

Mayer-Rokitansky-Kuster-Hauser Syndrome

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ABSTRACT

The Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome is characterized by congenital aplasia of the uterus and the upper part (2/3) of the vagina in women showing normal development of secondary sexual characteristics and a normal 46, XX karyotype. It affects at least one out of 4,500 women. MRKH may be isolated (type I) but it is more frequently associated with renal, vertebral and, to a lesser extent, auditory and cardiac defects (MRKH type II or MURCS association). The first sign of MRKH syndrome is a primary amenorrhea in young women presenting otherwise with normal development of secondary sexual characteristics and normal external genitalia, with normal and functional ovaries, and karyotype 46, XX without visible chromosomal anomaly. The phenotypic manifestations of MRKH syndrome overlap with various other syndromes or associations and thus require accurate delineation. For a long time, the syndrome has been considered as a sporadic anomaly, but increasing number of familial cases now supports the hypothesis of a genetic cause. In familial cases, the syndrome appears to be transmitted as an autosomal dominant trait with incomplete penetrance and variable expressivity. This suggests that the involvement of either mutations in a major developmental gene or a limited chromosomal imbalance. However, the etiology of MRKH syndrome still remains unclear. Treatment of vaginal aplasia, which consists in creation of a neovagina, can be offered to allow sexual intercourse. As psychological distress is very important in young women with MRKH, it is essential for the patients and their families to attend counseling before and throughout treatment.

Keywords: Mayer-Rokitansky-Kuster-Hauser syndrome, Congenital anomalies of uterus.

CASE REPORT

A 24-year-old female patient presented with primary infertility after 7 years of marriage and primary amenorrhea. History of undergoing vaginoplasty 7 years back .

There was no history of delayed menarche in the mother and sisters. Secondary sexual characters were normal.

The significant findings were on vaginal examination which showed a blind-ended vagina with 3 cm depth. The clitoris, labia majora and minora, and the vestibule were normal.

A clinical diagnosis of primary amenorrhea was made. Abdominopelvic ultrasound revealed normal liver, spleen and both kidneys. However, no uterine tissue was seen in the pelvis. The ovaries were visualized bilaterally. A diagnosis of congenital absence of the uterus was made. Hormonal assay was normal.

MRI reveals absent uterus with bilateral ovaries present.

The karyotype result also came out to be 46, XX and laparoscopy demonstrated ovoid, pearly white structures (in keeping with the ovaries) bilaterally. The fallopian tubes were also demonstrated bilaterally with hypoplastic mullerian buds (bipartite).

A diagnosis of mullerian duct anomaly was made subclassified as Mayer- Rokitansky - Kuster-Hauser syndrome (type B—incomplete aplasia).

Thus, here we report one case of Type B Mayer- Rokitansky-Kuster-Hauser syndrome.

MULLERIAN DUCT ANOMALIES

Developmental anomalies of the mullerian duct system represent some of the most fascinating disorders that obstetricians and gynecologists encounter. The mullerian ducts are the primordial anlage of the female reproductive tract. They differentiate to

form the fallopian tubes, uterus, uterine cervix and superior aspect of the vagina. A wide variety of malformations can occur when this system is disrupted. They range from uterine and vaginal agenesis to duplication of the uterus and vagina to minor uterine cavity abnormalities. Mullerian malformations are frequently associated with abnormalities of the renal and axial skeletal systems, and they are often the first encountered when patients are initially examined for associated conditions.

