Mayer–Rokitansky–Küster–Hauser syndrome: diagnosis and management

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Key content
- In Mayer–Rokitansky–Küster–Hauser syndrome (müllerian agenesis) there is congenital absence of the upper two-thirds of the vagina and the uterus is absent or rudimentary.
- A common presentation is primary amenorrhoea in a female with 46,XX karyotype and normal secondary sexual characteristics.
- There may be associated abnormalities of the kidneys, skeletal system, heart and auditory system.
- Magnetic resonance imaging is a useful diagnostic tool with which to assess the anatomical abnormalities.
- Management involves psychological support and creation of a neovagina for sexual function.

Objectives
- To understand the anatomical abnormalities of this entity.
- To learn about the clinical presentation and differential diagnosis.
- To understand the management issues.

Ethical issues
- If, in the future, uterine transplantation becomes safe and effective, will it be ethical for a woman to donate her uterus to her daughter?
- With many children awaiting adoption, should women with Mayer–Rokitansky–Küster–Hauser syndrome be encouraged to adopt rather than undergo surrogacy?
- Who should pay for assisted reproduction treatment, given the constraints of health service budgets?
- Should women with Mayer–Rokitansky–Küster–Hauser syndrome be managed in selected centres of excellence?

Keywords
assisted reproduction / magnetic resonance imaging (MRI) / primary amenorrhoea / ultrasound / vaginoplasty

Introduction

Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome (müllerian agenesis) is a malformation complex characterised by congenital absence of the upper two-thirds of the vagina and an absent or rudimentary uterus in women who have normal development of secondary sexual characteristics and a 46,XX karyotype. It results from agenesis or hypoplasia of the müllerian (paramesonephric) ducts. Associated abnormalities of the kidneys and other organ systems are often seen.

This entity was first described by Mayer in 1829. He described absent vagina in stillborn female fetuses with multiple birth defects. Later, in 1838, Rokitansky described 19 autopsy cases of uterovaginal agenesis, including three cases of unilateral renal agenesis. In 1910 Küster described several such cases with renal and skeletal abnormalities. In 1965 Hauser and colleagues stressed the importance of differentiating this condition from complete androgen insensitivity syndrome, which presents similarly.1

The incidence is reported as 1 in 4000–5000.2 The disorder is fairly common in women presenting with primary amenorrhoea. Synonyms include: müllerian agenesis, müllerian dysgenesis, CAVU (congenital absence of vagina and uterus), müllerian aplasia and GRES (genital renal ear syndrome).3

Classification

MRKH syndrome is classified into three types:4

1 Typical (type I): isolated symmetrical uterovaginal aplasia or hypoplasia
2 Atypical (type II): asymmetrical uterovaginal aplasia or hypoplasia, absence or hypoplasia of one or both fallopian tubes and malformation in the ovaries and/or the renal system
3 MURCS (müllerian duct aplasia, renal dysplasia and cervical somite anomalies) syndrome: uterovaginal aplasia
Mayer–Rokitansky–Küster–Hauser syndrome: diagnosis and management

Table 1. American Fertility Society classification of congenital uterine abnormalities (1988)

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hypoplasia/uterine agenesis</td>
</tr>
<tr>
<td>II</td>
<td>Unicornuate uterus</td>
</tr>
<tr>
<td>III</td>
<td>Uterus didelphys</td>
</tr>
<tr>
<td>IV</td>
<td>Bicornuate uterus</td>
</tr>
<tr>
<td>V</td>
<td>Septate uterus</td>
</tr>
<tr>
<td>VI</td>
<td>Arcuate uterus</td>
</tr>
<tr>
<td>VII</td>
<td>T-shaped uterus resulting from the use of diethylstilbestrol</td>
</tr>
</tbody>
</table>

or hypoplasia with malformation in the skeletal system
and or the heart, muscular weakness and renal malformation

In a meta-analysis of 521 cases of MRKH syndrome, Oppelt et al.\textsuperscript{4,5} observed that 64% showed a typical form, 24% were atypical and 12% were of MURCS syndrome. According to the American Fertility Society classification of congenital uterine abnormalities, agenesis or hypoplasia of the uterus in MRKH syndrome is grouped into class I (Table 1).\textsuperscript{6}

Embryology

The müllerian (paramesonephric) and wolffian (mesonephric) ducts are the primordia for the internal reproductive systems of females and males, respectively; they coexist in the undifferentiated embryo in pairs until the genetic sex triggers differentiation of the gonads into either ovaries or testes (Figure 1). In the presence of the SRY gene on the Y chromosome, the gonads differentiate into testes, which produce androgens and anti-müllerian hormone; together these hormones suppress the müllerian ducts and stimulate the wolffian ducts. In the absence of the Y chromosome the gonads differentiate into ovaries and the müllerian ducts into the fallopian tubes, uterus, cervix and upper part of the vagina, while the wolffian ducts degenerate (Figure 2).

