Mullerian Anomalies in the Pediatric and Adolescent Population: Diagnosis, Counseling and Treatment Options

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Abstract

Mullerian Anomalies (MAs) are relatively common in the general population and occur from errors in embryologic development of the female reproductive tract. Classification systems exist in order to characterize these malformations, the most well known system being that created by the American Society for Reproductive Medicine (ASRM). Diagnosis of an MA may be incidental on physical examination or during evaluation for a menstrual or pain-related complaint. The pelvic examination specifically for the pediatric and adolescent populations should be approached with the intent to minimize trauma for the patient. If an MA is suspected based on evaluation, ultrasound or MRI is helpful in further delineating the exact diagnosis. Depending on the particular anomaly, counseling regarding the need for intervention and timing as well as options for fertility and sexual function should be approached with the patient and guardian, if appropriate. Many patients will experience feelings of isolation and despair regarding a diagnosis of an MA. As many patients are diagnosed at a relatively young age, a multidisciplinary and longitudinal approach should be taken to optimize social, mental, sexual, and physical wellbeing.

General Overview of Mullerian Anomalies

Introduction

Congenital anomalies of the female reproductive tract are relatively common, occurring in 3% to 6% of fertile women, 4% to 7% of women with infertility, and up to 16% of women with recurrent miscarriage [1,2]. These anomalies result from errors of embryologic development, which may be caused by genetic mutations as well as hormonal or environmental insults. Though Mullerian Anomalies (MAs) are often asymptomatic, they remain clinically important due to their impact on fertility and female identity for some women. In the pediatric and adolescent population, MAs may be discovered on routine physical exam or during evaluation for menstrual absence or abnormalities [3,4]. Correctly identifying these malformations in order to adequately counsel patients and their guardians can be instrumental in the patient's future personal, sexual, and social well-being.

Embryology

Knowledge of normal embryologic development is critical to the understanding, diagnosis, and treatment of genital malformations. The urogenital system develops in close proximity to the reproductive tract, which partly explains the common association of urinary and reproductive tract malformations. An embryo's sex is determined genetically by chromosomes, with female development occurring in the presence of two X chromosomes and under the influence of several genes, including *WNT4* [5]. The ovaries, which develop at approximately seven weeks of gestation, are derived from the primordial germ cells of the mesothelial thickening. Differentiation of the female ductal system is not dependent on ovarian development.

In the presence of Anti-Mullerian Hormone (AMH), the Mullerian ducts appear as invaginations of the dorsal coelomic epithelium lateral to each Wolffian duct at week five of embryological development. Each Mullerian duct begins as a solid bud that elongates and canalizes to form a luminal structure. These ducts grow medially and caudally until they meet to fuse at the urogenital septum. Proper development of the female reproductive tract requires both fusion of the paired Mullerian ducts and resorption of the resulting septum to form a single uterovaginal canal. The cranial portion of the Mullerian ducts remains separate, forming the Fallopian tubes. The lower vagina is derived from the urogenital sinus, which joins with the ducts at the Mullerian tubercle. The sinovaginal bulb, formed by endodermal evagination, and the vaginal cord, derived from cellular proliferation of the lower Mullerian ducts, combine to form the vaginal plate [6]. At week twenty,
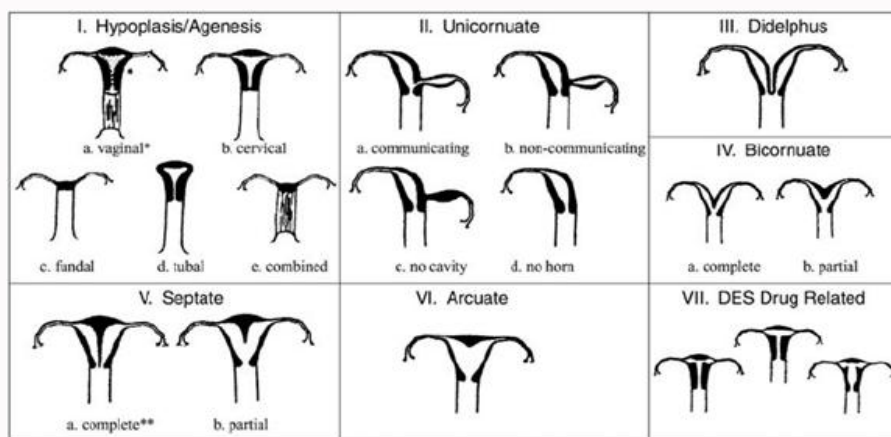
Figure 1: ASRM Classification of Mullerian anomalies [8].

stromal cells of the fused Müllerian ducts condense to form the cervix. Similarly, the mesenchyme surrounding the ducts condenses to form the musculature of the female genital tract [7].

