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Andrea R. Genazzani ·
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Amenorrhea

Volume 10: Frontiers in Gynecological Endocrinology

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- **Series Editor: Prof. Andrea R. Genazzani argenazzani@gmail.com and isge.aige@gmail.com**

Andrea R. Genazzani
Angelica Lindén Hirschberg
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Editors

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Editors
Andrea R. Genazzani
International Society of Gynecological Endocrinology
Pisa, Italy

Alessandro D. Genazzani
Department of Obstetrics and Gynecology
University of Modena and Reggio Emilia
MODENA, Modena, Italy

Svetlana Vujovic
Faculty of Medicine
Clinic of Endocrinology
Diabetes and Diseases of Metabolism
University of Belgrade
University Clinical Center of Serbia
Belgrade, Serbia

Angelica Lindén Hirschberg
Department of Gynecology and Reproductive Medicine
Karolinska University Hospital
Stockholm, Sweden

Rossella Nappi
Research Center for Reproductive Medicine, Gynecological Endocrinology and Menopause
IRCCS San Matteo Foundation
Pavia, Italy

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Efthymios Deligeoroglou and Vasileios Karountzos

Abbreviation

MM Müllerian malformations

1.1 Introduction

Müllerian malformations (MM) are the anomalies resulting from failure of fusion of the paramesonephric ducts in the middle line, during their connection with the urogenital sinus. They occur due to alterations in the formation of the upper vaginal lumen and the uterine lumen, and also because of non-absorption of the septum in the fusion of ducts. Their clinical expression varies from very light disorders to serious obstetrical conditions such as vaginal and uterine agenesis, which is called the Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome [1]. The prevalence of congenital uterine anomalies according to Saravelos et al. [2] was found to be 6.7% in general population, 7.3% in sterile women, and 16.7% in women who had recurrent miscarriages. The septate uterus seems to be the most common anomaly in infertile women and the arcuate uterus the most common among those who have habitual abortion. In another study, Nahum [3] found the above mentioned statistics to be 0.5%, 0.17%, and 3.5%, respectively. What is of great importance is that müllerian

E. Deligeoroglou (✉)
Medical School, National and Kapodistrian University of Athens, Athens, Greece

Division of Pediatric-Adolescent Gynecology, MITERA Children's Hospital, Athens, Greece

V. Karountzos
Division of Pediatric-Adolescent Gynecology, MITERA Children's Hospital, Athens, Greece

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anomalies present with great diversity giving many diagnostic and treatment options and doubts, while most of the studies include isolated cases or small case series focusing on the obstruction of menstrual flow, obstetric complications, and/or history of sterility [4].

1.2 Prevalence

The prevalence of congenital uterine anomalies in unselected populations is 5.5%, while in infertile patients is 8.0%. This prevalence, especially in infertile women, is not increased and it is approximately the same as that in fertile patients with normal reproductive outcomes [5]. When infertile and fertile women were included in the same study, septate uterus was found in 35%, bicornuate in 26%, arcuate in 18%, unicornuate in 10%, didelphys in 8%, while aplasia in 3% [5]. It is well understood that these frequencies vary regarding the populations that are studied, as well as the criteria that are used to identify these abnormalities. In another well-designed study, including patients with normal reproductive outcomes, septate uterus was found in 90%, bicornuate in 5%, while didelphys in 5% [6].

1.3 Etiopathology

Sexual differentiation is a continuous process that starts with the fertilization of the ovule by the sperm. In women, the normal absence of müllerian inhibitory factor results in degeneration of the mesonephric ducts to paramesonephric ducts. These structures, which are bilateral, suffer from stretching in around the ninth week of pregnancy and remain open and separated in the upper segment, thus originating in the fallopian tubes. In the lower segment, they form after their junction in the upper 2/3 of the vagina [1]. As the fusion has been completed, the septum between the paramesonephric ducts starts to be absorbed and finally the uterovaginal canal. Uterus has a normal shape around the 12th week of pregnancy and is totally completed in the 22nd week [7]. The development of the vagina depends on the fusion between the urogenital sinus with the müllerian structures. Therefore, the upper 4/5 of the vagina is of müllerian origin and the lower 1/5 has its origin in the urogenital sinus. The epithelium of the upper 1/3 of the vagina originates in the uterovaginal primordium and the lower 2/3 in the urogenital sinus, and the hymen is a sign of the endodermal membrane [8]. What is independent of this process is the ovaries, which are developed from cells of a different origin, and as a result they are not associated with müllerian anomalies [1, 9]. Due to the same mesodermal origin of the genital and urinary tracts, any paramesonephric anomaly could be associated with renal anomaly, which should always be investigated in these patients. Congenital malformation of female genital tracts is a result of a failure during embryogenesis, and the most common genes taking part in this procedure are HOXA13 (hand-foot-genital syndrome) [10] and HOXA10, expressed in the embryonic paramesonephric ducts [11]. Genital anomalies induced by environmental agents such as diethylstilbestrol

