Development of the Female Reproductive Tract and Associated Anomalies

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Opinion statement

Aberrations in the development of the female reproductive tract result in an array of anomalies. Because of the wide range of possible anomalies, the presentation of women with congenital anomalies of the reproductive tract is highly variable. While some women are asymptomatic, others present with symptoms of pain, menstrual abnormality, recurrent pregnancy loss, and/or poor obstetric outcomes. When providing care for patients with anomalies of the female reproductive tract, it is critical to be sensitive to both the patient's physical and psychological well-being. When an intervention is indicated, patient maturity, motivation, and ability to be an active participant in their care should be considered. Due to the rarity of some of the anomalies of the female reproductive tract, care at a center with special expertise in the care of these complex patients is at times warranted.

Introduction

The embryological development of the female reproductive organs

The development of the reproductive system begins at approximately 6 weeks gestational age. Initially the system consists of undifferentiated gonads and two paired ductal systems. The two ductal systems are the Wolffian ducts and the Müllerian ducts which represent the precursors to the male and female reproductive systems, respectively. Though gonads influence the development of the reproductive

organs, they have different embryologic origins and are typically unaffected in patients with Müllerian anomalies.

In males, the developing testes secrete two substances that influence the development of the male reproductive tract. The first substance is Müllerian Inhibiting Substance (MIS) which causes the Müllerian ducts to regress. The testes also produce testosterone which promotes Wolffian differentiation into the components of the male reproductive system.

In females, neither MIS nor testosterone is produced. The Wolffian ducts therefore regress while the Müllerian ducts persist. The Müllerian ducts extend in a cranial-caudal fashion and fuse at their caudal end to form a y-shaped structure, the uterovaginal primordium. This medial fusion event creates a septum which will subsequently regress, resulting in the formation of the uterus, the cervix, and the upper portion of the vagina. The cranial, unfused portions of the Müllerian ducts will become the paired fallopian tubes.

The caudal portion of the uterovaginal primordium fuses with the urogenital sinus, canalization of which results in the formation of the vagina and hymen. A portion of the vagina has traditionally been thought to be derived from the urogenital sinus. There is, however, significant debate with regard to the embryologic origins of the vagina. Regardless of its origins, the vagina's development is dependent on the concomitant development of the Müllerian ducts and estrogen.

At birth, the female reproductive system is comprised of paired ovaries and fallopian tubes, a single uterine body and cervix, and a single vagina. Aberrations in the embryological development of the female reproductive tract may result in any one of several different anomalies. The development of the female reproductive tract is closely linked to the developing renal system, and patients with Müllerian anomalies often have associated renal anomalies [1, 2].

Classification of anomalies of the female reproductive tract

Classification of anomalies of the female reproductive tract has been the subject of recent debate. The American Society of Reproductive Medicine (ASRM, formally American Fertility Society) first developed a classification system to describe anomalies of the Müllerian system in 1979. This was expanded in 1988 and is the

primary system for classification of anomalies of the female reproductive tract [3]. Alternate classification systems such as the Vagina Cervix Uterus Adnexa-associated Malformation (VCUAM) system [4], the European Society of Human Reproduction and Embryology (ESHRE), and the European Society for Gynecological Endoscopy (ESGE) have also been proposed [5, 6]. Though each of these systems has its own merits, for ease of discussion here, we will broadly discuss the anomalies of the reproductive tracts as they fall into one of three categories: (1) uterine aplasia, (2) obstructive anomalies, or (3) non-obstructive anomalies (summarized in Table 1).

Diagnosis and imaging

In females in whom a Müllerian anomaly is suspected, ultrasound is commonly the first imaging modality utilized to delineate pelvic structures. Though transvaginal ultrasound is the preferred means of imaging the female pelvis, this approach is not always feasible or tolerated in the pediatric and adolescent population. For these patients, transabdominal and translabial images can be helpful. Though the vagina and cervix are not well visualized using ultrasound, the uterine and ovarian anatomy can be well described using this imaging modality. Imaging is enhanced with the use of 3D ultrasound which can improve the accuracy in characterization of Müllerian anomalies to approximately 90 %.