The hymen is not derived from the Mullerian ducts and is a thin septum between the vaginal lumen above from the urogenital sinus below. Though the central portion of the hymen typically resorbs before birth, a thin fold of membrane may persist at the vaginal introitus in a variety of configurations. The external genitalia develop when the mesoderm around the cloacal membrane forms the genital tubercle with urogenital folds and labioscrotal swellings on each side. In the presence of estrogen, the genital tubercle forms the clitoris, the urogenital folds form the labia minora, and the labioscrotal swellings form the labia majora and mons pubis. An increase in androgen exposure causes masculinization of female external genitalia.

Classification of mullerian anomalies

The simplest and most frequently cited classification of Mullerian Anomalies was developed by the American Society of Reproductive Medicine (ASRM) (Figure 1) [8]. The ASRM system classifies anomalies based on a particular uterine structure and its implication on female fertility. As a result, this system does not accommodate all known anomalies. Another system, Congenital Uterine Anomalies (CONUTA), was developed by the European Society of Human Reproduction and Embryology (ESHRE) to more fully address the complexities and variations in these conditions (Figure 2) [9]. This system categorizes anomalies based on the specific configuration of the uterus, cervix, and vagina; therefore providing more precision. CONUTA also includes anomalies of non-Mullerian origin. However, neither system covers all possible variations of female reproductive tract development. Still others have proposed classification *via* embryologic origin due to the close relationship of renal and Mullerian anomalies; those systems have yet to be widely used or recognized [10]. The ASRM classifications are further described below.

Class I: Mayer-rokitansky-kuster-hausen (MRKH) syndrome

Classic Mullerian agenesis, or Mayer-Rokitansky-Kuster-Hausen (MRKH) Syndrome, is characterized by congenital absence of the uterus, cervix, and upper vagina due to a failure to develop the lower portion of the Mullerian ducts. These women will often have a shallow vaginal pouch, as the lower vagina develops separately from the vaginal plate. Likewise, Fallopian tubes are often present due to the development of the upper Mullerian ducts. Class I Mullerian anomalies have an incidence of 1 per 4,000 to 5,000 females [11,12]. Approximately 90% of these patients have some degree of lower Mullerian development, and up to 7% of these rudimentary structures contain active endometrium [13]. As a result, many patients with Mullerian agenesis still experience cyclic or chronic abdominal pain [14].

Class II: Unicornuate

In contrast to MRKH Syndrome, the underdevelopment in Class II anomalies is a unilateral event. These patients have a single fully-developed uterine horn, cervix, and upper vagina. The contralateral horn may either be rudimentary or absent, and a rudimentary horn may or may not communicate with the developed horn. If a non-communicating horn contains functional endometrium, it may produce cyclical pelvic pain due to hematometra [15]. An embryo could also implant into the functional endometrium in a rudimentary horn, which may lead to rupture in 50% to 70% of such pregnancies [16].

Class III: Didelphys

Class III anomalies occur due to failure of fusion of the paired uterine horns. These patients have widely splayed and fully developed uterine horns along with two fully developed, unfused cervixes. The upper vagina may fuse and the septum may dissolve to form a single canal, though a vaginal septum is present in nearly 75% of didelphys uteri [15].

Class IV: Bicornuate

As with Class III anomalies, Class IV anomalies occurs secondary to failed fusion of the uterine horns. However, the distinction between these anomalies depends on the level of non-fusion, with Class III featuring only vaginal fusion and Class IV resulting from partial uterine fusion. The mid-lower uterine horns, cervix, and upper vagina are fully fused. Approximately 25% of these patients have concurrent vaginal septa [15].