and thalidomide are also described in the literature. It is of great importance that the type of malformation depends on the moment that the failure occurs, and the earlier in pregnancy it takes place, the more serious the malformation is. Therefore, complete aplasia associated with urinary malfunctions may be seen if the pathology occurs between the 6th and 9th weeks of pregnancy, and on the other hand total or partial septation, rarely associated with urinary malformations, may be observed if the problem occurs between the 13th and 17th weeks of pregnancy.

1.4 Classification Systems

Starting from the nineteenth century, several classifications have been proposed based on embryology and development of müllerian ducts, but these classification systems have several difficulties not only in terminologies, but also in failure in the characterization of the anomalies. The goal was the same, in all cases, to make the diagnosis more accurate, as well as to help distinguish cases, but the problem remained with no consensus in relation to their use. Among those, the classification VCUAM (Vagina Cervix Uterus Adnex-associated Malformation) [12] can be cited as well as that proposed by Acien and Acien [6]. Currently, the most used is the one proposed by Buttram and Gibbons [13], accepted and modified in 1988 by the American Fertility Society (AFS), today the American Society of Reproductive Medicine (ASRM) [14], which separates the anomalies into seven classes (Fig. 1.1). The European Society of Human Reproduction and Embryology (ESHRE) and the European Society for Gynaecological Endoscopy (ESGE) [14] developed another

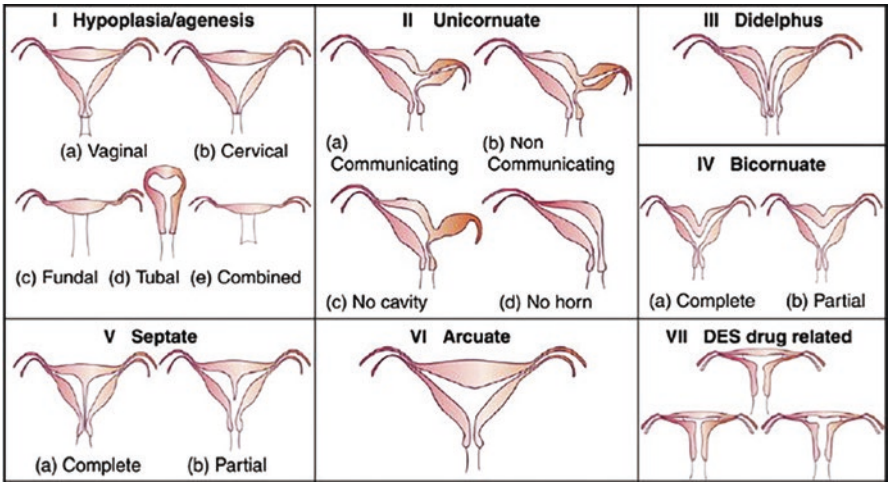

Fig. 1.1 The AFS/ASRM class ification system. Adapted by the American Fertility Society. The American Fertility Society classification of adnexal adhesions, distal tubal occlusion secondary or tubal ligation, tubal pregnancies, müllerian anomalies, and intrauterine adhesions. Fertil Steril 1988;49(6):944–55

