Sexual and Reproductive Performance in Patients with Mullerian Duct Anomalies (MDAs): A Clinical Application of Basic Embryology of the Female Internal Duct System.

A simplified Guide for Medical Students and Residents in Obstetrics and Gynecology in Developing Countries.

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Preface

The basic knowledge of embryology lays a solid foundation for clinicians to build on their clinical knowledge and skills in managing patients with congenital malformations. The field of embryology is often forgotten by clinicians, they only come to recall when they encounter congenital malformations in their field of clinical practice.

This article has briefly reviewed literature on the pathogenesis and types of the female duct system anomalies and their individual clinical applications in terms of sexual and reproductive functions. Furthermore the chapter has included a brief discussion of the challenges in diagnosis and management of mullerian duct anomalies in resource constrained settings.

In preparation of this chapter, many standard textbooks in basic embryology as well as published research papers and case reports were referred. I would at this point appreciate the efforts of these authors of these original works for their efforts that has laid a valuable foundation for generations to come. The list of consulted text books and publications are mentioned in superscript numbers within the text and listed at the end of this chapter. At this point I should therefore suggest that the readers take efforts to read the listed references for further understanding of the subject.

Basically the chapter is meant to shade light on sexual and obstetric outcomes in women with Mullerian duct anomalies for medical students, residents in Obstetrics and Gynecology as well as practicing doctors in resources limited setting.

I would like extend my gratitude to Professor Ainory Gessase, a professor in anatomy who inspired me to write something valuable in basic sciences that has a practical application in clinical medicine. His inspiration is highly valued.

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1. INTRODUCTION

Mullerian duct anomalies are generally rare clinical conditions encountered in clinical practice of Obstetrics and Gynaecology. The malformations result from disruption during the development of the female internal duct system which includes the fallopian tubes, uterus, cervix and the upper portion of the vagina. Mostly, the anomalies involve the uterus, cervix and upper vaginal while those involving the fallopian tubes are much rarer. These malformations are attributed to failure in organogenesis, fusion or reabsorption of the Müllerian ducts during early embryological development stages.

The causes of Müllerian anomalies have yet to be fully identified and clarified. The karyotypes are normal in most cases though in few patients abnormal karyotype has been described but do not appear to be the cause of the malformations. Failures in organogenesis are related to incomplete development of one or both Müllerian ducts, thereby leading to agenesis, uterine hypoplasia or a unicornuate uterus depending of severity.

Fusion defects on the other hand result from three possibilities:

a. Incomplete merging of the two mullerian ducts with each other or
b. Incomplete merging of the structures of the urogenital sinus with the Müllerian tubercle. Failures in fusion of the two ducts may result in uterus didelphys, bicornuate uterus or arcuate uterus
c. While when the defect occurs in fusion of mullerian with the urogenital sinus,, anomalies such as imperforate hymen, transverse vaginal septum, oblique vaginal septum or absence of the cervix may result.

Following caudal fusion of the ducts with the urogenital sinus, the remaining portion of the central septum is resorbed. Resorption failure results in a uterus with a partial or complete septum. Certain malformations of the uterine cavity also lead to the formation of hypoplastic uterus, infantile uterus, agenesis of the cervix and T-shaped uterus. Because the conditions are initially symptomless, the diagnosis is usually made later in life.

Diagnosis and management of most these anomalies sometimes require advanced and sophisticated equipment which may not be readily available in resource limited settings and therefore pose an enormous challenge to doctors working in such settings. Due to the complexity of clinical presentations, the diagnosing of Müllerian malformations requires the use of more than one imaging techniques in a significant number of cases.

Hysterosalpingography (HSG) has been widely used to diagnose some types of MDA's but its efficacy in diagnosing some anomalies is debatable and varies according to the specific type of malformation being investigated. It can detect the presence of uterine septa and other structural malformations inside the uterine cavity but its usefulness is limited in patients who have transverse vaginal septum or imperforate hymen and therefore in this case it does not allow the internal uterine anatomy to be visualized, which completely hampers the diagnosis of the upper mullerian duct anomalies.

Ultrasonography has a sensitivity of around 50% according to some studies. The specificity of this method varies depending on several factors including the type of malformation under evaluation, the patient's body composition, radiologist's experience and the type of transducer used. Transvaginal ultrasonography (TVS) allows a much more detailed analysis of the endometrium, uterine cavity and cervix and therefore may be preferred in many cases.

Magnetic Resonance imaging (MRI) has recently been reported to be gold standard in the diagnosis of mullerian duct anomalies .The specificity of this technique is estimated to be close to 100% though some factors as mentioned above may affect the effectiveness of this method.

Mullerian duct anomalies can be severe enough to result into total coital and reproductive failure. In some mild cases however, conception may be possible but the outcomes may be not be favorable because recurrent miscarriages remote from term is a common finding.