Class V: Septate

Septate anomalies occur due to failure of complete septal resorption within the uterine cavity. The uterine contour is largely normal because of appropriate midline fusion. In these patients, the uterine fundus is convex, flat, or minimally indented (less than 1cm of myometrium or septum protruding into the uterine cavity). The septum must measure greater than 1 cm to constitute a Class V anomaly. In a partially septate uterus, the septum does not reach the
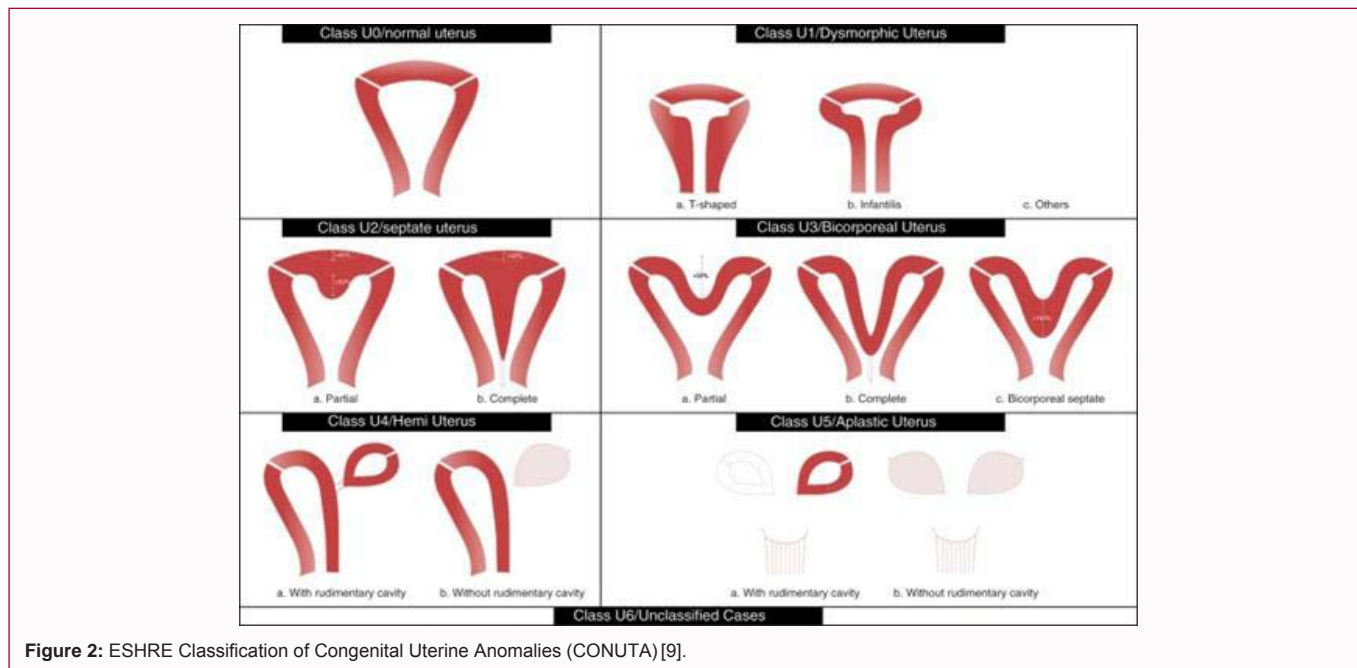
Figure 2: ESHRE Classification of Congenital Uterine Anomalies (CONUTA) [9].

cervix. In contrast, a complete septum extends to the external os of the cervix. In some cases, a vaginal septum may also be present, and the anatomy may mimic a didelphys uterus (separate uterine cavities, cervices, and vaginas) with midline fusion.

Class VI: Arcuate

As in Class V anomalies, this variant results from failure of resorption of the septum. The uterus has a normal fundal contour with minimal indentation of the myometrium or fibrous component into the uterine cavity. The uterine septum must measure less than 1 cm to constitute a Class VI anomaly.

Class VII: Diethylstilbestrol-related anomaly

Diethylstilbestrol (DES) is a synthetic estrogen that was used from 1938 until 1971 for a variety of pregnancy complications. Anomalies resulting from DES exposure include hypoplasia of the uterus, cervix, and Fallopian tubes; as well as adhesions within the uterine cavity [17]. The most common anomaly resulting from exposure includes a T-shaped uterine cavity with a single cervix, though narrow or irregularly shaped uterine cavities were also observed. As DES is no longer being used in clinical practice, these anomalies are becoming obsolete. However, occasional off-label use may still result in exposure in women of reproductive age.

Associated anomalies

There are several other female reproductive tract malformations that are not strictly considered Mullerian anomalies.

Hymenal variants

The hymen is a circumferential squamous tissue structure that exists at the junction of the perineum (derived from the urogenital sinus) and the vaginal canal (derived from the Mullerian structures). Typically, complete canalization of the vaginal opening occurs. In some instances the hymen remains intact, causing complete (imperforate hymen) or partial obstruction (i.e. micro perforate and septate hymen) [18]. Imperforate hymen is the most common obstructive uterovaginal anomaly, occurring in 1/2000 females [19].