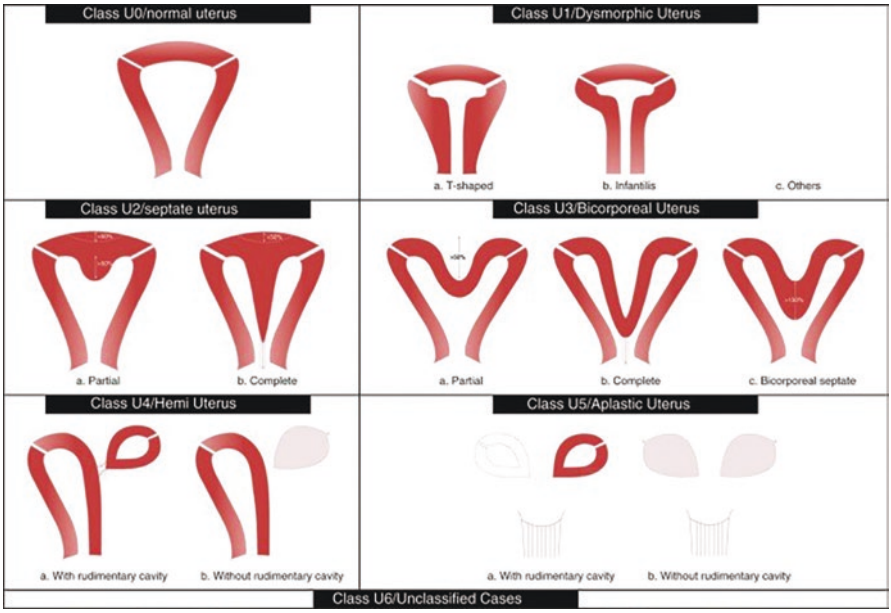

Fig. 1.2 The ESGE/ESHRE classification system. Adapted by Grimbizis GF, Di Spiezio Sardo A, Saravelos SH, Gordts S, Exacoustos C, Van Schoubroeck D, et al. The Thessaloniki ESHRE/ESGE consensus on diagnosis of female genital anomalies. Hum Reprod 2016;31(1):2–7

classification based on anatomy, embryological origin, degree of uterine deformity, and cervical and vaginal anomalies (Fig. 1.2). It is possible that no classification of müllerian anomalies can encompass all these types of malformations, which could present themselves in many different ways. Based on AFS-ASRM [12] and ESHRE/ESGE [14], the classification of anomalies is as follows (Fig. 1.3):

Class 1 (AFS)/U5bC4V4 (ESHRE/ESGE): Refers to agenesis or hypoplasia of uterus and vagina, which in its extreme form is known as the MRKH syndrome. As it can be easily understood, the problem occurs at the start of the development of müllerian ducts. It is characterized by agenesis or severe uterine hypoplasia, absence of the upper 2/3 of the vagina in patients with normal female karyotype (46,XX), and development of secondary sexual characters compatible with age [15]. The lower third of the vagina rarely passes 2 cm in depth. Its prevalence is of 1/4500–5000 women [1, 16] and, despite being a rare disease, is considered the second most common cause of primary amenorrhea, right after hypogonadism [17]. MRKH syndrome is classified into two groups: typical (isolated uterovaginal agenesis) and atypical (associated with extra genital malformations of the kidneys, skeleton, auditory system, and heart) [15]. The first clinical experience of these patients is primary amenorrhea and incapacity for vaginal coitus, while renal malformations are the commonest concomitant lesions, varying from 15 to 34%.