While most cases of mullerian duct anomalies are 'cold', at times they may present as surgical emergencies requiring immediate attention for the purpose of saving life of the mother particularly in cases where a pregnancy has occurred and implanted either within the cavity of

the malformed uterus or in a rudimentary horn and results in rupture of the uterus or rudimentary horn and culminates in abdominal ectopic pregnancy.

This chapter intends to review literature on the pathogenesis of MDAs and present the common mullerian duct anomalies and their sexual and reproductive outcomes while at the same time unveiling the challenges facing doctors working in low income countries (LIC) where the availability of advanced diagnostic tools is limited.

2. GENERAL CLINICAL APPROACH TO PATIENTS WITH MULLERIAN DUCT ANOMALIES.

Many patients with Mulllerian duct anomalies (MDAs) may not be aware of the problem until after puberty when menstrual, sexual and obstetric problems begin to manifest. Common presentation includes coital difficulties, menstruation related problems, failure of conception and failure to maintain pregnancy (repeated miscarriages).Normally it is at this point in time when most patients begin to seek medical consultations.

Normal development of secondary sexual characteristics, stature and other physical features frequently tend to mask the problem thus leading to late attendance to medical professionals. For doctors to arrive to the final diagnosis in these cases, it requires a combination of a theoretical foundational knowledge of embryology, gross anatomy of the female pelvic structures and clinical skills in the field of Obstetrics and Gynaecology.

Diagnosing a woman with severe forms of MDAs like hypoplasia may mean that the woman's chance of having her own biological children is jeopardized (depending on the degree of the malformation in question) and if they are married their marriage may be at stake particularly in African cultures where having children are an important marker of womanhood. It is this that makes its approach peculiar in our cultures because suicides, divorce and severe forms of depressions have been reported.

A detailed individualized and holistic approach to these patients is critically important. As a matter of fact, in-depth counseling may be the only treatment option available in some severe forms of MDAs.

As well, in low-income countries where sophisticated diagnostic equipment are not readily available, reaching the diagnosis MDAs can be challenging and therefore a high index of suspicion on the side of the clinician can be of great value if not the only option avaialable.

A thorough history taking and thorough clinical examination from head to toe coupled with a sensitive pelvic/rectal examination are important in these patients. Presence or absences of secondary sexual characteristics in the absence of menstruation in adolescent girls are important fingerposts towards the presence of mullerian duct anomaly during history taking and clinical examination.

AS pointed out earlier on in this chapter, patients with mild to moderate disease, conception may be possible but pregnancy outcomes may not be favorable and are usually disappointing because most of them end before term. The adverse pregnancy outcomes associated with MDAs include abdominal pregnancy due rupture of rudimentary horn or bicornuate uterus, preterm birth and repeated miscarriages depending on the type and degree of the malformation.

The psychological problems that these patients manifest with may be devastating and profound. The reaction by both the patient and parents varies considerably with the age of the patient and the severity of the malformations. Confusion, feeling of loneliness, rejection is not uncommon. Concerns about their future sexual and reproductive function tend to deepen their worry.

Psychological treatment and reconstruction surgery are in many cases, the main stay of patient management and patient should be made aware of the possibility of treatment failure and the counseling should Centre on the severity of the malformation in question.

Denial of the diagnosis is also a possible psychological outcome to be expected and patients may move from doctor to doctor, from clinic to clinic including spiritual healers in search of a satisfying answer for their problem and therefore it is not uncommon to find patients who have used a significant portion of their incomes, belongings and properties in search of cure for MDAs.

3. SEX DETERMINATION AND GONADAL DEVELOPMENT.

The development of the internal duct system in both male and female depend entirely on the type of gonads present (Testis or ovaries). It is of appreciable value to understand first the development of the gonads before the reader can appreciate the development of the duct system in the female.

The influence of differentiated gonads on the development of other genital organs is fundamental and the presence of the testis will lead to male genital organs, but if the testis does not form the individual will develop female genital organs whether ovaries are present or not [1].

The primitive gonads appear in the embryo around five weeks gestation. At this point coelomic epithelium develops on the medial aspect of the urogenital ridge and following proliferation leads to the establishment of gonadal ridge. At this point they are located in the cervical region. This elongated mass of undifferentiated cells is the sex gland anlage destined to become either the testis or the ovary while in the male the epithelial column or primary sex cord becomes separated from the surface (tunica albugenia) they subsequently differentiate into the seminiferous tubles, sertoli cells, interstitial cells of the testis.

In the female the tunica albugenia does not appear at this stage, and the cords of the epithelial cells breaks up into clumps and ultimately form the primitive follicles[2].

Following conception and fertilization, the normal embryo contains 46 chromosomes (22 autosomes and one sex chromosome) derived from each parent. The basis of mammalian development is that a 46 XY embryo will differentiate into a male while a 46xx will differentiate

into a female. It should however be appreciated at this point (as pointed out earlier on) that it is the presence of the Y chromosome which determines whether the gonads will develop into a testis or an ovary[1].