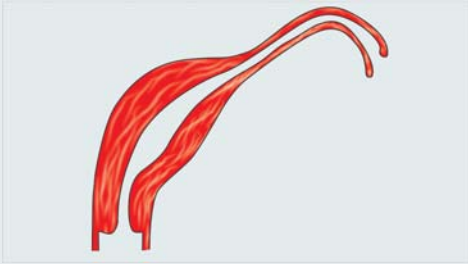
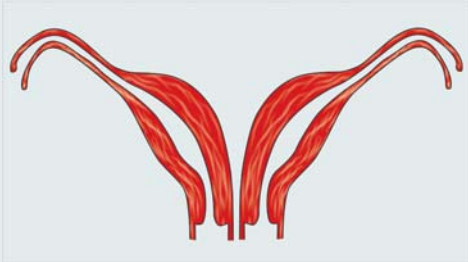
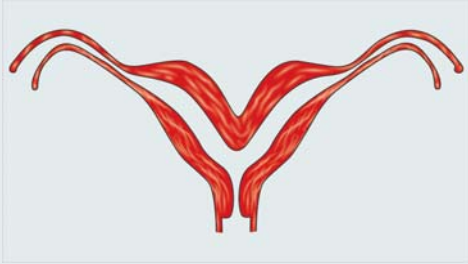
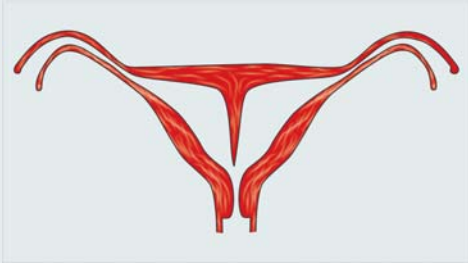
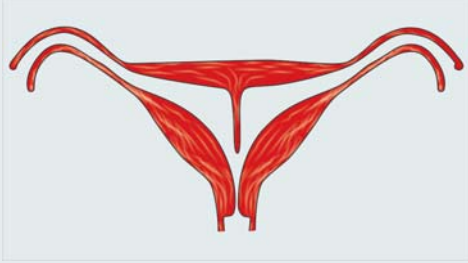
Most mullerian duct anomalies (MDAs) are associated with functioning ovaries and age-appropriate external genitalia. These abnormalities are often recognized after the onset of puberty. In the prepubertal period, normal external genitalia and age-appropriate developmental milestones often mask abnormalities 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.

Because of the wide variation in clinical presentations, mullerian duct anomalies may be difficult to diagnose. After an accurate diagnosis is rendered, many treatment options exist, and they are usually tailored to the specific mullerian anomaly. Refinements in surgical techniques, such as the Vecchietti and McIndoe procedures, have enabled many women with mullerian duct anomalies to have normal sexual relations. Other surgical advances have resulted in improved fertility and obstetric outcomes. In addition, developments in assisted reproductive technology allow some women with mullerian duct anomalies to conceive and deliver healthy babies.