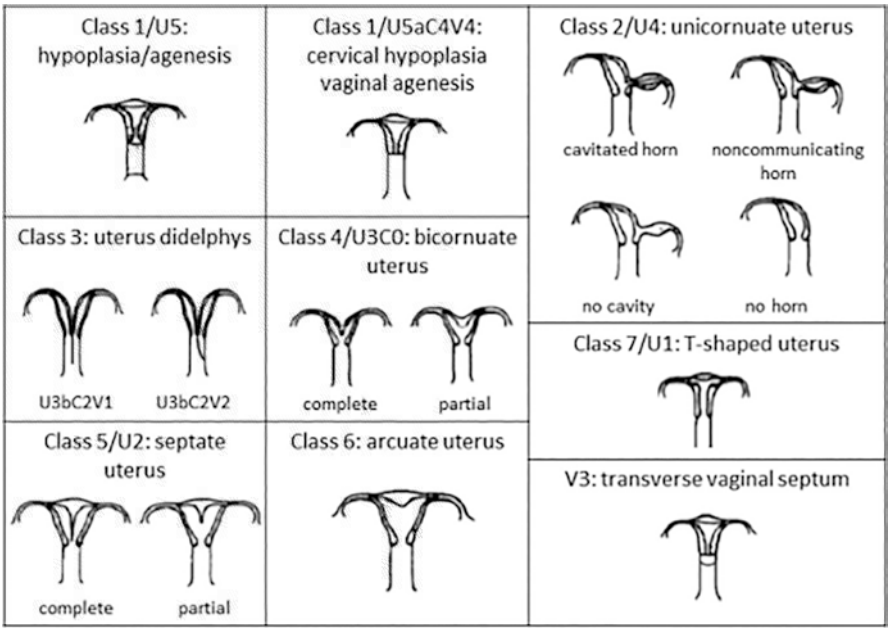

Fig. 1.3 The combination of ESHRE/ESGE and AFS/ASRM system. Adapted by Ludwin A, Ludwin I. Comparison of the ESHRE-ESGE and ASRM classifications of müllerian duct anomalies in everyday practice. Hum Reprod 2015; 30:569–80

Class 1/U5aC4V4 (ESHRE/ESGE): Congenital cervical atresia occurs in 1/80,000–1,000,000 women [18]. Most of the times, it is associated with total or partial aplasia of the vagina and renal anomalies. Not rarely, a hematometra is observed due to the menstrual blood that has no way to flow out, while the fallopian tubes can be distended leading in some cases to an acute hemorrhagic abdomen. It should be diagnosed and treated immediately due to its significant morbidity and mortality.

Class 2 (AFS)/U4 (ESHRE/ESGE): The unicornuate uterus is the result of inability of one of the müllerian ducts to migrate to its correct place; therefore, a failure in the unilateral development occurs. This uterine horn can be unique, when there is complete agenesis of one of the müllerian ducts (U4b), or accompanied by another rudimentary uterine horn, which could be of three types: without cavity (U4b), cavitated, or cavitated noncommunicating horn (U4a). What is of great importance is that the endometrium in the latter corn undergoes hormonal stimulation and its cavity progressively increases in volume due to the retention of menstrual blood, which has no way of flowing out. This causes pain many times of cyclic origin, leading to an increased volume in abdomen. These women unfortunately may have obstetrical complications such as miscarriages, restriction of intrauterine growth, and premature birth labor. Unicornuate uterus represents 0.3–4% of the uterine anomalies and occurs in 1/5400 women, while 74–90% are associated with rudimentary horn [19, 20].

Class 3 (AFS)/U3bC2V1 or U3bC2V2 (ESHRE/ESGE): Uterus didelphys occurs as a result of complete failure of fusion of both müllerian ducts. However, development of uterus continues individually, giving rise to two uterine cavities, two cervices, and two vaginas separated, and between them there will be a longitudinal septum, while menstrual flow is normal. In rare cases, the septum can obstruct one of the vaginas and cause menstrual flow retention of that hemi-uterus causing cyclic pelvic pain, with a result of hematocolpos, hematometra, hematosalpinx, and hematoperitoneum. If ipsilateral renal agenesis is observed, the syndrome is called Herlyn-Werner-Wunderlich (HWW) syndrome and represents 3–4% of the MM. The obstetric prognosis is good, and there are also reported cases of pregnancies with twins with a fetus in each uterus [21].

Class 4 (AFS)/U3C0 (ESHRE/ESGE): Bicornuate uterus occurs when there is a failure in the fusion of the two müllerian structures that results in two uterine horns and only one cervix. Complete or partial bicornuate uterus depends on the degree of deficiency of the fusion, so in complete case the cavities are separated up to the internal orifice of the cervix and are not linked and in partial case there is some linkage. It represents around 10% of the MM, is asymptomatic in the majority of cases, and can cause miscarriage or premature birth [22].

Class 5 (AFS)/U2 (ESHRE/ESGE): Septate uterus is the result of the deficit in reabsorption of the median septum after the fusion of müllerian structures. Depending on the moment when the failure occurs, the septum can be complete or partial and the external contour of the uterus is always normal. The structure of the septum can be muscular or fibrous, and this diagnostic is extremely important for therapeutic approach. It represents 55% of the malformations and is associated with recurrent miscarriage and premature birth. It is one of the malformations with the worst results in relation to reproduction [22, 23].

Class 6 (AFS): Arcuate uterus is also considered a variant of the normal with no clinical translation [12]. Eventually, it can be the cause of reproductive alteration when no other problem is detected. It occurs due to the failure in the final stage of reabsorption of the intermüllerian septum and does not need intervention.