The Y chromosome contains a gene sequence on the short arm of the chromosome which encodes for the testicular determining factor (TDF).This gene is known as the SRY gene (sex determining gene region on the Y chromosome)[1].

The mechanism through which the TDF induces differentiation seems to depend on the cell surface antigen known as the H-Y antigen[1].

The Y chromosome gives the all power and biological decision towards sex differentiation and in particular it determines the nature of the gonads. If the Y chromosome is present, the developing gonads become the testis through the power of the TDF. The testis produce the anti mullerian hormone (AMH) or Mullerian inhibitory factor (MIF) and testosterone and in this case the mullerian duct will regress as the effect of the AMH while the wolfian duct will develop as the effect of testosterone and the male duct system is established.

While on the other end the absence of the Y chromosome dictates that the gonads will become the ovaries and the mullerian ducts will develop into its derivatives (fallopian tubes, uterus, cervix and the upper vagina[2].

4. DEVELOPMENT OF THE FEMALE DUCT SYSTEM.

Before the reader can understand the mullerian duct anomalies, it's of critical importance that he/she gets to understand the basics of the duct system development in female. It's therefore important that this part of the article is read and understood before the reader continues to the next sections of the article.

The müllerian ducts are the primordial anlage of the female reproductive tract. They differentiate to form the fallopian tubes, uterus, the uterine cervix, and the upper part of the vagina. A wide variety of malformations can occur when this system is disrupted.

Normal development of the female reproductive tract involves a series of highly regulated, complex interactions that direct differentiation of the müllerian ducts and urogenital sinus (UGS) to form the internal female reproductive tract. Although they originate from different germ layers, the developmental fate of the müllerian ducts (mesoderm) and urogenital sinus (endoderm) are later on linked. The müllerian ducts differentiate to form the fallopian tubes, uterus, uterine cervix and upper part of the vagina while the UGS is thought to give rise to the lower and mid vagina[3,4].

When an interruption occurs in any of these dynamic processes of differentiation, migration, fusion, and canalization, a wide spectrum of müllerian duct anomalies can result[5]. Of importance is that, other defects frequently accompany müllerian abnormalities. The developing kidney and urinary system are closely related to the reproductive tract and their abnormalities are sometimes associated with defects in the reproductive system. The other anomalies that may accompany the mullerian duct anomalies are beyond the scope of this article. But just to mention a few, they include axial skeletal abnormalities.

Early in pregnancy, both female and male embryos contain two sets of paired genital ducts: the paramesonephric (müllerian) ducts and the mesonephric (wolffian) ducts. The genital systems are morphologically identical at this indifferent phase, though cellular differences are already present[6] and capable of developing. From this point onwards in the female there is degeneration of the wolfian ducts and marked growth of the mullerian duct system. In the male the opposite occur (regression of the mullerian ducts) as a result of production of mullerian inhibitory factor (MIF) by the developing testis.

Wolfian (pronephric duct and subsequently the mesonephric duct) run down the posterior coelomic wall in the urogenital ridge to join the fore part of the cloaca. In the male they persist as the vas deferens and epididymis and are connected to the testis by the vas deferentia and rete testis which are of mesonephric origin. In the female they begin to degenerate at 8-9th week and only remain in adult as rudimentary Gartners ducts.

As pointed out earlier in this chapter, the two paramesonephric ducts extend caudally until they reach the urogenital sinus at about 9weeks gestation. The blind ends of the ducts project into the posterior wall of the sinus to become the mullerian tubercle. Mullerian ducts gives rise to the development of the fallopian tubes the uterus, cervix and the upper part of the vagina.as pointed out previously, It's the presence of the tests that determines which of these ducts will regress or develop, a biological fact that that stands at the base of understanding the duct system development in both sexes.

The lower ends of the mullerian ducts come together in the midline, fuse and develop into the uterus and the cervix. The cephalic end remain separate and from the fallopian tubes. The thick muscular wall of the uterus and the cervix develop from the proliferation of mesonchyme around the fused portion of the ducts[1].

Emphasized in this paragraph is the fact that the development of the external genitalia doesn't depend on the presence of the ducts, the patient may have normal external genitalia while they have defects in the internal duct system. It should be understood at this point that the most common müllerian duct defects involve the upper and mid vagina and the uterus. Some of these anomalies may easily be corrected surgically. Fallopian tube agenesis is a rare condition.

As a matter of fact, isolated fallopian tube anomalies are much rarer and include accessory ostia, fallopian tube duplication, absent muscular layer, ectopic location, and luminal atresia. Most malformations of the fallopian tubes are not amenable to surgical management. When pregnancy is desired, assisted reproductive technology may provide a feasible option for these women. As mentioned in the introduction part of this article, patients in low in-come countries may not have access to this high tech assisted reproductive technology and therefore remain helpless and infertile.

5. DEVELOPMENTAL STAGES OF MULLERIAN DERIVATIVES

Complete formation and differentiation of the müllerian ducts into the segments of the female reproductive tract depend on completion of three phases of development namely:

a. Organogenesis of the ducts
b. Fusion (laterally and vertically)
c. Resorption of septa.