Complete or partial vaginal atresia

Vaginal atresia results from a lack of canalization of the space between the perineum and upper vagina [20]. Areolar tissue occupies the space between the obstructed vagina and the introitus [21]. Vaginal atresia may manifest as a pink vaginal dimple without evidence of hymenal tissue, along with a developed upper vagina, cervix, and uterus [9]. This condition is associated with anorectal and urologic anomalies [22]. Complete vaginal atresia occurs in 1 per 4,000 to 1 per 10,000 females [23].

Transverse vaginal septum

Transverse vaginal septa are horizontal partitions within the vagina resulting from either failed fusion of the caudal portion of the Mullerian ducts or failed canalization of the vaginal plate. These bands of fibrous tissue span across an otherwise structurally-normal vagina. Though they may occur at any level of the vagina, over 80% of septa occur in the mid and upper portion, at the embryologic junction of the Mullerian ducts and vaginal plate [24,25]. Septa are typically 1 cm thick, though they may be up to 8 cm near the cervix. Over 60% of transverse vaginal septa have small fenestrations and do not cause complete obstruction, though some may impede menstrual flow [26]. Transverse vaginal septa have an incidence of 1/30,000 females and present differently depending on the degree of obstruction, such that patients with obstructive septa present with primary amenorrhea or pelvic pain around menarche [27]. In contrast, patients with fenestrated septa may present with pyocolpos or pyometra resulting from ascending infection [19]. Transverse vaginal septa are rarely associated with urologic abnormalities but may also be associated with imperforate anus, bicornuate uterus, coarctation of the aorta, and spinal malformation [4].

Longitudinal vaginal septum

In contrast, longitudinal vaginal septa are characterized by vertical partitions within the vagina that result from incomplete lateral fusion or resorption of the caudal Mullerian ducts. These partitions may extend partially or entirely through the length of the vagina. Obstruction of one vaginal segment may occur, forming a so called

"hemivagina" which may become infected or accumulate products of menstruation. Longitudinal vaginal septa are commonly associated with uterine didelphys or may occur as a part of a syndrome such as Herlyn Werner Wunderlich (triad of uterus didelphys, obstructed hemivagina, ipsilateral renal agenesis), also known as Obstructed Hemivagina and Ipsilateral Renal Agenesis (OHVIRA) [28-30].

Diagnosis of Mullerian Anomalies in the Pediatric and Adolescent Population

Evaluating the prepubertal patient

As part of all well-child visits, the American Academy of Pediatrics recommends routine examination of the genitalia [31]. Genital examination of a prepubertal female patient should be performed carefully and by an experienced practitioner. This should only occur after explanation of the exam and addressing parental and patient concerns regarding the exam. Infants can be examined on a table, and toddlers may feel most comfortable being examined in a guardian's lap in either a frog-leg or modified lithotomy position. Older children may be examined on a table using either of these positions or in a knee-chest position, which maximizes the view of the distal vagina but requires examination from behind the child. Alternatively, using the Valsalva maneuver in a supine position can also improve visualization of the distal vagina. Bright light, optimal positioning, and gentle separation of the labia by the examiner, child, or guardian will facilitate increased visualization and expedite the exam. If specimen collection is needed or if vaginal atresia is suspected, a moistened swab may be introduced into the vagina, either for specimen collection or to evaluate vaginal length. The vaginal length is approximately 4 cm in newborns, 4 cm to 5 cm in early childhood, and 7 cm to 8.5 cm in the years prior to menarche (approximately 9 years to 13 years old). Care should be taken to avoid disrupting the hymen, which can be extremely tender. Additionally, penetrative exams can be traumatizing to the vaginal mucosa. If the child is unable to tolerate the exam in the office, exploration under anesthesia can be considered. It is also reasonable to defer the examination if a child remains anxious or reluctant to undergo evaluation, as the process can cause emotional and physical trauma [32].

Though not technically MAs as the hymen is not derived from the Mullerian ducts, imperforate or microperforate hymen may be noted in this age group on genital exam. Additionally, it may be possible to diagnose vaginal septa with direct visualization as above. However, given the fact that penetrative exams are not routinely performed in the prepubertal population, the non-obstructive disorders of Mullerian development are unlikely to be noted until coitarche. If an MA is suspected in a prepubertal patient, it is useful to screen for concomitant urinary tract anomalies, given their close developmental association. This can be performed with ultrasound but given the small size of the genitourinary tract in this age group as well as a desire to avoid penetrative vaginal exams and studies, MRI is generally preferred.

