surgery. The goals of treatment include allowing penetrative intercourse, as well as improving sexual function and psychological outcomes. Similar to clitoroplasty, there are no evidence-based practice guidelines regarding the ideal timing or method of vaginoplasty.

Vaginoplasty in the Neonate with Ambiguous Genitalia

When performed in infancy for virilised genitalia, current society guidelines recommend early separation of the common urogenital sinus with vaginoplasty at the time of genitoplasty [19, 40]. There are surgical considerations to suggest an advantage to early single stage procedures. For example, if performed at the time of clitoroplasty, the phallic skin can also be used as part of the vaginal reconstruction. It has been suggested that vaginal reconstruction in the neonatal period may be facilitated by a greater degree of elasticity of the vaginal tissue due to recent exposure to placental and maternal estrogens [4]. Lastly, by separation of the vagina and urethra at the time of vaginoplasty, potential urinary complications can be avoided.

More recently, there has been an increased interest in shifting management away from 'single-stage' procedures in infancy to deferring vaginoplasty until adolescence. This has been largely supported by evidence of high re-operation rates in patients in whom vaginoplasty was performed in infancy, predominantly related to extremely high rates of vaginal intriotal stenosis. Follow up series on those with vaginoplasty in infancy report rate of stenosis of 36–100 % [3, 23]. Nearly all patients will require further vaginal dilation or vaginal reconstruction in adolescence. In one follow up series, only 2 % of patients required no further treatment after initial feminising surgery [11].

Vaginoplasty for Vaginal Agenesis/ Hypoplasia

In cases of an absent or hypoplastic vagina, guidelines suggest that vaginoplasty be performed in adololescence when the patient is psychologically motivated and can be a participant in the decision. It is now consensus that non-surgical vaginal dilation be considered the first line treatment [2]. Vaginal dilation therapy is easy to perform, cost effective, avoids surgical risk, and can be highly successful. When utilized properly, success rates as high as 80 % have been reported as evidenced by adequate vaginal caliber and successful intercourse [21]. However, success of dilator therapy requires dedication and compliance on part of the patient and therefore should not be undertaken before adolescence. Roberts et al. found that patients younger than 18 years of age had a significant dilation failure rate [36]. Some patients find dilation unacceptable due to discomfort, pain, or feeling the regimen is shameful or "distasteful" [6]. In order to maximize compliance and success, treatment should be pursued in centers with multidisciplinary care, including specialist emotional and psychological support. Many centers have adopted specialized dilation support programs (Fig. 29.1).

In cases of vaginal dilation failure, or in patients with previous genital surgery and scarring making dilation difficult, surgical vaginoplasty may be indicated. Currently, various surgical techniques exist with no common agreement on the gold standard technique for vaginoplasty. As with other aspects of DSD care, there is a lack of medical literature reporting the long-term anatomical and functional outcomes of patients following vaginoplasty procedures. The technique utilized often relies on surgeon preference and expertise, genital anatomy, and previous genital surgery. Techniques include intestinal vaginoplasty, traction techniques (Vecchietti procedure), balloon vaginoplasty, peritoneal and skin flaps, and grafting techniques using amnion, skin (McIndoe), buccal mucosa, or auto grafts. Each procedure carries its own risks, most commonly vaginal stenosis, fistulae formation, vaginal dryness or increased vaginal discharge, and vaginal prolapse. In addition, malignancy has been reported following both skin graft and intestinal vaginoplasties [14]. Post operative long term vaginal dilation is universally required following surgical vaginoplasty to prevent stenosis and it is imperative that patients understand this pre-operatively.

Cosmesis Outcome Data

In addition to the functional outcomes discussed, concerns also exist regarding the long-term cosmesis following surgical feminisation in infancy or early childhood. There are no standardized methods available for cosmetic assessment and there is a scarcity of published data addressing this issue. After studying a population of adolescent patients following feminising genital surgery, Creighton et al. reported a number of important findings. Namely, 41 % of patients were judged by clinicians to have a poor cosmetic genital appearance. Thirty-nine percent showed clitoral re-growth despite a previous reductive surgery, which lends support to the deferment of surgery during childhood in cases of mild clitoromegaly [11]. In addition, upon self-assessment, a substantial proportion of patients are also unhappy with post-operative cosmetic results. In a study of 46, XY DSD patients following feminising genitoplasty, only 50 % of patients reported they were happy with the cosmetic appearance of their genitals, while 15 % reported they were very dissatisfied. These results were not influenced by the number of surgical procedures done [22].