Class 7 (AFS)/U1 (ESHRE/ESGE): This is induced by diethylstilbestrol, represented by a T-shaped uterus detected in daughters of women who used this drug during pregnancy. The uterine cavity is irregular and hypoplastic; there are poor chances for pregnancy and high risk of miscarriage or ectopic pregnancy [24]. Diethylstilbestrol was discontinued in 1971, and, for this reason, this is an increasingly rare anomaly, which tends to disappear.

V3 (ESHRE/ESGE): Transverse vaginal septum results from the failure of canalization of the vaginal plaque at the point where the urogenital sinus meets the müllerian duct, and it is not associated with other malformations. Women with a perforated septum take more time to have a diagnosis because they menstruate normally and there are few symptoms. The thickness and localization are extremely important to define the treatment: the lowest, the thinnest, and the perforated ones have better results, while the highest and the thickest ones have great chances of complications such as rectovaginal fistula and hysterectomy. Its occurrence is estimated to be between 1/2100 and 1/72,000 women [25].

1.5 Clinical Manifestations

Primary amenorrhea which is defined as the absence of menses at age 15, in the presence of normal growth and secondary sexual characteristics, is one of the commonest clinical expression of congenital uterine anomalies, especially in uterine and vaginal aplasia, while another common symptom is cyclic pelvic pain, in which a possible outflow tract obstruction should be evaluated or prolonged or otherwise there will be abnormal bleeding at the time of menarche, recurrent pregnancy loss, or preterm delivery, and thus may be identified in patients, including adolescents, who present with these disorders. Moreover, a longitudinal vaginal septum may be found in clinical examination, while others may be detected when imaging studies are performed to evaluate patients with infertility, symptoms related to nonreproductive organ systems, or trauma. As mentioned above, patients with congenital uterine anomalies are at increased risk of having renal, skeletal, or abdominal wall abnormalities, or a history of inguinal hernia, and vice versa. The most common renal anomalies are duplex collecting system, horseshoe kidney, pelvic kidney, and unilateral renal agenesis and are most commonly associated with an obstructed hemiuterus, obstructed hemivagina, and transverse vaginal septa.

Even though MM, in most cases, do not prevent conception and implantation, obstetric complications such as spontaneous abortion, recurrent miscarriage, fetal growth restriction, preterm delivery, antepartum and postpartum bleeding, placental attachment abnormalities, cervical insufficiency, fetal malpresentation, pregnancy-associated hypertension, increased possibility of cesarean delivery, and rarely rupture of a rudimentary horn may be observed [12, 17–25]. Some clinical expressions such as malpresentation and increased possibility of cesarean delivery can be explained easily by the small uterine cavity of the anomalous uterus, which may inhibit fetal movement to cephalic presentation [26], while growth restriction may be related to abnormal uterine vasculature. Postpartum hemorrhage may result from an abnormal attachment of placenta, while pregnancy-associated hypertension has been attributed to coexistent congenital renal abnormalities [22] and pregnancy loss may be related to implantation at an unfavorable site, especially in the presence of a septum [12]. Many patients are asymptomatic, and findings are first presented in a routine physical examination which leads to further evaluation and diagnosis.

1.6 Diagnostic Methods

Clinical examination is playing a crucial role in MM. In cases of primary amenorrhea, clinical examination should be focused on the presence of secondary sexual characteristics as well as on the presence or absence of the uterus. Blood tests focused on follicle-stimulating hormone (FSH) levels may be very helpful. If FSH is normal and clinical examination—ultrasound—indicates that the uterus is absent, the probable diagnosis is müllerian agenesis or androgen insensitivity syndrome. In the case of müllerian agenesis, the circulating testosterone is in the normal range for women, and in the case of androgen insensitivity, the circulating testosterone is in

the male range and testes may be present in the inguinal area or found intra-abdominal on ultrasound. Karyotype is always helpful in these cases because in agenesis karyotype is normal female 46,XX, in contrast to androgen insensitivity syndrome which is 46,XY. In addition, the vagina and cervix should be examined for anatomic abnormalities. Anatomic abnormalities that can cause primary amenorrhea include an intact hymen, transverse vaginal septum, or vaginal agenesis, also known as müllerian agenesis or Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome [4]. A careful genital examination should be performed for clitoral size, pubic hair development, intactness of the hymen, and vaginal length. If the vagina cannot be penetrated with a small cotton swab (Q-tip) or finger, rectal examination may allow evaluation of the internal organs.