When ultrasound alone is not sufficient to fully delineate the Müllerian anomaly, MRI is the imaging modality of choice and is considered the gold standard in imaging the female pelvis [8]. Furthermore, MRI may provide additional information of the renal system abnormalities of which are commonly associated with Müllerian anomalies.[7]

Uterine aplasia

- Mayer-Rokitansky-Küster-Hauser (MRKH)
- Complete Androgen Insensitivity Syndrome (CAIS)

Uterine aplasia, seen in Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome and disorders of sexual differentiation such as androgen insensitivity syndrome (AIS), typically presents in adolescence with

Table 1. Summary of uterine anomalies

Anomaly	Presentation	Associated symptoms	Pertinent exam findings	Intervention	Impact on reproduction
Uterine aplasia					
MRKH	Primary amenorrhea	Urologic and/or skeletal abnormalities; Pain if uterine remnant with functional endometrium	History of normal pubarche and thelarche; Normal external genitourinary exam findings; Blind vaginal pouch; Normal breast development XX karyotype	Counseling, Creation of neovagina through perineal dilation (preferred) or surgery, Possible excision of uterine remnants if symptomatic	Requires oocyte retrieval and gestational carrier for biologic child
CALS	Primary amenorrhea	Absence or paucity of axillary and pubic hair	History of normal thelarche; Normal external genitourinary exam findings; Blind vaginal pouch; Normal breast development XY karyotype	Counseling, Creation of neovagina through perineal dilation (preferred) or surgery, Gonadectomy after acquisition of secondary sexual characteristics	Unable to contribute genetic material for biologic child
Obstructive anomalies					
Imperforate hymen	Primary amenorrhea	Cyclic pain	Classic “blue-bulge” on external exam, palpation of distended vagina on rectal exam	Hymenectomy with evacuation of hematocolpos	None after surgical correction
Transverse vaginal septum	Primary amenorrhea	Cyclic pain	Normal external genitalia, inability to see the cervix on exam, palpation of distended vagina on rectal exam; Imaging required to determine level and extent of obstruction	Excision of transverse septum, reanastomosis of vaginal mucosa	None after surgical correction
OHVIRA	Significant and/or progressive dysmenorrhea	Unilateral renal anomaly	Vaginal bulge along lateral aspect of vagina. Imaging to confirm diagnosis	Single-stage excision of obstructing longitudinal vaginal septum	None after surgical correction
Vaginal atresia	Primary amenorrhea	Cyclic pain	Normal external genitalia, inability to see the cervix on exam, palpation of distended vagina on rectal exam; Imaging required to determine level and extent of obstruction	Excision of atretic portion of vagina, vaginal pull-through with reanastomosis of vaginal mucosa to the perineum; may require tissue grafting if inadequate native vaginal tissue present	None after surgical correction
Non-obstructive anomalies					
Unicornuate uterus	Recurrent pregnancy loss/ Poor obstetric history	Urologic abnormality	Requires imaging for characterization	Counseling	Decreased term birth rates, increased rates of growth restriction, malpresentation, cesarean section
Septate uterus	Recurrent pregnancy loss/ Poor obstetric history	Urologic abnormality	Requires imaging for characterization	Counseling, consider metroplasty in those patients with recurrent pregnancy loss	Recurrent pregnancy loss
Uterine didelphys	Incidental finding, Recurrent	Urologic abnormality; longitudinal vaginal septum	Two cervixes identifiable on vaginal exam, may have two vaginal canals	Counseling, consider excision of vaginal septum present and symptomatic	Decreased term birth rates, increased rates of growth restriction,

Table 1. (Continued)

