Embryological basis of malformed female genital tract and various classifications

1Richa Niranjana, 2A K Singha, 3Anjoo Yadav
1Associate Professor, 2Professor, Department of Anatomy, Government Medical College, Haldwani, Uttar Pradesh
3Assistant Professor of Anatomy, Government Medical College, Kanauj, Uttar Pradesh

Abstract

Developmental anomalies of the Mullerian duct system represent some of the most fascinating disorders that obstetricians and gynaecologists encounter. The uterus is formed during embryogenesis by the fusion of the two paramesonephric ducts (Mullerian ducts). This process usually fuses the two Mullerian ducts into a single uterine body, but fails to take place in the affected women who maintain their double Mullerian systems. A bicornuate uterus is a type of a uterine malformation where upper part of uterus forms two horns. The fusion process of upper part of Mullerian duct is altered. As a result, cranial part of the uterus becomes bifurcated. As Mullerian duct anomalies are of anatomic interest, this article discusses epidemiology, embryological development, genetics of development and malformation and lastly various classifications based on Mullerian duct development. Pregnancy in bicornuate uterus is usually of high risk with reproductive outcomes like recurrent abortions, preterm delivery or malpresentation. Classifying Mullerian duct anomalies bears merit because it correlates anatomic anomalies with arrests in morphogenesis. Establishing an accurate diagnosis is essential for planning treatment and management strategies.

Key words: Mullerian duct, bicornuate uterus, infertility

Introduction

The majority of women with Mullerian duct anomalies (MDA) have little problem in conceiving and they have higher associated rates of spontaneous abortion, premature delivery and abnormal fetal lie and dystocia at delivery1,2.

Most studies report an approximate frequency of 25% for associated reproductive problems, compared to 10% in the general population3,4. The prevalence of uterine malformation is estimated to be 6.7% in the general population, slightly higher (7.3%) in the infertility population, and significantly higher in a population of women with a history of recurrent miscarriages (16%)5.

The majority of Mullerian duct anomalies are considered to be sporadic or multifactorial in nature; however, polygenic and genetic patterns of inheritance have been described in the expression of these anomalies6,7. Extraterine and intrauterine environmental factors, such as exposure to ionizing radiation, intrauterine infections, and drugs with teratogenic effects such as thalidomide and diethylstilbestrol (DES), can also cause defects of the developing fetal genital tracts3.

Dept. of Anatomy, Govt. Medical College, Haldwani received an anomalous uterus specimen from Dept. of Obstetrics & Gynaecology after hysterectomy. It was bicornuate unicollis uterus which is a Mullerian duct anomaly (MDA). As Mullerian duct anomalies are of anatomic interest, this article discusses epidemiology, embryological development, genetics of development and malformation and lastly various classifications based on Mullerian duct development.

Embryology

At 6 weeks of development, the male and female genital systems are indistinguishable in appearance, constituting two sets of paired genital ducts: the paramesonephric (Mullerian) ducts (PMD) and the mesonephric (Wolfian) ducts. In the absence of the testis-determining factor (TDF) of the Y chromosome, the mesonephric ducts begin to degenerate and form a matrix for the developing paramesonephric ducts (PMD).
Synchronously, the paramesonephric ducts develop bidirectionally along the lateral aspects of the gonads. The uterus is formed at around 8-16 weeks of fetal life from the development of the two paired paramesonephric ducts, called Mullerian ducts. The process involves three main stages:

i. Organogenesis: the development of both Mullerian ducts. PMD originate as longitudinal invagination of coelomic epithelium on anterolateral surface of the urogenital ridge.

ii. Fusion: the lower Mullerian ducts fuse to form a ‘Y’ shape urovesical primordium (forming upper vagina, cervix and uterus), this is termed lateral fusion. The upper cranial part of the Mullerian ducts will remain unfused and form the Fallopian tubes. (The proximal segments derived from coelomic epithelium, open into the peritoneal cavity to form the fallopian tubes. They are rarely involved in Mullerian duct anomalies). Paired PMDs initially separated by a septum.

iii. Septal absorption: After the lower Mullerian ducts fuse, a central septum is left which starts to resorb at 9 weeks eventually leaving a single uterine cavity and cervix. (Regression of the uterine septum has been proposed to be a result of apoptosis, mediated by the Bcl2 gene. Absence of this gene has been implicated in persistence of the septum).