Failures of any of the three processes will results into one or more malformations

These malformations include malformations of the tubes, uterus, cervix and the upper vagina. And they can take the form of complete absence of the mulerian ducts resulting in the absence of the most of the vagina, fallopian, tubes, uterus and the cervix a condition called Mayer-Rokitansky-Kuster-Hauser syndrome (MRKH) named after the people who described them.

Again mullerian anomalies may affect the upper parts ie. the tubes and the uterus where it may occur as hypoplasia/agenesis, unicornuate, didelphys, bircornuate, septate, arcuate or Diethylstilbestrol **(**DES) related anomalies. Mullerian duct malformation may involve only the lower parts (cervix and upper vagina in the form of stenosis, atresia, hypoplasia, double cervix, double vagina, imperforate hymen etc. In the prepubertal period, normal external genitalia and age-appropriate developmental milestones often mask abnormalities of the internal reproductive organs.

After the onset of puberty, young women often present to the gynecologist with menstrual disorders. Late presentations include infertility and obstetric complications particularly recurrent fetal wastages. Because of the wide variation in clinical presentations, MDAs may be difficult to diagnose. After an accurate diagnosis is rendered, many treatment options exist, and they are usually tailored to the specific müllerian anomaly. Nevertheless limited options are available and accessible in resource limited settings.

There are seven types of mullerian duct anomalies according to the American society for Reproductive Medicine classification of mullerian anomalies as summarized below in tabular form **(Fertility and sterility 1988;vol 49 (6); 944-45)[7].**

CLASSIFICATION	ANOMALY
Class I (Agenesis of hypoplasia)	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 this category.
Class II (Unicornuate uterus)	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
Class III (Didelphys uterus)	Complete or partial duplication of the vagina, cervix, and uterus characterizes this anomaly
Class IV (bicornuate)	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.
Class V (septate uterus)	A complete or partial midline septum is present within a single uterus.
Class VI (Arcuate uterus)	A small septate indentation is present at the fundus.
Class VII(DES-related abnormalities	A *T* -shaped uterine cavity with or without dilated horns is evident

6. CLINICAL APPROACH TO DIAGNOSIS AND MANAGEMENT OF INDIVIDUAL MULLERIAN DUCT ANOMALIES.

Because there are many malformations involving the mullerian ducts derivatives each with its set of presenting features, they will be discussed separately in this section for a better understanding of the individual malformations.

Class I (Agenesis/hypoplasia/Aplasia)

Müllerian aplasia is generally uncommon finding in clinical practice. It is estimated to occur in 1 for every 5000 newborn females[8]. In about 10% of women with müllerian aplasia, there is a possibility of occurrence of a rudimentary uterus with functional endometrium, as reported by some case reports[9]. But practically, this rudimentary horn does not provide any advantage in terms of obstetric performance.

Mullerian aplasia mainly can occur in two forms:

- Partial müllerian aplasia is characterized by a normal but obstructed uterine cavity and small vaginal pouch distal to the cervix and generally much rarer encounter. As well, because it is obstructed, it has no functional capability.
- Complete müllerian aplasia (Also known as MRKH syndrome) is the most common variant encountered and it is characterized by congenital absence of the vagina and the uterus in most cases. The fallopian tubes are normal, and the ovaries have normal endocrine and oocyte function[10].

It should also be noted that Müllerian aplasia can be an isolated finding although associated anomalies often coexist but they are beyond the scope of this article.

Diagnosis:

As pointed out earlier in this chapter, the diagnosis of MDAs is normally not made early in life because there is usually no symptomatology. They are normally diagnosed at puberty when adolescents present to the gynecologist with primary amenorrhea. It is reported in literature to be one of the most common causes of primary amenorrhea in adolescents[11]. Apart from amenorrhea, there may be no other positive findings obtained from history.

Physical examination reveals normal growth and development with age-appropriate secondary sexual characteristics. External genitalia are as well normal. Pelvic inspection often reveals a normally functioning urethra[12].

Appearances of both introitus and vagina can vary significantly in young adolescents. The vaginal vault can be either completely absent or a short vaginal pouch can be present. In some cases, a short vaginal dimple is present. A uterus is not palpated on bimanual rectal examination. On pelvic examination, a blind ending vaginal canal in encountered with no cervix or uterus palpable.

Ultrasonographic findings can be used to support the clinical findings by revealing the absence of uterus and fallopian tubes in the presence of normal ovaries. MRI is much more reliable; absence of the vagina and uterus on a technically adequate image confirms the diagnosis of agenesis or hypoplasia[13].This modality can also unveil a rudimentary uterus and any coexisting renal abnormalities which may be associated with MDAs [14] .