Anomaly	Presentation	Associated symptoms	Pertinent exam findings	Intervention	Impact on reproduction
Bicornuate uterus	pregnancy loss/ Poor obstetric history Recurrent pregnancy loss/ Poor obstetric history	Urologic abnormality; longitudinal vaginal septum	Requires imaging for characterization	Counseling, consider excision of vaginal septum present and symptomatic	malpresentation, cesarean section Decreased term birth rates, increased rates of growth restriction, malpresentation, cesarean section
Longitudinal vaginal septum	Pain with intercourse or difficult tampon use	Possible uterine didelphys, bicornuate uterus, or septate uterus	Complete or incomplete longitudinal vaginal septum	In symptomatic patients, excision of longitudinal vaginal septum with reanastomosis of vaginal mucosa	If not excised may cause labor dystocia during attempted vaginal delivery, laceration

primary amenorrhea. External exam of these patients will reveal normal external genitalia with either a blind vaginal pouch or a vaginal dimple. Imaging is then utilized to assess for the presence or absence of the uterus, cervix and upper vagina. When uterine aplasia is observed, it is important to further characterize the patient as the underlying syndrome will guide further management. A karyotype is essential to differentiating MRKH from AIS [9].

MRKH

Uterine aplasia is most commonly associated with MRKH, affecting 1:4000–1:10,000 women [10]. The disorder occurs in females with an XX karyotype in whom the Müllerian ducts failed to develop, resulting in an absent vagina [11]. The ovaries, being of different embryologic origins than the Müllerian ducts, are unaffected. Affected females will report a history of normal female sexual maturation with thelarche and pubarche but no menarche. Though the majority of patients with MRKH have complete uterine aplasia, a number of patients will have fallopian tubes and/or rudimentary uterine horns. Though these uterine horns are typically non-functional, 2–7 % of these rudimentary horns will have a functional endometrium and present with cyclic abdominal pain due to the obstruction of outflow [12]. Additional congenital anomalies, particularly of the urologic and skeletal systems, are observed in 25–50 % of patients with MRKH [10, 11]. As such, imaging of the renal system is also warranted when a diagnosis of MRKH is made.

AIS

AIS should also be considered in patients with uterine aplasia. AIS results from a defect in the androgen receptor (AR) and occurs with an incidence of 1:20,000–1:99,000 genetic males [13, 14]. AIS is inherited in an X-linked recessive pattern with variable presentations based on the inherited AR mutation. Those mutations which limit all signaling through the AR result in complete AIS (CAIS). CAIS is observed in XY individuals who, despite having normal testicular production of testosterone, develop a female phenotype. During embryogenesis in patient with CAIS, the Wolffian system is unresponsive to the circulating testosterone and does not differentiate into male structures. The developing testes also produce MIS which suppresses development of the Müllerian system, resulting in uterine aplasia. Testosterone serves as a precursor to estrogen which promotes thelarche in individuals with AIS at the time of puberty. Patients with CAIS will often not undergo pubarche and will have scant or absent pubic hair [14]. Due to the body's inability to respond to the effects of testosterone, individuals with CAIS typically identify as female, concordant with their phenotype [15]. Both partial and mild forms of AIS exist with varying effects on development.

Treatment Options for Uterine Aplasia

Treatment of the patient with uterine aplasia first begins with a consideration of the psychological impact of the diagnosis on the patient. As previously noted, uterine aplasia is commonly diagnosed in adolescence, a time of significant emotional flux. Understanding the diagnosis and addressing options for treatment are often distressing to adolescents and require a high degree of

motivation. As these conversations will likely be difficult for the adolescent female, it is important to work closely with the patient, her family, and a counselor to allow the patient to best face her diagnosis [15, 16].

Once a patient is ready for intervention, attention is turned to the creation of a vagina. Though a number of surgical approaches have been described for the creation of a vaginal space, progressive perineal dilation is highly effective and is the preferred means of vaginal creation [11, 17, 18]. Several surgical approaches have been utilized for the creation of a neovagina and are reserved for those who have been unsuccessful at progressive vaginal dilation. These surgical procedures are described elsewhere and should be performed in a center with expertise with these procedures [19, 20]. To achieve the best surgical outcome, patients should be prepared to participate with postoperative dilation or vaginal stenting. In those patients with pain related to a uterine remnant with functional endometrium, laparoscopic excision is warranted to mitigate symptoms.

Those patients who present with uterine aplasia due to CAIS are treated similarly to those with MRKH. Discordance of gender of identity and genetic sex can be psychologically distressing to the female with CAIS and counseling remains a key component of care. The majority of females with CAIS will identify as female [15] and will benefit from creation of a neovagina. In contrast to the MRKH patient, the patient with CAIS has testes which are at increased risk for germ cell tumors. Excision of the male gonad should be considered after the female has obtained secondary sexual characteristics. After gonadectomy, it is recommended for patients to continue supplemental estrogen with annual DEXA scans to evaluate bone health [21].