Evaluating the pubertal patient

Much like in prepubertal patients, examination of the genitalia should be part of all well-child visits in the adolescent females to facilitate healthy conversation about physical changes, sexual maturity, and safe sex practices. Routine genital examinations during these visits can make future exams for screening or diagnostic purposes less unfamiliar and anxiety provoking.

Indications for a pelvic exam, besides routine well-checks, include concerns for precocious puberty, amenorrhea or abnormal menstrual cycles, and urinary symptoms; suspected or confirmed sexual abuse; pregnancy; assessment for normal development and pubertal staging; symptomatic complaints such as vaginal bleeding or discharge; and infectious disease screening in sexually active patients [32]. MAs, though frequently asymptomatic, may be diagnosed in this age group more frequently than in prepubertal patients given that affected patients normally present with concerns about primary amenorrhea, abnormal menstruation, pelvic pain, or difficulty with vaginal penetration. In pubertal females who desire or achieve pregnancy, an MA could be diagnosed as part of an evaluation for recurrent pregnancy loss, intrauterine growth restriction, fetal malpresentation, preterm labor, or preterm premature rupture of membranes [3,4].

Prior to a physical exam, a thorough history should be taken including information about menarche and menstruation, tampon use, pelvic pain, and sexual activity. It is helpful to discuss the patient's concerns or symptoms with her alone, so that she feels free to relay concerns or fears about her body or the pelvic exam. However, she should also be given the opportunity to have a support person present in the room during both the interview and exam. The patient should remain fully clothed during the history portion of the encounter and only undress for the physical exam. Additionally, it is helpful for the provider to sit at a lower level than the patient, promoting a sense of empowerment for the patient [31]. Prior to proceeding, it can also be helpful to explain to the patient that she is in control of the exam, and that it can be stopped at any time if she is too uncomfortable. This statement can increase the patient's confidence and sense of control during this vulnerable encounter.

Given the sensitivity of the pelvic exam, it is important to proceed in a professional, deliberate, and respectful manner. A chaperone should be present, and care should be taken to protect the patient's modesty with appropriate draping. If a patient becomes traumatized by the physical exam, it is possible that she will experience anxiety regarding physical intimacy or pelvic exams in the future. Thus, careful consideration of patient comfort is necessary. If the patient chooses to have a support person present in the room, this person should be encouraged to stand or sit at the head of the patient. The exam should begin with an overview of the steps of the exam, including the use of diagrams and a hand-mirror, if desired by the patient. The examiner should first examine the external genitalia for hair pattern as well as any evidence of skin irritation. Next, after gently separating the labia with gloved hands, the urethral meatus and vestibular glands can be examined. Additionally, the introitus and hymen are noted. At this stage, as in pre-pubertal patients, imperforate hymen, hymenal remnants, or vaginal septum may be easily diagnosed [32].

The use of a speculum is not routinely indicated unless in the cases of persistent vaginal bleeding or discharge, concern for injury or foreign body, sexual assault, suspected anatomic abnormality, or for routine cervical cancer screening. If a speculum is required for an exam in an adolescent patient, use of a Huffman (for virginal patients) or Pederson (for sexually active patients) speculum, both with narrow blades, is preferred. The patient should be given the opportunity to familiarize herself with the speculum prior to its use [32]. The exam can be made less uncomfortable with the use of water-based lubricants or by running warm water over the blades of the speculum prior to insertion. During insertion, care should be taken to avoid pinching the labia or traumatizing the urethra or hymen. The examiner should take note of the vaginal mucosa, any discharge, the presence or absence of lesions and lacerations, and the presence

or absence of a cervix and its characteristics. The vagina should be evaluated for the presence of a septum that may cause pain with vaginal penetration. In the case of a complete vaginal septum, a blind-ending pouch may be noted, and a hemivagina or blind pouch may not accommodate a speculum. Insertion of a tampon into this pouch may be painful and would not absorb menstrual bleeding if the cervix is on the contralateral side. In the case of a patient with amenorrhea, a digital or speculum exam may reveal a shortened vagina or absent cervix, indicating possible uterovaginal atresia.

The speculum should be removed carefully, without traumatizing the cervix or vaginal mucosa. A bimanual exam is helpful in assessing for abnormalities in the upper reproductive tract in the adolescent and young adult. For patients who are not sexually active, a gloved finger examination with a single digit will decrease patient discomfort. The examiner can note the relative vaginal length, presence or absence of the cervix, and presence or absence of tenderness. With the examiner's abdominal hand, the relative size, shape, position, and possible laterality of the uterus can be assessed. Uterine length is approximately 8 cm in nulliparous postmenarcheal females and 10 cm to 12 cm in postmenarcheal females [32]. The adnexae can also be palpated for the presence of any masses or tenderness.