At week 12, the uterus exhibits its normally developed configuration: a fused external uterine contour of the myometrium derived from adjacent mesenchyme and a triangular-shaped cavity lined by endometrium derived from lining of the Mullerian ducts and endometrial stroma is derived from adjacent mesenchyme. Entire process completes by 22 weeks, resulting in uterus, cervix and single uterine cavity.

Vagina develops from two different embryological structures, urovesical primordium (mesodermal origin) and urogenital sinus (UGS - endodermal origin). The distal segment of urovesical primordium, progress caudad-medially contacting the posterior aspect of the urogenital sinus at the level of the Mullerian or sinus tubercle. These distal segments of the urovesical primordium give rise to the uterus and upper third of the vagina. The sinus tubercle induces endodermal thickening, sinovaginal bulbs fuse to form vaginal plate. Later the central cells of the plate break down in a caudal to cephalad manner, forming the lumen of the vagina, which gives rise to the lower two third of the vagina. The vaginal fibromuscular wall develops from surrounding mesenchyme. The vaginal plate elongates during the 3rd-5th month, and its interface with the urogenital sinus forms the hymen, which usually ruptures during the perinatal period. The ovaries arise from the mesenchyme and epithelium of the gonadal ridge and are not influenced by the formation of the mesonephric or paramesonephric ducts.

It is also important to note the role of the mesonephric (or Wolffian) ducts. These are precursors and inducers of female reproductive tract development, and play a crucial role in renal development. In addition, they act with the Mullerian tubercle to form part of the vagina. As a result, abnormalities originating from mesonephric maldevelopment may also have an effect on genital tract and uterine formation. Shared connection between PMD and urinary tract structures explains the frequent association observed between Mullerian duct agenesis and renal-urinary system malformation.

This is reflected in the fact that up to 60% of women with unilateral renal agenesis have been shown to have genital anomalies, most commonly a unicornuate uterus. Interestingly, 40% of all patients with a unicornuate uterus suffer from renal abnormalities, while one study showed that >80% of patients with a uterus didelphys suffered from renal agenesis. Consequently, the detection of a congenital renal abnormality should alert the physician to look for associated genital anomalies and vice versa.

Genetics

In 2008, Hammoud et al. showed that there was strong evidence for familial contribution to congenital
uterine anomalies, with first-degree relatives having a 12-fold risk of developing an abnormality. However, a specific genetic aetiology for each type of anomaly was considered unlikely, as members of the same family had different phenotypic expressions of uterine anomalies.

Nevertheless, there has been recent progress in understanding certain genetic processes that underlie genital tract development. Several genes, such as Pax2 (paired box gene 2), Pax8 (paired box gene 8), Lim1 (LIM homeobox 1) and Emx2 (empty spiracles homeobox 2), have been implicated in the development of the Wolffian and Mullerian ducts, although most data has been derived from mouse knockout studies.

Mullerian agenesis has been associated with variants of the galactose-1-phosphate uridylyltransferase (GALT) enzyme as galactose exposure leads to agenesis. Mutations in either the antimullerian hormone or Mullerian inhibitory substance (MIS) gene or its receptor gene are responsible for this disorder. Early developmental control genes, homeobox HOXA9-HOXA13 and their DNA-binding transcription factors, have also been considered candidate genes involved in human Mullerian aplasia. In mice, the corresponding WNT4 protein is involved in development of the Mullerian ducts. The described mutation patient indicated that an association between the WNT4 gene and Mullerian duct differentiation may also exist in humans. Mutation in the WNT4 gene was associated with Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome, unilateral renal agenesis, and androgen excess with virilisation.