Uterine aplasia has a significant impact on a patient's reproductive options. Patients with MRKH have normal ovaries and may serve as an oocyte donor to achieve genetic offspring. Until recently, the only option for these patients was in vitro fertilization with the use of a gestational carrier. However, this requirement was recently bypassed in a patient with MRKH who delivered a live birth after uterine transplantation [22]. Though this procedure remains experimental, it may become a feasible option for women with uterine aplasia as the technology advances. Unfortunately, females with AIS do not maintain their reproductive potential.

Obstructive anomalies of the female reproductive tract

- Imperforate hymen
- Transverse vaginal septum
- Obstructive hemi-vagina with ipsilateral renal anomaly
- Vaginal atresia

Obstructive anomalies of the female reproductive tract often present in adolescence with a complaint of pain due to the obstruction of menstrual outflow. Obstruction may occur at any level of the outflow tract, ranging from the level of the hymen, as observed with imperforate

hymen, to the cervix, as observed in cervical atresia. Definitive management requires surgical intervention, which, depending on the level of obstruction, may be simple or extensive. Those patients requiring extensive surgical procedures may not be emotionally or psychologically mature enough to participate in the postoperative management which often requires the use of a vaginal dilator. In patients who elect to delay surgical intervention, suppression of the menstrual cycle through hormonal suppression is a reasonable option. Suppression may be in the form of a combined oral contraceptive, progesterone injection, or with gonadotropin-releasing hormone agonists such as Depo-lupron [23]. Menstrual suppression prevents further accumulation of menstrual products and allows the patient time for emotional maturation until surgical intervention can be pursued.

Imperforate hymen

The most common example of an obstructive anomaly is the imperforate hymen with an incidence of approximately 1:1000 [24]. Patients with imperforate hymen will present with primary amenorrhea and may report cyclic pain. On exam, there is a classic “blue-bulge” due to distension of the hymen. The presence of an imperforate hymen is further supported by having the patient Valsalva. The imperforate hymen, comprised of a thin layer of tissue, will bulge as the intra-abdominal pressure rises. Additional information may be obtained from rectal exam with a fullness felt immediately past the anal sphincter. If the diagnosis is still not certain after a thorough exam, ultrasound and/or MRI will help determine the diagnosis.

The imperforate hymen may also be observed in neonates, who, under the influence of maternal estrogen, develop vaginal secretions which accumulate and form a hydrocolpos and/or mucocolpos [20]. If the patient is asymptomatic, intervention may be delayed until puberty. If a significant accumulation has occurred, resulting in symptoms, excision of the hymen is warranted to allow for efflux of the accumulated fluid. Simple aspiration is contraindicated due to the risk of subsequent infection.

The treatment of the imperforate hymen is a cruciate incision of the hymen, allowing for efflux of menstrual fluid. This is typically performed during an exam under anesthesia, during which excess tissue may be excised as indicated [20]. Following the evacuation of the retained menstrual fluid, inspection of the vagina and cervix may also be performed. The hymen is derived from the urogenital sinus and, as such, is typically an isolated finding, without concomitant Müllerian or renal anomalies. Though rare, there have been case reports of associated anomalies detected at the time of treatment for an imperforate hymen [25–28].

Transverse vaginal septum

Transverse vaginal septa are the rarest congenital anomaly with an incidence of 1:80,000 women [24]. A transverse vaginal septum arises either from incomplete vertical fusion of the Müllerian ducts and the urogenital sinus derivatives, or incomplete canalization of the fused structures. Therefore, patients with a transverse vaginal septum typically have normal upper tracts and renal systems [20].