Tarry and Duckett Classification

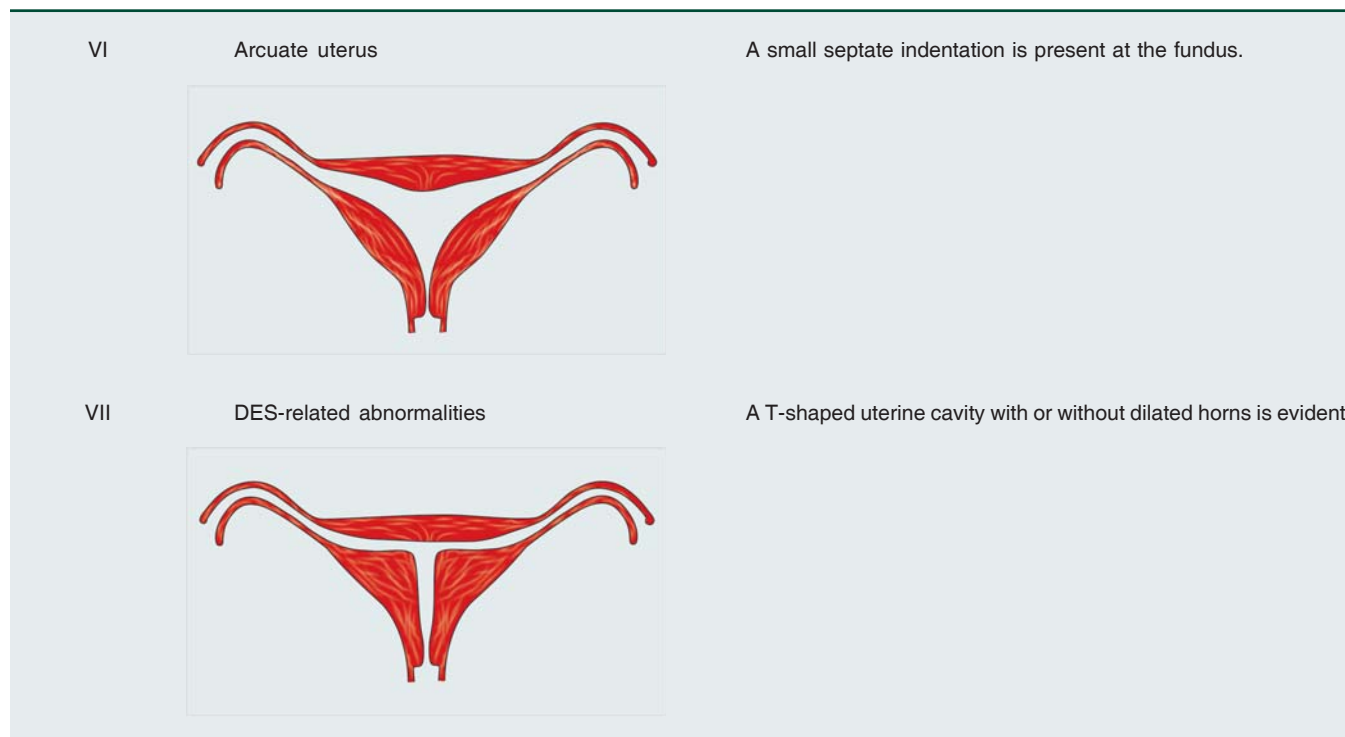
It is based on physical and ultrasound examinations or laparoscopy, and prognostic implications regarding fertility and

Table 1: AFS classification of anomalies of mullerian duct

Classification	Clinical finding	Description
I	Segmental or complete agenesis or 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
II	Unicornuate uterus with or without a rudimentary horn 	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 ²⁻⁴
III	Didelphys uterus 	Complete or partial duplication of the vagina, cervix and uterus characterizes this anomaly
IV	Complete or partial bicornuate uterus 	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
V	Complete or partial septate uterus  	A complete or partial midline septum is present within a single uterus.

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menstruation.⁵ The grade 0 to 4 refers to the extent of mullerian system affected. Each side is graded individually. The letter M refers to mullerian defects (Table 1). Fortuitously, the M stands for Mayer-Rokitansky as well. The grading is described as follows:

- M0-unilateral system normally formed but unfused or septum retained
- M1-vaginal agenesis alone
- M2-vaginal and uterine agenesis
- M3-mullerian agenesis total
- M4-mullerian and ovarian agenesis.

Our patient had Mayer-Rokitansky-Kuster-Hauser syndrome (type B—incomplete aplasia). Let us review the literature of MRKH syndrome.

MRKH SYNDROME

Introduction

Agenesis of the vagina in karyotypic female subjects may be accompanied by other defects of the urogenital and skeletal system. The combination of these anomalies has been designated as Mayer-Rokitansky-Kuster-Hauser syndrome (MRKHS) based on the findings reported by the various authors. We performed a computerized Medline search, Google search, SpringerLink search, HighWire search and manual bibliographical review of relevant articles on MRKHS, and the embryological, endocrinological, clinical, psychosocial, diagnostic and therapeutic features of this syndrome are discussed.