Over the past years, imaging diagnostic tools have been constantly improving. The initial diagnostic method is the two-dimensional ultrasound (US2D), but also used are three-dimensional ultrasound (US3D), MRI, hysterosalpingo-contrast sonography, X-ray hysterosalpingography, video hysteroscopy, and video laparoscopy.

US2D is the initial method because it is simple, noninvasive, low cost, and usually available and provides good information; however, it is highly dependent on the experience of the examiner [26–28]. US3D has good reproducibility and high level of agreement among different observers, provides additional and more reliable images, and allows for the evaluation of the cervix and the vagina; however, it is less available and requires more specialized training than the US2D [26–29].

MRI is considered the gold standard method and offers objective and reliable tridimensional information about all aspects of anatomy, except for the tubes; it can be used in all cases, including obstructive malformations. It is more expensive and less available than the US and needs a qualified professional to interpret the results [26, 30–32]. MRI is also very helpful in girls who develop endometriosis from retrograde menstruation from obstructed uterine horns.

Hysterosalpingo-contrast sonography is a minimally invasive and low-cost method and provides good information about the cervix and uterine cavity but is highly dependent on the examiner, and the distention of the uterine cavity can modify its internal contours generating false-negative images [26, 33]. X-ray hysterosalpingography provides information only about the uterine cavity and tubes and is used more in cases of infertility. It is an invasive, painful exam and does not evaluate the external contour, does not differentiate the septate uterus from the bicornuate one, does not diagnose the noncommunicating uterine horn, and cannot be used in vaginal and cervical obstructions [26, 34].

Hysteroscopy is minimally invasive and provides reliable information about the vagina, cervical canal, and uterine cavity, although it does not evaluate the external contours or the thickness of the uterine wall and does not differentiate the septate uterus from the bicornuate one [26]. Laparoscopy evaluates the external contour of the uterus and the peritoneal structures, but it is an invasive exam, does not evaluate the thickness of the uterine wall, and completely depends on the experience and subjective evaluation of the examiner [26]. When obstructed uterine horns with the presence of active endometrium without an associated cervix and upper vagina are

identified, then laparoscopic removal of the unilateral or bilateral obstructed uterine structures should be performed [35]. In most cases, surgical excision of the uterine horn results in improvement of the endometriosis [5].

Multiple studies have confirmed the prevalence of renal anomalies in patients with müllerian agenesis to be 27–29%; therefore, ultrasound evaluation of the kidneys is warranted for all patients [36, 37]. Skeletal anomalies (e.g., scoliosis, vertebral arch disturbances, hypoplasia of the wrist) have been reported in approximately 8–32% of patients; therefore, spine radiography (X-ray) may reveal a skeletal anomaly even in asymptomatic patients [36–38].

1.7 Treatment

1.7.1 Which Classification Is Better for Patient Management?

According to the authors of the ESHRE/ESGE system, their classification contains a clear definition of all types of anomaly, and the anomalies are categorized in well-described classes and subclasses as mentioned above, and the ESHRE/ESGE criteria allow objective classification of uterine morphology [26]. However, other studies have shown that the ESHRE/ESGE classification system for main classes has significant methodologic issues [39, 40]. Importantly, three groups of researchers have highlighted that the ESHRE/ESGE system can lead to unnecessary surgical procedures for conditions that appear to be benign uterine variants [40–42]. Moreover, the ESHRE/ESGE system and their criteria included updated definitions and were not created for patient management as authors stated [14, 26]. A recent systematic review indicates that current evidence favors continued use of the ASRM classification [43]. In conclusion, it is still very difficult to answer the question of which system is better, because all systems have potential advantages and disadvantages. All systems are arbitrary, with overlapping features.

1.7.2 Congenital Uterine Malformations by Experts (CUME): Definitions 2018

The use of different criteria and definitions, especially in Europe and the United States, as well as different local classifications is a significant barrier for communication between practitioners, experts, and researchers. What would be a good idea is the creation of a single global classification system using the most voted options of independent international top experts as reference to find a common language for classification of anomalies. Recently, the Congenital Uterine Malformations by Experts (CUME) group was created for that reason and is the first definition, which is available in order to reflect the diagnosis made most often by experts for distinguishing normal/arcuate and septate uterus [44].