If a patient's physical exam findings and history are suspicious for an MA, an imaging study is recommended. Specifically, 3D ultrasonography provides a thorough representation of uterine contour that is not appreciated with traditional 2D ultrasonography or hysterosalpingography and is highly sensitive, correctly diagnosing exact anomalies in 88% to 100% of cases [33-35]. Given the need for a transvaginal ultrasound to ensure accurate imaging, this modality is recommended for post-pubertal, sexually active patients. MRI may be preferred for virginal patients and is an acceptable and comparable alternative to 3D ultrasonography [36,37].

Because concomitant urinary tract anomalies are noted in up to 25% to 50% of cases, patients diagnosed with Mullerian agenesis should have evaluation of the kidneys and collecting system [36-38]. Associated defects include renal malformations such as horseshoe kidney, renal agenesis, irregularity or duplication of the ureters, and hydronephrosis. Additionally, MRKH Syndrome has also been associated with skeletal dysplasia in 10% to 15% of patients and VACTERL (vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities) more uncommonly [39,40]. There are no particular diagnostic serum tests for patients with Mullerian anomalies. These patients have the expected XX karyotype with typical female phenotype including breast development, axillary and pubic hair, and external genitalia all within normal limits for developmental stage [41].

Counseling and Implications

Counseling strategies

Given its potential detrimental impact on identity, sexuality, relationships, and childbearing; it is unsurprising that a diagnosis of MA is associated with suboptimal emotional well-being for many women [43]. Thus, the American College of Obstetricians and Gynecologists recommends that counseling regarding the implications and potential management strategies should begin at the time of diagnosis [9]. Patients receiving a diagnosis of MA often experience a variety of reactions including shock, depression, confusion, feelings of isolation, and fear of partner rejection [43-45]. Women may also experience an altered sense of self following

diagnosis, including doubts about female identity and feeling incomplete [46,47]. In particular, patients report difficulty learning that they may be unable to have penetrative intercourse or carry a pregnancy [46,48,49].

Initial counseling typically involves addressing the psychological adaptation of the patient, including possible approaches to vaginal dilation if necessary and assisting the patient in processing her reduced fertility. However, counseling may be beneficial to patients during other critical periods besides diagnosis, including during dilation therapy or formation of a neovagina, initiation of sexual relationships, and as patients begin to pursue parenthood [44-46,48,50]. As women diagnosed with MAs will experience a variety of emotional responses throughout the process of diagnosis and treatment, counseling must be sensitive to the individual's current needs as well as her particular cultural context. Though approaches will vary based on the individual's psychological condition, one approach that has been shown to be beneficial is coping through conceptualization of life goals [44]. Health care providers should also be direct and intentional in the language used to discuss MAs to help the patient most accurately understand her condition from both a medical and psychosocial standpoint. Patients should be assured that many patients with MAs report no impairment of quality of life following appropriate treatment by a multi-disciplinary team [51].

Depending on a patient's age at diagnosis, some counseling may be done without a parent present, though this should depend on individual patient preference. Parental support has been shown to improve the likelihood of positive treatment outcomes, thus parental involvement in counseling and decision-making is often recommended [45,48,52]. In some cases, parents and guardians may benefit from counseling on the most beneficial ways provide support to their child still respecting her autonomy [9]. Patients diagnosed at a young age should be assured that there is rarely need to intervene prior to puberty; anticipatory guidance is key in this population. However, a post-pubertal patient may desire treatment if her MA is prohibitive to penetrative intercourse or sexual expression.

Establishing community

Sharing diagnoses of MAs with partners and peers can often be difficult for patients due to anxiety about peers' perceptions and implications on romantic relationships. As a result, few individuals are eager to discuss their diagnoses [42,53]. However, disclosure has been shown to increase social support and self-acceptance [53]. Motivators for disclosure may include significant trust between partners, a desire to share the burden of the diagnosis, and a sense of responsibility to be honest with a potential long-term partner. Conversely, the most common barrier to disclosure is fear of rejection, particularly in the adolescent age group when desire for partner and peer acceptance is particularly strong [49,53]. Most affected women did not receive disclosure counseling at their diagnosis, though many of them wish that they had [53]. This highlights the important role that primary care and specialist physicians have in educating and counseling patients throughout all stages of diagnosis and treatment.