Embryology

Griffin (1988) described the embryological possibilities for the origin of MRKH syndrome. The Mullerian duct (MD, ductus paramesonephricus) develops independent of the celomic epithelium above the mesonephros. This part of the duct gives rise to the infundibulum with its fimbriated ostium abdominale. The part of the duct which lies along the mesonephros as far as its caudal pole makes a contribution to the ampulla and less often to the isthmus. In the area of the mesonephros, the MD fuses with the Wolffian duct (WD; ductus mesonephricus). The WD gives rise to the ampulla and the isthmus. Below the caudal pole of the mesonephros as well as beyond the attachment point of the inguinal ligament of the mesonephros, the later round ligament of the uterus, the MD develops as an outgrowth of the WD and no longer as an independent structure. The MRKH syndrome is, in its formal genesis, a non-fusion of the MD with the WD. This explains the fact that in a classic case of MRKH syndrome, the fallopian tube with a very small part of the cornu uteri extends only as far as the connection with the round ligament of the uterus. It is suggested that the cause of the development of MRKH syndrome could be the deficiency of gestagen and/or estrogen receptors. This would also explain the various forms of the rudimentary vagina.⁶ Ghirardini et al (1982) described etiopathogenetical problems in MRKH syndrome, supporting Hauser's hypothesis of an inhibition of the mullerian duct development by MIF production, allowing to consider it as the slightest form of female pseudohermaphroditism. Moreover, the terms used to delineate this condition, like mullerian aplasia, mullerian duct aplasia,

mullerian duct agenesis and uterovaginal agenesis, may be misleading and the term of “mullerian dysgenesis syndrome” is proposed.⁷

Genetics and Molecular Basis of MRKHS

Pavanello et al (1988) stated that genetic problems are interwoven with unilateral or bilateral renal agenesis, especially that associated with mullerian anomalies as seen in MRKH syndrome. The gene is single and autosomal dominant with variable expression.⁸ Ghirardini et al (1982) described the histological appearance of the rudimentary uterus, endometrium, uterine tube, Gartner's duct, round ligament, vagina and ovary in 10 cases of the MRKH syndrome. Their findings suggested that this syndrome is due to the deficiency of estrogen and gestagen receptors. This deficiency may inhibit the further development of the embryonic mullerian duct and account for the subsequent faulty differentiation of its existing elements. It is still undecided why, in cases of the MRKH syndrome, development of the mullerian duct ceases at the attachment of the caudal mesonephric ligament (later the round ligament).⁹ Cramer et al (1996) reported that vaginal agenesis might be associated with decreased activity of galactose-1-phosphate uridyl transferase (GALT). They studied activity and genotype of GALT in 13 daughters with vaginal agenesis and their mothers. They concluded that fetal or maternal GALT mutations that decrease GALT activity may be associated with vaginal agenesis and have, as their possible biological basis, increased intrauterine exposure to galactose which has been demonstrated in rodents to cause decreased oocyte survival and delayed vaginal opening in offspring.¹⁰

Review of Literature

Mayer-Rokitansky-Kuster Hauser (MRKH) syndrome is a congenital malformation characterized by an absence of vagina associated with a variable abnormality of the uterus and the urinary tract but functional ovaries. In 1829, Mayer had described partial and complete duplication of vagina in four stillborns along with other anomalies, like cleft lip, limb and cardiac defects along with urinary tract anomalies.¹¹ Subsequently in 1838, Rokitansky reported 19 cases of uterovaginal agenesis along with renal agenesis in three cases.¹² Kuster (1910) described several cases of similar anomaly with various musculoskeletal defects. Hauser et al (1961), emphasized the importance of distinguishing this syndrome from that of testicular feminization in both of which vaginal development is defective.¹³ The various mullerian defects described are agenesis of vagina or uterus, rudimentary/atretic vagina or uterus. Unilateral renal and skeletal anomalies are associated in 50% and 12% of cases respectively.¹⁴ The skeletal abnormalities reported are fusion anomaly of vertebrae, congenital scoliosis and limb deformities, like brachymesophalangy of digits, small distal phalanx of digits, long proximal phalanx of digits and long metacarpals of digits.