### Classification of Mullerian duct anomalies

The most basic classification of Mullerian duct defects consists of agenesis and hypoplasia, defects of vertical fusion, and defects of lateral fusion. In 1979, Buttram and Gibbons proposed a classification of

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<tr>
<th>Classification</th>
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<tr>
<td>I</td>
<td>Segmental or complete agenesis or hypoplasia</td>
<td>Agenesis and hypoplasia may involve the vagina, cervix, fundus, tubes, or any combination of these structures. Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome is the most common example. In 1 in 5000 women in this category. In 7-10% of women with vaginal agenesis, normal, but obstructed uterus or a rudimentary uterus with functional endometrium is present.</td>
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<td>II</td>
<td>Unicoronal uterus with or without a rudimentary horn (6-25%)</td>
<td>When an associated horn is present, this class is subdivided into communicating (continuity with the main uterine cavity is evident) and noncommunicating (no continuity with the main uterine cavity). The noncommunicating type is further subdivided on the basis of whether an endometrial cavity is present in the rudimentary horn. These malformations have previously been classified under asymmetric lateral fusion defects. The clinical significance of this classification is that they are invariably accompanied by ipsilateral renal and ureter agenesis.</td>
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<td>III</td>
<td>Didelphys uterus (5-11%)</td>
<td>Complete or partial duplication of the vagina, cervix, and uterus characterizes this anomaly. Both Mullerian ducts develop but fail to fuse, thus the patient has a “double uterus.”</td>
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<td>IV</td>
<td>Complete or partial bicornuate uterus (10-39% next commonest)</td>
<td>Only the upper part of that part of the Mullerian system that forms the uterus fails to fuse, thus the caudal part of the uterus is normal, the cranial part is bifurcated. Complete bicornuate uterus is characterized by a uterine septum that extends from the fundus to the cervical os. The partial bicornuate uterus demonstrates a septum, which is located at the fundus. In both variants, the vagina and cervix each have a single chamber.</td>
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<td>V</td>
<td>Complete or partial septate uterus (34-55% commonest)</td>
<td>The two Mullerian ducts have fused, but the partition between them is still present, splitting the system into two parts. A complete or partial midline septum is present within a single uterus, located in fundal region composed of poorly vascularised fibromuscular tissue.</td>
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<td>VI</td>
<td>Arcuate uterus (7%)</td>
<td>A small septate indentation is present at the fundus. Most commonly observed uterine anomaly detected on HSG finding.</td>
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<td>VII</td>
<td>DES-related abnormalities</td>
<td>A T-shaped uterine cavity with or without dilated horns is evident. Mid fundal constrictions, endometrial filling defects, irregular margin and a hypoplastic uterus.</td>
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Mullerian duct anomalies that was based on the degree of failure of normal development, and they separated these anomalies into classes that demonstrated similar clinical manifestations, treatment, and prognosis for fetal salvage. This classification was modified in 1988 by a subcommittee of the American Fertility Society - AFS (now the American Society of Reproductive Medicine)\textsuperscript{[30-36]}

Because of the variability and overlap of features of associated cervical and vaginal malformations, these changes generally are not incorporated into the basic schematics and are reported as a subset of the primary uterine defect. Secondary classification systems also have been introduced that further dissect and elaborate on the original Buttram and Gibbons scheme. In 1984, Toaff et al\textsuperscript{[37]} described nine subtypes of septate and bicornuate uteri that are characterized by the presence of a communication between two otherwise separate uterocervical cavities.

A rudimentary uterus is a uterine remnant not connected to cervix and vagina and may be found on the other side of a unicornuate uterus.