Furthermore, surgical approaches to treating MM are always evolving. Advances in imaging have allowed for noninvasive and more accurate diagnosis of anomalies,

which has resulted in better surgical planning with fewer diagnostic surgeries needed. Technologic advances in surgical equipment, as well as laparoscopy, have helped in better correction of these anomalies. In addition, past surgical approaches with the focus on correction of MM for patient's symptom relief, without any consideration for future fertility, are not nowadays in the surgical plan and most experts allow individuals to take part in their future reproductive option, which is well discussed most of the times with their parents.

Moreover, minimally invasive techniques have today replaced all past surgical approaches. The most significant impact has been with the hysteroscopic incision of uterine septum, which replaced the Jones [45] or Tompkins [46] metroplasty performed at laparotomy [47]. The hysteroscopic septum incision can be done as a same-day surgery, with significantly shorter recovery and less pain, and importantly allows the young girl to have a vaginal delivery without a significant risk of uterine rupture [8]. In some cases, hysteroscopic septum incision is performed under laparoscopic control, in order to prevent excessive incision and fundal perforation. Currently, ultrasound guidance, later performed abdominally [48], has replaced more invasive laparoscopy [40]. Resection of the septum hysteroscopically can improve pregnancy outcome [49]. Other examples for past procedures that now have been replaced by others in order to preserve the reproductive function include hysterectomy for treatment of a patient with a high transverse vaginal septum or cervical agenesis, hemi-hysterectomy with vaginectomy for obstructed hemiuterus in blind hemivagina, and amputative or ablative surgery of blind obstructed hemicavity in Robert septate uterus [50].

In case of uterus didelphys, 20% of patients also have unilateral anomalies, such as an obstructed hemivagina and ipsilateral renal agenesis. In addition, there may be a microcommunication between the patent vagina and the obstructed vagina, resulting in an infected obstructed hemivagina, while bilateral complete obstruction is also possible and presents with primary amenorrhea. Treatment involves resection of the wall of the obstructed vagina followed by creation of a single vaginal vault.

Metroplasty should be considered for patients with pelvic pain, recurrent miscarriages, or a history of preterm delivery. Today's data do not support the fact that abdominal repair of the didelphic uterus improves pregnancy outcomes. In the unicornuate uterus, care should be taken to assess for the presence of a noncommunicating or rudimentary horn. Even though most rudimentary horns are asymptomatic, some contain functional, but not necessarily normal [51], endometrium that is shed cyclically. But if a rudimentary horn is obstructed (without communication to the other uterus or cervix), as mentioned above, the patient may develop cyclic or chronic abdominopelvic pain and may require surgical excision of the obstructed horn [51].

Bicornuate uterus is not a cause of difficulty conceiving, but rather a recurrent miscarriage in the second trimester of pregnancy and premature birth. When no other cause is identified, Strassman's metroplasty can be recommended, with good results and a 90% rate of full pregnancy [52]. Transverse vaginal septum should be treated with surgical resection and anastomosis of the proximal and distal vaginas. The choice of the technique depends on its localization and thickness, which is diagnosed in a

physical exam, US, and MRI, and it can be vaginal or laparoscopic. The lowest, the thinnest, and the perforated ones have the best results, and the main complications are stenosis, re-obstruction, dyspareunia, and psychological difficulties. Vaginal dilatation is generally recommended after surgery to improve the result [53].

In case of MRKH syndrome, primary vaginal elongation by dilation is the appropriate first-line approach in most patients because it is safer, patient controlled, and more cost effective than surgery. Vaginal dilation is successful for more than 90–96% of patients; therefore, surgery should be reserved for the rare patient who is unsuccessful with primary dilator therapy or who prefers surgery after a thorough informed consent discussion with her gynecologic care provider and her respective parent(s). Regardless of the surgical technique chosen, referrals to centers with expertise should be offered and the surgeon must be experienced with the procedure. The primary aim of surgery is the creation of a vaginal canal to allow penetrative intercourse. The timing of the surgery depends on the patient and the type of procedure planned. Surgical procedures often are performed in late adolescence or young adulthood when the patient is mature enough to agree to the procedure and to be able to adhere to postoperative dilation. Common complications in vaginoplasty include bladder or rectal perforation, graft necrosis, hair-bearing vaginal skin, and fistulae [54].