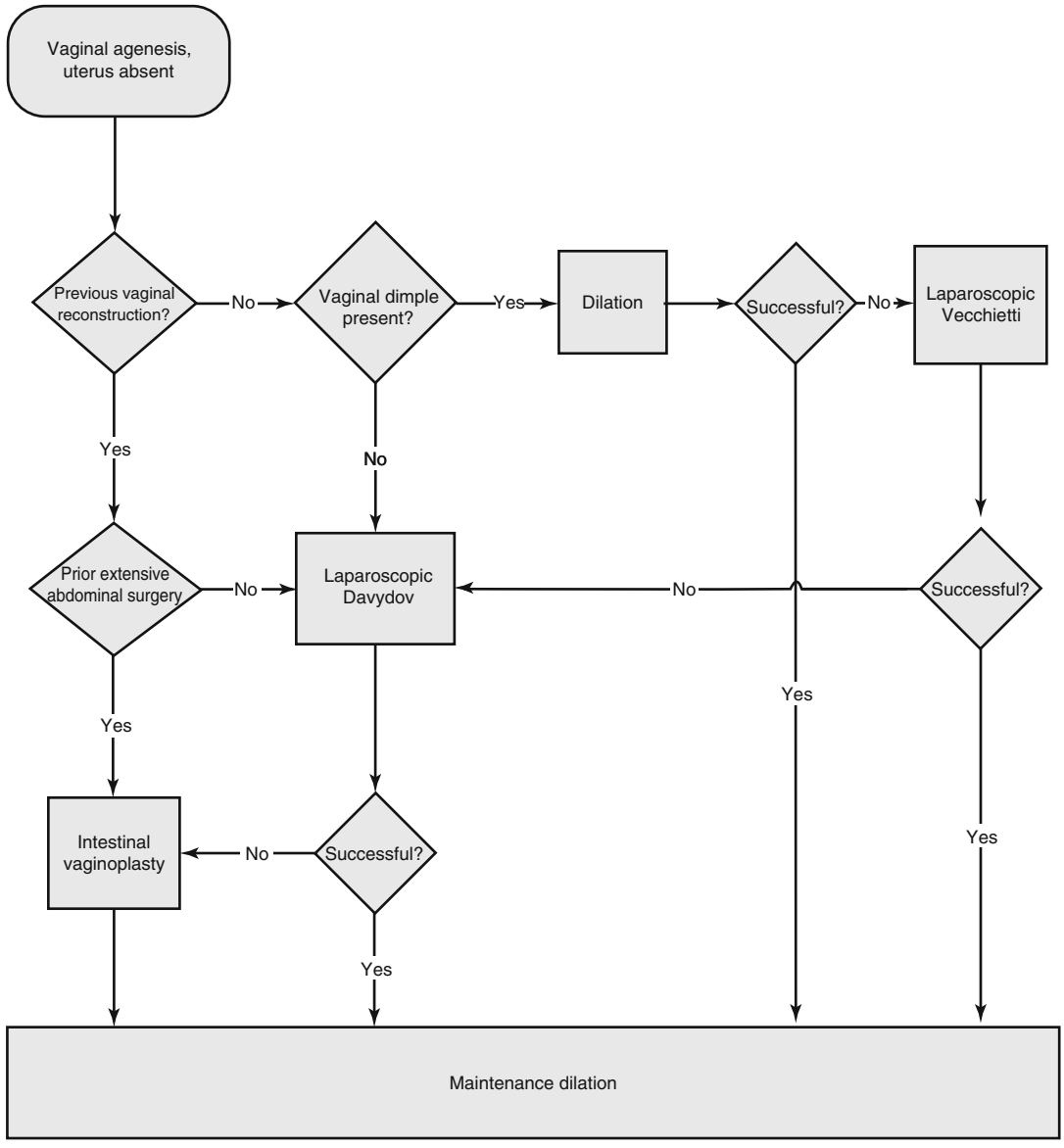

Fig. 29.1 University College Hospital vaginal agenesis treatment algorithm (Reprinted with permission from Michala et al. [27])

In addition to the cosmetic outcomes described, it is important to appreciate the large variation in the appearance of female external genitalia. Recent literature has demonstrated a wide variation in all parameters of the genitalia in normal women, with the clitoris, for example, ranging in size from 5 to 35 mm [25]. Therefore, given this variety and a lack of normative data, the need for and amount of reconstruction necessary is subjective [38]. It is also important to note that cosmetic appearance will change with age. At puberty, the growth of pubic hair and increased fat deposition in the mons and labia can cause a previously prominent clitoris to appear less so.

Gonadectomy

Gonadectomy is traditionally recommended in XY women due to the increased risk of gonadal malignancy. Germ cell tumors, specifically the non-invasive precursors carcinoma *in situ* (CIS) and gonadoblastoma, and their invasive counterparts seminoma/dysgerminoma and non-seminoma, occur with increased frequency in patients with DSD and Y chromosomal material. Recent data indicates that it is not the Y chromosome itself that determines this risk, but a candidate gene, the testis specific protein Y (TSPY) on a specific region of the Y chromosome. It is the abberant expression of the TSPY gene that is thought to lead to increased proliferation of germ cells and therefore oncogenic activity [26].