Patients with a transverse vaginal septum typically present with primary amenorrhea. The septum is commonly located in the upper third of the vagina and may therefore not be readily apparent on external exam [29]. The transverse vaginal septum can vary in thickness and the surgical management and outcomes vary based on whether the septum is thin (<1 cm) or thick (>1 cm). In those individuals in whom a transverse septum is suspected, ultrasound or MRI may be utilized to characterize the patient's anatomy. MRI is superior in its ability to visualize the vagina and cervix and can provide information regarding the thickness of the vaginal septum [20, 30].

Though the majority of transverse septa occupy the mid to upper vagina, 14 % are located in the lower vagina. These may be difficult to differentiate from an imperforate hymen or vaginal agenesis. Appropriate classification of the anomaly is critical as the management of each is markedly different. As previously noted, individuals with an imperforate hymen will demonstrate a further bulge of the hymen during Valsalva. A transverse vaginal septum will not demonstrate this mobility. A rectal exam may also be performed to distinguish an obstructive process from vaginal atresia. Those patients with a distal obstruction will have a palpable vaginal bulge on rectal exam due to accumulation and distension of the vagina with menstrual fluid; patients with vaginal atresia will not have such a bulge. As previously noted, ultrasound and/or MRI may be required to confirm the diagnosis and guide surgical management [20, 23].

Surgical excision of the transverse vaginal septum is the standard of care. Excision is easiest to perform when a hematocolpos is present and the septum is thin. Complete excision of the septum with reanastomosis of the vaginal mucosa on either sides of the excision is required to prevent vaginal stenosis. Using a spinal needle, the vaginal septum is pierced and the obstructed menstrual fluid is aspirated, confirming that the operator has entered the region of the vagina cephalad to the obstruction. Ultrasound guidance may also be useful. The vaginal septum should then be further excised, to allow for passage of a foley catheter into the upper vagina. This allows maintenance of access to the upper vagina and helps to delineate the boundaries of the septum. The presence of a preoperative hematocolpos provides distention of the vagina, the redundant mucosa of which facilitates reanastomosis of the vaginal mucosa [20].

Alternatively, the "Z-plasty" technique may be utilized for thicker septa or where there is not enough normal mucosa to reapproximate end to end [31]. In this procedure, the mucosa lining the inferior aspect of the septum is incised by two incisions, creating four triangular flaps. The intervening fibrous tissue that comprises the septum is then excised. The superior mucosal edge is then incised in a similar fashion, creating four additional triangular flaps of vaginal mucosa. When creating this second incision, care should be taken to rotate the position of the incision by 45 degrees relative to the incision in the inferior mucosa to allow for the resulting flaps to interdigitate. The upper and lower flaps are then undermined to allow for anastomosis and the free edges of the upper and lower triangular flaps are sewn together to form a Z plasty.

Because of the risk of postoperative vaginal strictures, patients should be prepared to use dilators postoperatively [31, 32]. If there is concern for patient compliance with postoperative vaginal dilation, excision may be delayed until the patient is mature enough to use dilators. In these scenarios, suppression of menstruation is warranted. It may be tempting to simply drain the hematometrocolpos as a means of postponing surgery. This should be avoided as a microperforation can allow for ascending infections.

Obstructive hemi-vagina with ipsilateral renal anomaly

Recent attention has been paid to the coexistence of a uterine didelphys, a portion of which is obstructed by a longitudinal vaginal septum, and ipsilateral renal anomaly. The diagnosis of this syndrome, termed obstructive hemi-vagina with ipsilateral renal anomaly (OHVIRA) [33], is often delayed. Dysmenorrhea does not necessarily develop until there has been significant distension of the obstructed hemivagina and uterine horn. In addition, it is not uncommon for patients with this syndrome to be misdiagnosed by their primary provider as demonstrated in a series in which the actual diagnosis had been missed in 100 % of referred cases [34]. In a recent cohort of women with anomalies, confirmation of the diagnosis of OHVIRA was made, on average, 27 months after the initial presentation of symptoms, compared to one month after the onset of symptoms in those patients with a transverse vaginal septum [35].

Patients with OHVIRA will commonly present with initially cyclic and eventually constant pelvic pain [20]. On physical exam, the obstructed hemivagina may be visualized as a bulge in the vaginal sidewall [33]. Though uterine didelphys is the most common uterine anomaly appreciated with the syndrome, other uterine variants such as the septated uterus, a single uterus with two cervices, and bicornuate uterus have been described in this syndrome [36–38]. As with other anomalies, preoperative imaging with ultrasound and MRI are the preferred imaging modalities to diagnose and characterize OHVIRA [7, 8].