**Defects not classified by American Fertility Society**

Imperforate hymen - an imperforate and occasional microperforate hymen may present as an obstructive anomaly. Adolescents may present with cyclic pain, amenorrhea (imperforate hymen), menstrual irregularities (microperforate hymen) or difficult urination. After menarche pelvic or abdominal mass may present (hematocolpos)\textsuperscript{[38]}. Transverse vaginal septum- incomplete vertical fusion between mullerian tubercle and sinovaginal bulbs or canalization failure of vaginal plate results in formation of transverse vaginal septum (TVS) which can divide vagina into two segments and reduces its functional length. Most are located in the superior vagina at junction between the vaginal plate and caudal aspect of the urovaginal primordium (46%) other location mid vagina (40%) and inferior vagina (14%)\textsuperscript{[39]}. TVS is very rare(1/70,000 female)\textsuperscript{[40 & 41]}. Vaginal atresia- occurs when the UGS fails to contribute to inferior portion of vagina. Mullerian structures are usually normal, but lower portion of the vagina is replaced by fibrous tissue. Some authors have described vaginal atresia as a component of a syndrome with middle ear ossicle anomalies and renal dysgenesis\textsuperscript{[42]}.  

Figure 1: Classification of congenital uterine anomalies as described by the American Fertility Society (1988)

Figure 2. Classification criteria for differentiation of septate from bicornuate uteri. A, when apex (3) of the fundal external contour occurs below a straight line between the tubal ostia (1,2) or B, 3mm (arrow) above it, the uterus is bicornuate. C, when apex is more than 5 mm (arrow) above the line, uterus is septate. D, in arcuate uterus, the ratio of H to L is less than 10%.
Another drawback of above classification is that it does not specify the diagnostic methods or criteria that should be used in order to diagnose the anomalies and as a result, this is solely based on the subjective impression of the clinician performing the test\(^5\).

For this reason, the American Fertility Society classification system should function as a framework for the description of anomalies, rather than an exhaustive list of all possible anomaly types. Another more recent classification proposed by Oppelt et al. (2005)\(^6\)-the VCUAM classification which intends to make the description of complex genital anomalies easier by subdividing external and internal female genital organs into the following subgroups: vagina (V), cervix (C), uterus (U), adnexa (A) and associated malformations (M). An anomaly is therefore graded individually for each anatomical structure. For example, a particular case of uterus didelphys could be described

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<tr>
<td>1</td>
<td>Agenesis or hypoplasia of a whole urogenital ridge</td>
<td>Unicorneate uterus with uterine, tubal, ovarian and renal agenesis on the contralateral side.</td>
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<td>2</td>
<td>Mesonephric anomalies with absence of the Wolffian duct opening to the urogenital sinus and of the ureteral bud sprouting (and therefore, renal agenesis).</td>
<td>The 'inductor' function of the Wolffian duct on the Mu'Ierian duct is also failing and there is usually: Utero-vaginal duplicity plus blind hemivagina ipsilateral with the renal agenesis, clinically presented as: a) Large unilateral hematocolpos* b) Gartner's pseudocyst on the anterolateral wall of the vagina* c) Partial reabsorption of intervascular septum, seen as a 'buttonhole' on the anterolateral wall of the normal vagina which allows access to the genital organs on the renal agenesis side. d) Vaginal or complete cervico-vaginal unilateral agenesis, ipsilateral with the renal agenesis, and (1) with no communication, or (2) with communication between both hemiuteri (communicating uterus).</td>
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<tr>
<td>3</td>
<td>Isolated Mu'Ierian anomalies affecting</td>
<td>a) Mu'Ierian ducts: they are the common uterine malformations as unicorneate (generally, with uterine rudimentary horn), bicornuate, septate and didelphys uterus b) Mu'Ierian tubercle: cervico-vaginal atresia and segmentary anomalies such as transverse vaginal septum. c) Both, Mu'Ierian tubercle and ducts: (uni- or bilateral) Mayer-Rokitansky-Kuster-Hauser syndrome.</td>
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<tr>
<td>4</td>
<td>Anomalies of the urogenital sinus</td>
<td>cloacal anomalies and others.</td>
</tr>
<tr>
<td>5</td>
<td>Malformative combinations</td>
<td>Wolffian, Mu'Ierian and cloacal anomalies</td>
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*These types can associate a vaginal ectopic ureter and interseptal or interuterine communication
as: V2b (complete septate vagina), C1 (duplex cervix), U2 (bicornate uterus), A0 (normal adnexa) and M0 (no associated malformations). The VCUAM classification for the first time makes it possible to reflect even complex malformations in a precise and individual fashion, taking associated malformations into account. The classification makes it easier to provide appropriate clinical care for the affected patients.