Because the uterus, fallopian tubes, cervix and the mid-upper vagina may be completely absent, obstetric carrier may not be a subject for discussion in these cases unless advanced assisted reproductive technology (ART) involving ovum harvest and retrieval and surrogacy can be done in well-equipped hospitals. However normal sexual activity may be possible.

Class II (Unicornuate Uterus).

The unicornuate uterus occurs when one müllerian duct completely or incompletely fails to elongate while the other develops normally. However, reports describing the coexistence of a unicornuate uterus with ipsilateral ovarian agenesis has led some authorities to consider that, in some cases, the unicornuate uterus may arise as a consequence of agenesis involving all structures derived from one urogenital ridge[15,16,17].It should however be noted at this point that functioning ovaries in both sides is the commonest finding because the mullerian ducts and the gonads devlop differently.

Unicornuate uterus is reported to account for about 15% of all müllerian anomalies[18]. In one retrospective longitudinal review, the incidence of unicornuate uterus was less reported to be than 1% for the examined population, which included more than 3000 women of reproductive age who visited infertility clinics[19].

This class of uterine structural defects is anatomically present in different forms. It may occur alone, but it is frequently associated with a rudimentary horn[20]. The American Fertility Society (AFS) classification divides this group into four categories based on the presence or absence of a rudimentary horn. The accessory horn can have a uterine cavity with functional endometrium, and, in some cases, a communication may exist with the main endometrial cavity. Associated urologic anomalies, may be present in up to 44% of cases especially in the presence of an obstructed horn. The urological anomalies include ipsilateral renal agenesis, horseshoe kidneys, and ipsilateral pelvic kidney[19].

Non-communicating accessory horns that have an endometrial cavity are the most common unicornuate subtype and are the most clinically significant. This subtype is associated with more pronounced clinical presentation. When the accessory horn becomes obstructed, several complications, such as hematometra, can develop. There is also an increased risk of developing endometriosis as a result of retrograde menstruation, which is reported to resolve after excision of the horn, provided that an early diagnosis was reached[21].

In this category, normal pregnancies can occur though obstetric outcomes are generally poor. It is associated with the poorest fetal survival among all müllerian anomalies and if a pregnancy proceed to an advanced stage or to term or near term Cesarean delivery rates are high. Other likely obstetrical complications include malpresentations, intrauterine growth retardation, and preterm birth[22].

As mentioned above, a review of compiled data from several studies of uterine anomalies and pregnancy outcomes it has been revealed that the unicornuate uterus has the poorest overall reproductive outcomes of all the uterine anomalies. Problems with reproduction have been attributed to abnormal uterine vasculature and diminished myometrial mass of the unicornuate

uterus. In one study, it has further been revealed that the frequency of occurrence of pregnancy complications is as follows 43.3% preterm deliveries, 54.2% live births, 4.3% ectopic pregnancies, and 34.4% spontaneous abortions while up to 2% of the pregnancies occurred in the accessory horn[23].

Other adverse obstetric complications can also involve the accessory horn and include ectopic pregnancy, missed abortion, and uterine rupture[24]. For these reasons, it is advised that the horn be excised prior to pregnancy as a preventative measure. Pregnancy in a non-communicating horn is uncommon and if it occurs, it is thought to be due to transperitoneal sperm migration into the fallopian tube of the rudimentary horn. Most obstetric complications occur in the first 20 weeks and can result in abortion, uterine rupture, and ultimately maternal death[25].

Diagnosis:

Although HSG is useful in diagnosing a unicornuate uterus, it does pick a non-communicating horn. MRI reliably helps in making this distinction and should be one of the first diagnostic tools used in evaluating such patients. MRI reveals a slender, laterally deviated banana-shaped uterus. Only one fallopian tube is identified. Of importance is a challenge in low income countries where MRI cannot be easily available and accessible and therefore the diagnosis may be missed.

Class III (Uterus Didelphys)

Didelphys uterus arises when midline fusion of the müllerian ducts is arrested, either completely or incompletely. It is reported that about 10% of uterine malformations are didelphys uterus. Its complete form is characterized by two hemiuteri, two endocervical canals with cervices fused at the lower uterine segment. Each hemiuteri has its own fallopian tube. Ovarian malposition may occasionally be present. The vagina may be single or double. The double vagina manifests as a longitudinal septum that extends either completely or partially from the cervices to the introitus. A complete longitudinal vaginal septum occurs in about 80%.[26].In some cases obstruction can be due to transverse vaginal septa.

Patients with a uterine didelphys are generally asymptomatic, unless an obstruction is present. In such cases, hematometrocolpos, hematometra, and hematosalpinx may develop.

Renal agenesis most commonly occurs in association with uterine didelphys than with any other type of müllerian anomaly. The reported incidence of renal anomalies in this group is reported to be about 20%.[27]. Obstructed unilateral vagina in patients with uterus didelphys is frequently associated with ipsilateral renal and ureter agenesis; this is known as Wunderlich-Herlyn-Werner syndrome, a rare but well-established anomaly.[28]. This finding has been reported and supported by other published case reports[29,30].