The standard of care for OHVIRA is a single-stage excision of the obstructing longitudinal vaginal septum and evacuation of hematometrocolpos [33]. Subsequent pregnancies have been observed in previously obstructed uterine horns [37, 39–42], underscoring the potential benefit of preservation of the previously obstructed uterine horn. Techniques utilized in aiding excision of the transverse vaginal septum such as the use of ultrasound guidance, needle aspiration, and foley catheter may also prove useful in assisting excision of the obstructing longitudinal septum [43]. As with other obstructive anomalies, decompressive transvaginal needle aspiration of the hematocolpos is contraindicated.

Vaginal atresia

Vaginal atresia may occur concomitantly with uterine aplasia as is seen in MRKH and CAIS, or it may occur in patients with normal Müllerian structures. These latter patients will also present with primary amenorrhea but will often have pain due to the obstruction of cervical secretions and/or menstrual fluid. A rectal exam may be useful in palpating the upper vagina which will likely be distended due to obstruction. If the diagnosis is not confirmed on exam, a pelvic ultrasound or MRI may be necessary to evaluate for the presence or absence of Müllerian structures. In those patients

with isolated vaginal atresia, the atretic portion of the vagina can be excised from a perineal approach with or without laparoscopy [20, 44, 45]. Ideally, the procedure is performed when a hematocolpos is present as it serves as a natural tissue expander and allows for the mucosa of the upper vagina to be mobilized and brought to the perineum [20]. Postoperatively, patients are at variable risks of stricture formation and may benefit from postoperative use of a vaginal dilator [44].

Non-obstructive anomalies of the female reproductive tract

- Unicornuate Uterus
- Septate Uterus
- Bicornuate Uterus
- Uterine Didelphys

The non-obstructive anomalies of the female reproductive tract are often incidentally found or identified in women with obstetrical complications ranging from recurrent pregnancy loss, fetal malposition, and preterm labor. The incidence of these anomalies is approximately 2 % in the general population but may be as high as 6–7 % in those women with a history of recurrent pregnancy loss [2].

The unicornuate uterus results from failure of one of the Müllerian ducts to develop, resulting in a smaller, deviated cavity, commonly with a single fallopian tube [2]. It may be accompanied by a rudimentary uterine horn which may or may not be communicating. Removal of a non-communicating horn is indicated due to pain associated with menses and the possibility of ectopic pregnancy. This uterine malformation is associated with poor obstetrical outcomes including cervical insufficiency, preterm birth, growth restriction and stillbirth. Live birth rates are low for those women with a unicornuate uterus, ranging from 29.2 % in one cohort to 49.9 % in a recent review of the literature [46].

The septate uterus is the most common Müllerian duct abnormality and is the uterine anomaly most commonly associated with poor obstetric outcomes [2]. In this variant, the two Müllerian ducts have fused but there has been incomplete resorption of the intervening septum. Though hysteroscopic resection of the septum may improve obstetric outcomes [47], no randomized control trials have been performed to date to support the therapeutic benefit of metroplasty [48].

Partial fusion of Müllerian ducts during embryogenesis results in the bicornuate uterus which is characterized by two uterine horns, joined to a single cervix and a single vagina. Similarly to the unicornuate uterus, the bicornuate uterus is associated with an increased miscarriage rate. Unification procedures are possible but should be reserved for those with well-established poor obstetric outcomes [2].

Uterine didelphys results from complete failure in the medial fusion of the Müllerian ducts, the result of which is a duplicated system with two uterine horns and two cervixes. Approximately 75 % of these patients will have a concomitant longitudinal septum which may or may not be symptomatic. Women with a transverse longitudinal septum who report dyspareunia or an inability to control menstrual flow with a tampon benefit from surgical excision of the septum [20].

Compliance with Ethical Standards

Conflict of Interest

Janeen L. Arbuckle declares that she has no conflict of interest. Kimberly H. Hoover declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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