Finally, Acien et al. (2004) have stressed the importance of considering the embryological origin of the different elements of the genitourinary tract in order to understand and effectively treat complex genital tract anomalies. For this reason, they proposed the revised 'Clinical and embryological classification of the malformations of the female genital tract,' (Table II) which classifies anomalies according to their embryological origin, and includes changes in the vagina, adnexa and renal system in addition to those of the uterus.

Acien et al (2004)5 studied the three new types of complex malformations: (i) unilateral cervico-vaginal atresia or (only atretic hemivagina) with renal agenesis, with or without communication between hemiuteri; (ii) unilateral Rokitansky syndrome; and (iii) the combination in the same patient of unilateral Rokitansky syndrome (Willemian defect) on one side and blind vagina and ipsilateral renal agenesis syndrome (Wolffian defect) on the other side.

**Associated anomaly with Mullerian duct defect**

1. Urinary tract and skeletal deformity - the incidence of urological anomaly with vaginal agenesis varies as 15 - 40%. Skeletal abnormalities such as congenital absence of vertebra and fusion of vertebra vary from 15-50%. Association of MRKH with Klieppel-Fiel syndrome been reported. MRKH also seen associated with MURCS, characterized by Mullerian duct agenesis, renal aplasia and cervicothoracic somite dysplasia.

2. Endometriosis- association of high incidence 77% seen.

3. Obstetric problems associated with uterovaginal anomaly:
   - High or abnormal presentation
   - Premature birth
   - Dystocia
   - Retained placenta
   - Still birth
   - IUGR
   - Spontaneous abortion(40%)33

4. Gynecological problems associated with uterovaginal anomaly:
   - Hydrocolpos or hematocolpos
   - Primary amenorrhea
   - Dyspareunia
   - Ectopic pregnancy
   - Incompetent cervix

**Diagnostic modalities**

Once MDAs are suggested based on evidence from patient's history or physical examination, clinician may opt for imaging workup for distinguishing forms of uterine anomalies which are based on the configuration of endometrial cavity and uterine fundus. First examination ordered is a pelvic, two dimensional (2D) sonography which is effective (75-100% sensitivity and 95% specificity). Newer 3 dimensional (3D) sonographic techniques offer higher sensitivity (100%) and specificity (100%). Post 3-D scanning has higher positive predictive value (100%) compared to 2 D scanning (50%).

HSG (Hysterosalpingography) allows evaluation of uterine cavity and tubal patency with high resolution and anomalies are suggested. But as images are limited only to endoluminal contour, in case of septate, didelphys and bicornuate uteri, precise diagnosis is non specific.

MRI is considered the criterion standard for imaging uterine anomalies. In addition, it can help to evaluate the urinary tract for concomitant anomalies. Most types of uterine anomalies can be diagnosed confidently using
pelvic MRI. MRI has high sensitivity and specificity in evaluating uterine anomalies. It has 100% accuracy compared to 92% by endovaginal sonography. MRI is extremely useful; lack of visualization of the vagina and uterus indicates agenesis or hypoplasia.

Conclusion

Müllerian anomalies are a morphologically diverse group of developmental disorders that involve the internal female reproductive tract. Classifying Müllerian duct anomalies by using the methods described above bears merit because it correlates anatomic anomalies with arrests in morphogenesis. However, AFS classification is confusing for clinicians and researchers, especially in standardizing, comparing data and planning treatment strategies. Other classification schemes have been developed to include combinations of different malformations. Establishing an accurate diagnosis is essential for planning treatment and management strategies.

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Address for Communication:
Dr. Richa Niranjan
Associate Professor of Anatomy, Government Medical College Campus, Haldwani - 263 139, Uttar Pradesh
Mobile: 09889051511
e-mail ID: niranjanricha@yahoo.co.in