In addition, some patients might have distinct radial dysplasia and abnormalities of the carpals.¹⁵ It has been analyzed whether the MRKH syndrome can be considered as a single clinical entity or whether two or more syndromes lie behind the title of MRKH syndrome. Two different syndromes in these patients have been described, namely an isolated form of congenital agenesis of the vagina and uterus (typical) and a more generalized condition, in which agenesis of the vagina and uterus is a major and perhaps even obligatory characteristic (atypical). Heidenreich et al (1988) observed that the patients with the Mayer-Rokitansky-Kuster (MRK) syndrome had the typical findings of vaginal aplasia and bipartite solid uterine buds but they proposed that the term “MRKH syndrome” should no longer be used for cases with extragenital malformations.¹⁶ Strubbe (1992) described that the typical form (type A) is characterized by symmetrical nonfunctioning muscular buds (the mullerian duct remnants) and normal fallopian tubes, and the atypical form by aplasia of one or both buds, one bud smaller than the contralateral one, with or without dysplasia of one or both fallopian tubes. Radiographs of the spine showed that congenital spinal abnormalities, especially the Klippel-Feil (KF) syndrome, were seen more in patients with the typical form. Renal agenesis or ectopia together with the MRKH and KF syndromes, known as the MURCS association (MU: Mullerian duct aplasia; R: Renal agenesis/ectopia; CS: Cervical somite dysplasia), was also diagnosed in patients in the atypical group. From their results, they concluded that additional cervical spine films in patients with the MRKH syndrome are indicated only in the atypical form of the syndrome. In those cases, where the MRKH syndrome is associated with the KF syndrome, the MURCS association should be considered.¹⁷ Strubbe et al (1994) conducted a multidisciplinary study on a total of 100 women with congenital absence of vagina and uterus, the Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome. The purpose of this study was to discriminate typical (type A) from atypical (type B) Mayer-Rokitansky-Kuster-Hauser syndrome (congenital absence of vagina and uterus) and determine their association with renal anomalies and ovarian disease. Complete gynecological and laparoscopic data were available on all of the patients. The patients were divided into two groups on the basis of the laparoscopic data; a typical and an atypical form of the MRKH syndrome. Associated anomalies were most common in the group with the atypical form of the MRKH syndrome. These findings suggest that there might be two different syndromes in this patient group, namely an isolated form of congenital agenesis of the vagina and uterus (typical/type A) and a more generalized condition, in which agenesis of the vagina and uterus is a major and perhaps even obligatory characteristic (atypical/type B). Hence, they proposed that the term MRKH syndrome should no longer be used for the atypical group. A suggestion has been made to call this type the GRES [genital (G), renal (R), ear (E), skeletal (S)] syndrome.¹⁸ Strubbe et al

(1993),^{19,20} emphasised that discrimination between type A and type B of MRKH syndrome is important because associated renal and ovarian abnormalities occur only in type B. Laparoscopy is still needed to discriminate between these two forms.²⁶

Urinary Tract Anomalies in MRKHS

Unilateral renal anomalies are associated with 50% of the patients. The various urinary tract anomalies reported are renal agenesis, pelvic kidney, fusion anomaly, like horse-shoe kidney and vesicoureteric reflux.

Endocrine Function in MRKHS

In most of the cases, both ovaries are normal and affected women have normal sexual activity. Occasionally, one ovary with ipsilateral fallopian tube may be absent. Hormone profile and secondary sexual characteristics are normal in the cases of Mayer-Rokitansky-Kuster-Hauser syndrome.²¹

Karyotype and Familial Syndrome

Smith et al (1982) reported that patients with MRKH have a normal female karyotype and normal secondary sexual development.²² Cabra el (1998) and Orozco-Sanchez et al (1991), performed blood genetics tests and biopsy of ovarian tissue which showed 46, XX karyotype with no structural anomalies.²³ Smith used the appellation "Rokitansky malformation sequence" to designate the mullerian agenesis in any clinical setting and stated that about 4% of the cases in which ovaries and fallopian tubes are present but which lack the body of the uterus and upper vagina are familial with affected female siblings.²²

Other Syndromes and Anomalies in Association to MRKHS

The various other associated anomalies reported are Klippel-Feil syndrome, Sprengel's deformity, and congenital stapedial ankylosis and ovarian cysts.²⁴