In addition to disclosing her diagnosis to peers and potential partners, a woman may wish to discuss her experience with other women affected by MAs. Discussions through support groups have been positively impactful for the majority of participating women, helping to solidify a feeling of solidarity with others and enhancing opportunities to exchange information and resources [52]. Such groups may be particularly beneficial for women mourning reduced

fertility, with a recent study indicating that support groups alleviate distress and promote a sense of community for many such women [43].

Sexual function

Besides being detrimental to psychiatric well-being, MAs are associated with compromised sexual wellness [42,55]. In women with either isolated or complicated vaginal atresia, fears about pain or their variant anatomy may cause anxiety or dampen the experience of penetrative sexual intercourse. Women who have undergone neovaginal formation via any technique remain likely to suffer from dyspareunia, difficulty achieving orgasm, and lack of adequate lubrication [55-58]. From an emotional standpoint, women's primary concerns include feelings of self-doubt as well as fears of disappointing a partner or sustaining vaginal pain or injury [55].

Despite these challenges, many patients with MAs that have received appropriate management are able to enjoy a level of sexual satisfaction that is similar to the general population [51,55,56,59]. Likewise, women with MAs following neovaginal formation report subjective sexual arousal that is comparable to a normal population [57]. Thus it is important for health care providers to inform patients of the high success rates for psychological and sexual functioning following treatment. Patient's sexual satisfaction can be facilitated by use of vaginal estrogen when indicated, counseling on the importance of using lubricants, and psychological counseling that seeks to enhance women's sexual self-esteem. Patients who experience more severe sexual or coping problems should be promptly evaluated and referred to the appropriate medical or mental health provider.

Fertility considerations

As some women with MA will be unable or unlikely to carry a pregnancy, discussion of fertility options is a critical aspect of the management of these patients. This conversation will differ greatly depending on the patient's individual uterine anatomy. For patients with some childbearing potential (such as those with ASRM Class II-VI anomalies), referral to fertility specialist is important. Among those with complete Mullerian agenesis, many women feel that alternative routes to parenthood, such as adoption or surrogacy via Assisted Reproductive Technologies (ART), are acceptable and even desirable [44]. There have been reports in the literature of a successful uterine transplant followed by a live birth in a recipient affected by MRKH Syndrome [60]. This procedure is not currently widely performed but is a promising potential future treatment for patients with Class I MAs.

Gynecologic providers should be prepared to discuss these options with patients and to normalize various means of achieving parenthood. These providers also have the unique opportunity to provide resources regarding adoption or ART, as well as to connect patients to support groups for women or couples suffering from infertility. As the inability to bear children has distinct implications in different societies, it is important to consider a patient's cultural context and individual life circumstances when discussing her potentially reduced fertility. Informing young women and girls of the possibility of future parenthood may be helpful in coping with the diagnosis and is thus an important part of early management of MAs [9].

Treatment Options

Depending on the age of the patient and the classification of her

MA, invasive treatment may or may not be warranted. As mentioned above, extensive and often multidisciplinary counseling is imperative in the management of patients with MAs, particularly for those patients with more severe anomalies such as isolated vaginal agenesis or MRKH Syndrome. There is a role for expectant management of all MAs, particularly in the pediatric and adolescent population, taking into account surgical morbidity and a patient's or guardian's desire for intervention.

Since ASRM Class I MAs involve agenesis of a crucial portion of the reproductive tract including the uterus, cervix, and upper vagina, treatment options largely target ways to improve the functionality of the lower vagina. For MAs in this category that include vaginal atresia, this involves sequential dilation to progressively increase the diameter of the rudimentary vagina [61]. This treatment is successful in approximately 95% of affected women but does require daily dedication to the relatively painless but potentially tedious and long-term process [62,63]. The timing of treatment is largely dependent on patient readiness, which often coincides with coitarche. Unsuccessful dilation is usually secondary to noncompliance or long periods of non-use of the neovagina; however the dilation process can be resumed at any time. Most of the literature discussing sequential dilation details findings in women over the age of 18. However, definitive guidelines for timing of initiation of dilator therapy have not been established. It is reasonable to discuss this option with motivated adolescent patients who desire penetrative intercourse, along with routine counseling on general sexual health including barrier contraception for the prevention of STDs. Frequent follow-up visits to assess progress and provide support is recommended. Sequential dilation has relatively few complications but could potentially cause vaginal irritation, breakdown, and necrosis; as well as fistulas and possible prolapsed [64].