Several techniques have been used for vaginoplasty, and there is not a worldwide consensus for the best, in order to afford the best functional outcome and sexual satisfaction [55]. Historically, the most common surgical procedure used to create a neovagina has been the modified Abbe–McIndoe operation. This procedure involves the dissection of a space between the rectum and bladder, placement of a stent covered with a split-thickness skin graft into the space, and diligent use of vaginal dilation postoperatively. Other procedures for the creation of neovagina are the Vecchietti procedure and other laparoscopic modifications of operations previously performed by laparotomy [56]. The laparoscopic Vecchietti procedure is a modification of the open technique in which a neovagina is created using an external traction device that is affixed temporarily to the abdominal wall [57]. Another procedure, the Davydov procedure, was developed as a three-stage operation that requires dissection of the rectovesicular space with abdominal mobilization of a segment of the peritoneum and subsequent attachment of the peritoneum to the introitus [58–61]. Other vaginoplasty graft options include bowel, buccal mucosa, amnion and various other allografts. Last but not least, Williams vaginoplasty is a very reliable and worldwide used method of vaginoplasty. The Creatsas modification of Williams vaginoplasty is a fast and simple technique, in which a perineal skin flap is used to create a perineal pouch. During this procedure, the tissues of the perineum are mobilized and the inner skin margins of the created flap are stitched together using absorbable sutures. Regarding this technique, we have a large series of neovagina creation, with more than 247 adolescents, with no past surgical complications and perfect sexual life as reported by women later in their life.

Another issue in MRKH syndrome is uterine transplantation. This is an innovative approach to treat fertility due to MM [62]. Procurement of the donor uterus has traditionally been performed at laparotomy from a living or deceased donor. Traditionally, uterus harvest for a live transplant involves a long and complicated procedure to remove

the uterus and its vascular supply without causing undue trauma to the donor. Recently, the first case report of robotic assisted laparoscopic harvesting was described for procurement of a uterus from a live donor [63]. The donor undergoes a procedure similar to a radical hysterectomy, with removal of the ovaries to obtain adequate ovarian vascular pedicles, both arterial and venous, to allow perfusion of the uterus in the recipient. As the robotic assisted laparoscopic approach has become common place for performing a radical hysterectomy, it is natural that this approach may be used for the uterus donor and allows for a quicker recovery.

1.8 Controversies

1.8.1 Uterovaginal Anastomosis for Cervical Agenesis

As surgical approaches evolve to take into consideration reproductive choices and patient input, controversies in management have developed. Management of cervical agenesis has traditionally involved performing a hysterectomy primarily to treat the pain caused by hematometra and sequelae of retrograde menstruation, including endometriosis, hematosalpinx, and hematoperitoneum. Some case series evaluating outcomes of uterovaginal fistula showed poor outcomes. The frequency of reoperation and hysterectomy of girls undergoing uterovaginal reconstruction for cervical agenesis ranged from 10 to >50%, while sepsis is always an issue in these cases and sometimes is fatal [64–67]. Pregnancies reported after uterovaginal anastomosis are few [65, 66], due to the high incidence of tubal damage and adhesive disease from retrograde menstruation. On the other hand, surgical approaches are evolving; therefore, in one study of 18 cases, all of the women had successful reconstruction and only one woman experienced restenosis, which was treated successfully with the use of canalization [68]. Pregnancy occurred without assistance in ten women, and four women had a successful delivery via cesarean section at 36–38 weeks. Another case series of laparoscopic assisted uterovaginal anastomosis involved 14 patients, with 9 undergoing concomitant vaginoplasty [69]. Only one patient underwent hysterectomy, owing to restenosis and infection. Unassisted pregnancy was achieved in three of five patients who were sexually active. The better outcomes in these studies have brought into question which management is appropriate. Although hysterectomy is a "safer" option because it avoids potential complications of restenosis, infection, and death, it does not allow for the individual to preserve her uterus for cultural or emotional reasons or to carry a pregnancy.

1.8.2 Surgery of Septate Uterus by Different Definitions

Septate uterus as a definition is under controversies through all these years, while an issue always arises according to whether or not surgical treatment improves clinical outcomes. As discussed above, the ASRM and ESHRE/ESGE classification systems differ in the diagnosis of septate uterus [44]. The median internal indentation in those diagnosed as septate according to the ESHRE/ESGE criteria was 10.7 mm