In substantial numbers of cases, intercourse is often possible in both vaginas. Moreover, simultaneous pregnancies in each uterus have also been reported. In this case the twins are always dizygotic. Some Literature have reported intervals of delivery between first and second twin to be hour, days or even weeks[31].

Management of delivery is controversial. Some authorities believe that vaginal delivery can be safely achieved, whereas others advocate cesarean delivery. It has been reported in literature that one twin was delivered by means of cesarean delivery at 25 weeks' gestation, and the second twin was delivered by means of spontaneous vaginal delivery at 35 weeks. Both twins survived[32]. Because twin didelphys pregnancies are rare, data in the literature about obstetric outcomes are scarce. Other reported complications include unilateral placental abruption and unilateral premature labor[33].

Compiled data from some studies revealed the following possible outcomes: 24.4% preterm end in deliveries, 68.6% in live births, 2.3% in ectopic pregnancies, and 20.9% in spontaneous abortions[23].The poor reproductive outcomes are thought to be associated with diminished uterine volumes and decreased perfusion of each hemiuteri.

Diagnosis:

As usual, non-obstructive uterus didelphys is usually asymptomatic until menarche. The most frequent complaint is failure to contain menstrual flow by a tampon. The diagnosis is often reached during the initial pelvic examination, when two cervices are identified. A history of second-trimester spontaneous abortion is often a clue to this diagnosis.

In hemivaginal obstruction, the clinical presentations are variable and depend on the degree of obstruction and whether the obstruction has an opening. The most common presenting symptoms are onset of dysmenorrhea within the first years following menarche and progressive pelvic pain. A unilateral pelvic mass is detected on examination with the right affected nearly twice as frequently as the left. Presenting symptoms of marked rectal pain and constipation, secondary to hematocolpos impingement, have been reported in some case reports[34].

Diagnostic modalities are similar to those used for unicornuate uterus. Workup should include HSG, MRI, and IVP to confirm or exclude associated urinary tract anomalies. MRI reveals two widely separated uterine horns, and two cervices are typically identified. Ultrasonography may be a valuable adjunct[35].

Class IV (Bicornuate Uterus)

The bicornuate uterus is formed when the müllerian ducts incompletely fuse at the level of the uterine fundus. In this anomaly, the lower uterus and cervix are completely fused, resulting in two separate but communicating endometrial cavities, a single-chamber cervix and vagina. A muscular intrauterine septum is also present, and this defect corresponds externally to an indentation or groove at the fundus. The depth of the groove and length of the uterine septum depend in the adult uterus on the length of the incompletely fused müllerian ducts in the fetus[36].

Some scholars have further subclassified this anomaly. Subclassification into complete or partial categories depends on septum length. Complete uterine septa that extend either to the internal or external os are known as bicornuateunicollis uterus and bicornuatebicollis uterus, respectively. When the septum is confined to the fundal region, it is considered a partial bicornuate uterus.

Bicornuate uterus is considered an incidental finding because women with this anomaly usually have few reproductive-associated problems. The condition usually remains undiagnosed until cesarean delivery or other procedures reveal its existence.

In one large study of infertile women, the incidence of bicornuate uterus was not significantly different from that of the fertile control group, suggesting that these patients usually have no difficulty becoming pregnant[19,37]. Most of these patients can expect to deliver a viable infant, though in some cases they may present with late abortion or premature labor[38]. Ruptured uterus has also been reported in case reports[39].

Obstetric outcomes may be related to length of the muscular septum, ie, whether the bicornuate uterus is partial or complete. In one report, women with a partial bicornuate uterus had a spontaneous abortion rate of 28%, and the preterm delivery rate was 20%. However these finding contrasts with other reported incidences of spontaneous abortions in 66% and preterm deliveries in women with complete bicornuate uterus[40].In rare cases, a twin pregnancy can occur in a single horn of the bicornuate uterus though the outcomes are not favorable.

Diagnosis:

The most important issue is to distinguish the bicornuate uterus from the septate uterus because the two may resemble. An accurate, definitive diagnosis must be reached because their treatment strategies and reproductive outcomes are markedly different. Indeed, uterine bicornuate does not usually require surgery and is associated with minimal sexual and reproductive problems, while the septate uterus can be surgically corrected and has a high association with reproductive failure.

Evaluation of bicornuate uterus should begin with ultrasonography though it does not help in accurately distinguishing a septate uterus from a bicornuate uterus.

Further evaluation by MRI can help make this distinction. On MRI, two uterine bodies and a single cervix characterize the bicornuate uterus. The myometrial tissue that separates the two horns can also be visualized[41].The external contour is outward concave, which contrasts with the outward convexity of normal and septate uteri[14].MRI findings of the septate uterus reveal a persistent longitudinal septum partially dividing the uterine cavity.

Laparoscopic examination of the fundal contour can readily distinguish the bicornuate uterus from the septate uterus. The major difference between the two is the anatomic appearance of the external uterine fundus. The bicornuate uterus has two horns, whereas the appearance of external fundus of the septate uterus is normal.