Investigations

These tests included general physical examination, radiographs of the vertebral column, the upper extremities and intravenous urography (IVU), general otorhinolaryngological and ossicular chain examinations. Ultrasound (US) of the abdomen and pelvis, which might show a dilated uterus with hematometra, the lesion with functioning uterine anlage, cervical dysgenesis and an obstructed uterine horn besides the delineation of kidneys and ovaries. Many investigators feel that transabdominal ultrasound (US) may not provide a completely reliable picture in Mullerian duct anomalies. Hence, magnetic resonance imaging (MRI) is now gaining wide acceptance in imaging congenital abnormalities of the genital tract.²⁵ Genitography can further provide anatomical details specially in cases of partial vaginal agenesis or coexistent genitourinary fistula.

Management

The management of vaginal agenesis in Mayer-Rokitansky-Kuster-Hauser syndrome has always been a controversial topic. The choice of procedure and patient age at reconstruction depend upon individual anatomy, fertility potential and psychological and social factors. Initially, the arguments centered on whether to do surgery or try passive dilation as well as at what age to intervene. As surgical techniques have recently become refined, the question is, if surgery is selected, what type of tissue should one use (bowel vs skin graft) and, if skin graft, from what area to select. The aims are satisfactory sexual activity with good anatomical and functional vagina along with mechanical long-term outcomes. Until now, the recommended treatment, when resection of a rudimentary horn was indicated, was laparotomy. The same goal can now be achieved by laparoscopy. Laparoscopy is not only useful for diagnosis of uterine malformations but can also be valuable for any treatment required for this type of malformation along with creation of an artificial vagina (laparoscopic assisted vaginoplasty).^{26,27}

Psychological Aspect

Patients with MRKH syndrome might suffer from severe distortions of body image, anxiety, depression, interpersonal sensitivity and face a lot of psychological distress at diagnosis. Langer et al (1990) studied psychosocial sequelae of and coping with malformation and treatment with semistructured interviews and the Giessen test. Anatomical and functional results of the vaginoplastic operation were excellent and sexual satisfaction correlated with coping. 7/11 MRKH patients were capable of good to fair adaptation to the malformation. The malformation caused narcissistic damage in all cases.²⁸ Behavioral problems of the adolescent patients can be avoided by early appropriate guidance and reassurance.

Can a Woman with MRKHS and Absent Uterus have a Child? Its Medicolegal Implications

Until recently, treatment for patients with vaginal agenesis (Mayer-Rokitansky-Kuster-Hauser syndrome) has centered on the creation of a functional vagina. The technology of *in vitro* fertilization and embryo transfer, allowing for collection of oocytes from the genetic mother. Fertilization by the genetic father and placement into a gestational carrier, enables a woman without a uterus to have her own genetic child. The specific medical and legal issues involved in facilitating genetic offspring in these instances must be considered; these include the initial matching of the genetic parents with the gestational carrier, cycle synchronization for *in vitro* fertilization and embryo transfer, anatomic difficulties of oocyte retrieval, birth certificate documentation and the current legal status of a gestational carrier.^{29,30}

CONCLUSION

Mayer-Rokitansky-Kuster-Hauser syndrome (MRKHS) is a congenital malformation characterized by an absence of vagina associated with a variable abnormality of the uterus and the urinary tract, but functional ovaries. It is not only worthwhile to be alert for urinary tract anomalies in patients with the MRKH syndrome but also to study the skeletal and auditory systems in these patients. Psychological consideration of patients with uterovaginal agenesis may dictate the need for early vaginoplasty, which hitherto has been delayed until just before marriage. Surgical correction many times requires the creation of a neovaginal canal by the performance of a neovaginoplasty which can be done by open surgical or laparoscopic assisted techniques. The technology of *in vitro* fertilization and embryo transfer, allowing for collection of oocytes from the genetic mother, fertilization by the genetic father and placement into a gestational carrier enables a woman without a uterus to have her own genetic children.

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