There are also surgical options for the treatment of vaginal atresia, including a pull-through procedure in cases of isolated vaginal atresia and formation of a neovagina. Given the morbidity of the neovagina creation procedure, an approximately 10% complication rate including potential for injury to surrounding organs and formation of scar tissue, it is often pursued by patients who have failed or declined dilator therapy [65]. Patients with Class I MAs and their guardians should be counseled on this option at diagnosis and referred to a specialist for further counseling, if desired. Some patients with these diagnoses may have functional endometrial tissue in the rudimentary or underdeveloped upper genital tract. In post-menarcheal patients, this can cause menstrual symptoms and potentially hematocolpos in the case of an obstructive MA. Medical suppression of endometrial activity can be achieved with hormonal therapy in the form of combined or progesterone-only contraceptive pills. Additionally, gonadotropin releasing agonist injections with progesterone add-back therapy for long-term use may be used but should be dosed with caution in adolescent populations given known side effect of bone loss [66]. As mentioned in the previous section, counseling and anticipatory guidance are paramount in the management of Class I MAs because they have the potential to carry long term consequences on the personal, sexual, social, and gender identity of the patient [9].

ASRM Class II malformations include findings of a unicornuate uterus with variations of an incompletely-developed rudimentary contralateral horn. The underdeveloped remnant may or may not communicate with the full-sized contralateral side and may or may not contain functional endometrium. For those patients who

experience cyclic pelvic pain secondary to an obstructed rudimentary horn, medical management with ovulation suppression is reasonable, such as with continuous oral contraceptive pills or with leuprolide acetate, as in Class I malformations. There are reports in the literature of minimally invasive surgical procedures to remove a symptomatic rudimentary horn for pain refractory to medical management [67]. Patients desiring surgical intervention should be referred to a sub-specialist.

Treatment for uterine didelphys (Class III malformations) first includes evaluation for a vaginal septum, which is present in 75% of cases, and removal if symptomatic or prior to attempting pregnancy or vaginal delivery. Patients with obstructive vaginal septa may have painful hematocolpos and should not have simple incision and drainage given possibility of ascending infection. Instead, the septa should be excised with a procedure. There is no specific surgical treatment for uterine didelphys itself given that the two uterine horns are fully functional and not fused at the endometrium. Similarly, for patients with a bicornuate uterus (Class II malformation), there are no widely accepted surgical treatments. This contrasts with patients with uterine septa, which can be removed hysteroscopically, sometimes in a staged fashion depending on size and thickness [22].

Given that all of the classes MAs contain variants, all patients considering surgical management of MAs should be referred to a center with experts specializing in these particular procedures and their management. Additionally, pre-procedural imaging should be reviewed by specialists in pelvic anatomy and anomalies [22]. A patient's particular anatomy may be unpredictable given the known association of MAs with urinary tract anomalies, so comprehensive knowledge of pelvic anatomy is paramount. Timing of treatment for these procedures varies depending on the anomaly. For example, an imperforate hymen causing ureteral obstruction in a neonate should be addressed immediately, while a vaginal septum could be removed at the time of coitarche or prior to attempting pregnancy. In the case of preconception counseling, a uterine septum could be removed prior to attempting spontaneous conception or ART. As there is a higher incidence of infertility in patients with MAs, many of these treatments may be pursued with the intent to improve chances of successful pregnancy and subsequent live birth. If a patient does not wish to become pregnant and is asymptomatic from her MA, then no invasive intervention is warranted. It is especially important to counsel patients and guardians in the pediatric and adolescent population about the role of expectant management.

Conclusion

The provision of optimal care for women with MAs requires early diagnosis, appropriate timing of surgical or medical management, and adequate counseling throughout the woman's reproductive life. Diagnosis will often occur in the pediatric and adolescent age range, occasionally during a routine physical exam. A diagnosis of an MA is emotionally challenging for most women given possible reduced fertility and altered sexual expression, so physicians should feel empowered to fully counsel patients on the implications of their condition and treatment options. In order to achieve ideal outcomes, a multi-disciplinary team that includes physicians, mental health providers, and care coordinators is necessary. For younger patients, inclusion of parents or guardians may also be beneficial. Patients should be counseled that with appropriate treatment, many women with MAs experience positive sexual and reproductive outcomes. Continued research is needed to determine the most effective way to

identify patients who may need additional psychosocial support, ideal timing of surgical intervention if warranted, and ways to increase awareness and support for patients with MAs in the pediatric, adolescent, and adult populations.

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