Another important diagnostic evaluation tool for most uterine structural anomalies is HSG; however, it cannot reliably distinguish bicornuate from septate uteri because their uterine cavity images are similar (ie, double uterus)[42,43].The accuracy of HSG in differentiating bicornuate from septate is reported to be about 55%[44]. Combined HSG and Laparascopy improves the accuracy of diagnosis up to 95%[45].

Class V (Septate Uterus)

Septate uterus is the most common structural abnormality of all müllerian duct defects. It results from incomplete resorption of the medial septum after complete fusion of the müllerian ducts has occurred. The septum, located in the midline fundal region, is composed of poorly vascularized fibromuscular tissue[19].Numerous septal variations exist. The complete septum extends from the fundal area to the internal os and divides the endometrial cavity into two components. This anomaly is often associated with a longitudinal vaginal septum[40].The partial septum does not extend to the os. Some septa may be segmental, permitting partial communication between the endometrial cavities[46].

A variant septate anomaly characterized by the triad of complete septate uterus, duplicated cervix, and vaginal septum is recognized and may be more common than previously reported[47,48].The most common presenting symptoms are dyspareunia, dysmenorrhea and primary or secondary infertility[49]. Pregnancy loss and obstetrical complications also occur in this anomaly.

Because of the presence of two cervices, this entity should be distinguished from the didelphys uterus because each has different reproductive outcomes and treatment strategies. In general, a complete septum would be removed hysteroscopically while no surgical intervention would be

recommended for the uterine didelphys. On laparoscopy, the uterine fundus has a normal, smooth contour[49].

A rare variant septate uterus is the Robert uterus[50].This entity is characterized by a complete septum and noncommunicatinghemiuteri with a blind horn. Patients usually present with unilateral hematometra and dysmenorrhea. Pregnancy is possible as reported in one case report though it was terminated at around 26 weeks as a result of fetal death[51].

Fertility does not appear to be substantially compromised in patients with a septate uterus. Yet, this anomaly is associated with poor outcomes. A comprehensive review of combined data from several studies that addressed reproductive outcomes of the septate uterus revealed the following outcomes: 10% preterm deliveries (58.1% live birth 1.9% ectopics, and 75.7% spontaneous abortions[23] .

Diagnosis:

As usual, a combination of diagnostic modalities is needed to arrive at a definitive diagnosis. The most frequently used approaches are HSG, hysteroscopy, and laparoscopy. Ultrasonography and MRI are also useful. HSG reveals a two chambered uterus. The length and thickness of the septum can be assessed, and tubal patency can be concomitantly assessed. However, neither HSG nor hysteroscopy help in distinguishing a septate uterus from a bicornuate uterus[52]. Laparoscopy aimed at determining normal fundal contour is best for distinguishing these entities.

Transvaginal ultrasonography is a useful aid in diagnosing septate uterus. It has been demonstrated in some studies that the sensivity and specificity are about 100% and 80% respectively[43].Results from combining transvaginal ultrasonography with color Doppler imaging resulted in 95% sensitivity and 99.3% specificity for septate diagnoses[53].

MRI provides excellent tissue characterization and helps in reliably differentiating a septate uterus from a bicornuate uterus[14,54].

Class VI (Arcuate Uterus)

The arcuate uterus results from near-complete resorption of the uterovaginal septum. It is characterized by a Thin and small intrauterine indentation shorter located in the fundal region. This anomaly is easily picked up by HSG[55].

Classification of this anomaly has been challenging and still debated. Some classificationsystems considerit as a mild form of bicornuate uteruswhile the AFS classification system, a separate class was proposed for this anomaly on the basis of its external unification, which distinguishes it from the septate uterus[7]. By either classifications system, there are still speculations whether the arcuate uterus is a normal variant. Compared with other müllerian malformations, arcuate uterus is clinically benign and its rarely associated with adverse obstetric outcomes, and may not affect reproductive outcomes[40].

Diagnosis and management of arcuate uterus

Because arcuate uterus is usually asymptomatic,the literature regarding the diagnosis, management, and reproductive outcomes is limited and conflicting. HSG reveals a single uterine cavity with a saddle-shaped fundal indentation. MRI findings show convex or flat external uterine contour. The indentation is broad and smooth[55].Normal zonal anatomy is evident. Renal ultrasound and IVP may be performed to help exclude any associated urinary tract anomalies; however, these studies are not part of a standard evaluation. Arcuate uterus is usually managed similarly to septate uterus, and only selected patients who fulfill poor reproductive performance criteria are recommended for surgical correction.

7. INCIDENCE AND PREVALENCE OF MDAS IN CLINICAL PRACTICE

Incidence rates vary widely and depend on the studied population. Most authors report incidences of 0.1-3.5%[27,57,]. In 2001, Grimbizis and colleagues reported that the mean incidence of uterine malformations was 4.3% for the general population.