The exact risk of the development of germ cell tumors in women with XY DSD is presently under debate. In CAIS where the testis is histologically normal, the incidence has been estimated at 1–3 % [10]. However, these figures are derived from paediatric studies with short follow-up and inclusion of post-gonadectomy patients. The incidence is likely higher in adulthood [15]. The risk appears higher in other diagnoses such as partially virilised XY DSD, although the exact incidence in these rare syndromes remains to be elucidated. In gonadal dysgenesis, on the other hand, characterized by a poorly differentiated dysgenic gonad, the mean risk is markedly higher. Overall, the risk has been estimated at 30–40 %, with gonadoblastoma often arising at a young age [28].

In high risk groups, such as 46, XY pure gonadal dysgenesis, early gonadectomy should be performed at time of diagnosis [7]. In patients with disorders of androgen synthesis being raised female, the gonads should be removed before puberty or at the time of diagnosis to avoid virilisation.

In patients with CAIS, traditionally the gonads were removed at the time of diagnosis. Current recommendations have changed to suggest gonadal conservation with subsequent removal following the completion of puberty. Delaying gonadectomy until after puberty allows for spontaneous pubertal development without hormone replacement and allows the adolescent to be involved in the decision regarding timing of surgery. In light of these benefits, postponing gonadectomy does not greatly increase the risk of malignancy given the tumor risk in this population has been shown to be very low before puberty (0.8–2.0 %) [9, 19]. In further support, there have been reports of loss of libido following gonadectomy and concerns about long-term hormonal replacement.

However there is a trend of adult women with CAIS now choosing gonadal conservation. These women may site reasons including fears regarding surgical risk, inconvenience of surgery, difficulties with acceptance of their diagnosis, reluctance to take hormonal replacement post-operatively, or concerns regarding fertility [15]. Currently, there are no reliable screening modalities for pre-malignant or malignant testicular disease in this population. In patients with CAIS, gonads are most commonly intra-abdominal and therefore non-palpable. Unfortunately, imaging techniques, including US and MRI, have been shown to have poor sensitivity in detecting malignant changes [32]. Additionally, tumor markers are not reliable.

For these reasons, it seems appropriate to maintain the current recommendation to proceed with gonadectomy following puberty. Women who do not undergo gonadectomy should be counseled regarding the risks of malignancy. Currently, guidelines for conservative follow-up of these patients have not been established. Yearly history and physical, MRI, and tumor markers including AFP, Bhcg, Ca 125, and LDH should be considered in this setting.

Disclosure

In a 1953 landmark paper on Androgen Insensitivity Syndrome, gynecologist John Morris argued against full disclosure of the diagnosis to XY women living with androgen insensitivity due to his concern for resultant psychiatric morbidity. This sentiment established the mindset of management of XY disorders of sex development for

decades to follow [8]. As the ethicolegal mileu of medicine changed, with increased emphasis on patient autonomy and informed consent, acceptance of Morris' method of non-disclosure decreased. Even still, the specific issue of revealing the karyotype to XY women remained debated until has recently as the late 1990s.

In contrast to Morris' theory, when asked, many patients express a sense of relief after learning the truth of their diagnosis. Patients surveyed have conveyed a sense of understanding of themselves and childhood experiences following disclosure. Some have revealed that they take comfort in the ability to talk about their condition and share their experiences with those close to them [13]. Moreover, many patients feel that secrecy and the concealment of their diagnosis contributed more to their suffering than the condition itself. In fact, only an extremely small proportion of patients wish they were not told of their diagnosis [24]. Case series also report patients expressing anger and regret over irreversible surgical procedures done during their childhood, suffering from complications and shame of someone else's doing.

Recognizing the importance of patient autonomy, the 2006 Consensus statement recommends open communication between the medical care team, patients, and families. In addition, patient participation in decision-making is encouraged [19]. Whenever possible, irreversible surgical intervention should be delayed until adulthood, allowing the patient to be an active participant in the informed consent process.

Recent data suggests that practice in disclosure has changed in a positive direction. In a study of 100 patients with DSD, Laio et al. reported that patients diagnosed more recently were more likely to feel they were informed of their diagnosis in an appropriate and timely manner. Even still only 49 % of these patients had received full disclosure by mid-adolescence, suggesting that room for improvement remains [24].

It is now established practice to disclose the genotype of these women at the time of diagnosis. Experts agree that sensitive disclosure with appropriate social and psychological support can aid in self-acceptance, adjustment and development of identity.

Conclusion

Growing dissatisfaction over the care of patients with atypical sex development has lead to a reclassification and reassessment of the traditional approaches to management. The Chicago Consensus Statement aimed to provide a simple and logical classification of the causes of DSD while remaining sensitive to patients concerns. Future research will benefit from the use of a universal terminology amongst healthcare professionals. Still, many questions as to best practices remain unanswered. It is clear that more research is needed to gather information on clinical outcomes in order to refine medical, psychological, and surgical management. It is becoming universally accepted that a multidisciplinary and holistic approach to the care of these patients is crucial to successful outcomes. Whenever possible, there is increasing support for more conservative approaches to management, with deferment of irreversible interventions until the patient can be a fully informed participant in decision-making and informed consent.

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