In women with fertility problems, the incidence of müllerian duct anomalies is slightly higher at 3-6% and in women with recurrent abortions have an incidence of 5-10%, with the highest incidence of müllerian defects occurring in patients having third-trimester miscarriages[19,59].The

most commonly reported müllerian duct anomalies are septate, arcuate, didelphys, unicornuate, or hypoplastic uteri. The distribution of these anomalies however depends on the study and on the geographic location[19,59].

8. GENERAL CLINICAL PRESENTATION

Most müllerian duct anomalies (MDAs) are associated with functioning ovaries and a normal age-appropriate external genitalia. These abnormalities are often diagnosed after the onset of puberty. In the prepubertal period, normal external genitalia and age-appropriate developmental milestones often mask abnormalities of the internal reproductive organs. After the onset of puberty, young women often present to the gynecologist with menstrual disorders. Late presentations include infertility and obstetric complications.

Sexual and Obstetric outcome in patients with mullerian duct anomalies vary significantly depending of the type of the anomaly in question but in general following outcomes are possible.

Class I (Agenesis or hypoplasia)

The anomaly involves absence of the vagina, cervix , uterine fundus, fallopian tube or a combination of one or more of these.

The clinical presentation is therefore primary amenorrhea after the girl is past menarche. Because the gonads are usually present, the growth and secondary sexual characteristics are almost always normal. External genialia is usually normally found but with A small vaginal pouch which barely admit a tip of finger.

Bimanual Digital rectal examination reveals no uterus. An ultrasound examination may reveal the absence of the uterus though it may as well be inconclusive in some cases. In these cases advanced imaging studies like MRI or Diagnostic laparoscopy may be requested.

In these cases sexual activity and fertility are not compatible. Reconstructive surgery or vaginoplasty may be instituted but just to permit sexual function and not to achieve reproductive capability and therefore psychological treatment plays a major role.

Class II (**Unicornuate Uterus)**

Involves the absence or incomplete development of one Mullerian ducts resulting into presence of only one fallopian tube. In these patients the external genitalia, secondary sexual characteristics are usually normal. The vaginal and the cervix may be normal only that they open into one patent uterine horn. Menstrual cycle may be normal though the volume may be minimal. Sexual activity may not be affected. Diagnosis is therefore quite challenging and commonly made after complications arise. Conception may be possible but maintaining pregnancy in one horn presents a significant challenge. Commonly these patients presents with miscarriages, premature labor, malpresentations of the fetus and uterine rupture.

Failure of fusion of the two Mullerian ducts.

The degree of failure of fusion determines the sexual and reproductive outcomes of the individual in questions. In this respect, the shape of the uterine cavity carries a heavier share in determine the obstetric outcome. In this group of malformations, the following have been described:

- Class III (Uterus Didelphys)
- Class IV (Bicornuate uterus)
- Class V (Septate and subseptate uterus)
- Class VI (Arcuate uterus)
- Class VII (DES-related anomalies)

In these patients menstrual cycle may be normal because the uterus is present though not in a normal structure. However abnormalities of menstruation like menorrhagia, and dysmenorrhea may be present. Sexual difficulties may present though not severe enough to impair sexual performance. Low fertility has also been reported in severe forms of fusion malformation though a significant proportion of patients may conceive without difficulty.

In terms of obstetric outcomes, these patients present with repeated misccariages, premature labor, malpresentations, curnal pregnancies with uterine rupture, obstructed labor and inefficient uterine contraction resulting into possibility of postpartum hamerhage. Twin pregnancies in different horns have also been reported in case reports.

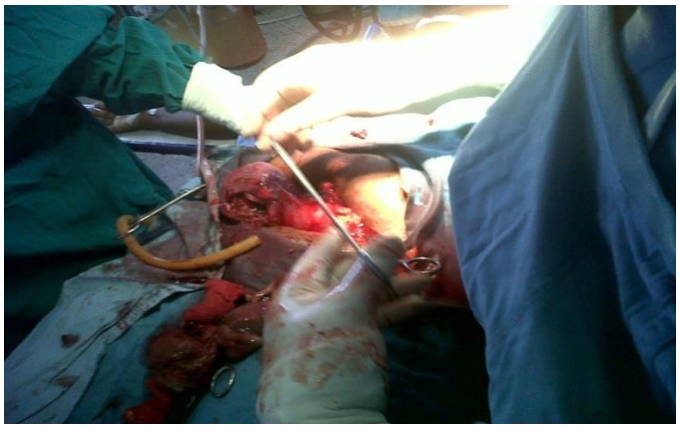

Fig 1:Picture showing the two uterine horns and the implantation site on the larger hornsin a patient with bicornuate uterus (placenta removed). A case at out Teaching Hospital exemplifying surgical emergencies that can arise from mullerian dust anomalies

Fig 2: Picture of an 18 weeks, 300g male fetus delivered at laparatomy for abdominal pregnancy at our Teaching Hospital

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