In females the müllerian duct appears by the sixth week as an invagination of the coelomic epithelium and runs parallel and lateral to the wolffian duct. It crosses the wolffian duct

![Figure 1. Genital development: the undifferentiated stage](image1)

![Figure 2. Female genital development](image2)
caudally and fuses with its counterpart from the other side during the 12th week of development. The fusion continues distally until it reaches the posterior wall of the urogenital sinus. Two solid evaginations called sinovaginal bulbs grow out from this point. They proliferate into a solid vaginal plate which canalises to form the lower part of the vagina. The upper unfused part of the mullerian ducts develop into the fallopian tubes; the lower part fuses with its counterpart on the opposite side to become the uterus, cervix and upper part of the vagina. Initially the vagina and uterus are solid; they then become septate. Complete canalisation occurs by resorption of the septum in a cephalad direction, usually by the fifth month of development. 7

In MRKH syndrome there is partial or complete failure of development of the mullerian duct system. 8 Failure of development of the caudal part results in vaginal agenesis. Failure of development of the middle portion results in abnormal development of the uterus. Involvement of the upper part leads to maldevelopment of the fallopian tubes. The close association between the mullerian and wolffian duct derivatives and the metanephric duct explains the associated renal abnormalities. Skeletal malformations associated with MURCS syndrome are attributed to alteration of the blastemas of the lower cervical and upper thoracic somites (which develop into the vertebrae and muscles of the back and the body wall), arm buds and pronephric ducts, all of which have an intimate spatial relationship at the end of the fourth week of fetal life. 5

Anatomical abnormalities
In type I MRKH syndrome the caudal portions of the mullerian ducts are involved. This is characterised by the presence of two rudimentary uterine buds connected by a peritoneal fold, normal fallopian tubes and absence of the upper part of the vagina (Figure 3).

In type II MRKH syndrome there is asymmetrical hypoplasia of the uterine buds with or without hypoplasia of one or both fallopian tubes; 4, 9–11 7–10% of these women have a rudimentary uterus with functional endometrium and as many as 25% have cavitated mullerian remnants. 12, 13 The ovaries are absent, hypoplastic or extrapelvic (pelvic brim) in 10–15% of cases. 3, 10–12

Other organ abnormalities
Renal abnormalities are reported in up to 40% of women in certain case series. These abnormalities include renal agenesis, ectopic kidney, horseshoe kidney and ectopic ureter. 3, 4, 12 Skeletal abnormalities are reported in 12–20% of women affected, comprising Klippel–Fiel anomaly, fused vertebrae, radial aplasia, absent thumb, scoliosis and radial hypoplasia. 3, 4, 10, 12

Auditory malformations are seen in 10–25% of cases. Conductive deafness due to stapedial ankylosis and sensorineural deafness are reported. Malformations of the ear and auditory canal are also reported. 3, 4, 9

Rarely, major cardiac malformations such as tetralogy of Fallot, patent ductus arteriosus and truncus arteriosus are reported. 3, 4, 9

Aetiology
The aetiology of this condition remains unknown. Teratogenic exposure during the early embryonic stages has been suggested but no specific teratogen has been linked. 3 This condition is considered to be of sporadic origin with polygenic/multifactorial inheritance. Familial clustering has been observed and autosomal dominant inheritance with variable penetrance and expressivity of a single mutant gene is attributed to these familial cases. 3, 13 Several candidate genes, including genes encoding anti-mullerian hormone and its receptor, have been studied but no abnormalities have been found. Hox genes play a major role in mullerian development and in the development of the kidneys and skeletal system. As abnormalities of these two organ systems are associated with MRKH syndrome, these genes have been studied but no abnormalities have been identified. 13 WNT4 genes are associated with gonadal differentiation and mullerian duct development. 13, 14 Mutation of the WNT4 gene was reported in adolescent girls with primary amenorrhoea, mullerian aplasia and hyperandrogenism but was absent in other women with MRKH syndrome without hyperandrogenism. 13
Clinical presentation
Between 70–80% of women present with primary amenorrhea. Examination reveals normal secondary sexual characteristics and a short, blind-ending vagina. General examination may show associated musculoskeletal abnormalities. If functioning endometrium is present, cyclical abdominal pain may be the presenting symptom, necessitating removal of the horns. Other rare presenting complaints are subfertility and dyspareunia.

Differential diagnosis
Complete androgen insensitivity syndrome (CAIS) can easily be mistaken for MRKH syndrome. In CAIS, the phenotype is female with a short, blind-ending vagina but the karyotype is 46,XY and the patient has no axillary or pubic hair. Other differential diagnoses are imperforate hymen and agenesis of the lower part of the vagina and transverse lower vaginal septum, but the uterus and tubes are normal in these conditions.

Diagnosis
Two-dimensional ultrasound is the initial investigation of choice as it is cheap, easily available and non-invasive. It is useful for diagnosing an absent uterus and associated renal abnormalities but less useful for evaluating a rudimentary uterus. Three-dimensional ultrasound is more accurate in diagnosing uterine abnormalities but its availability is limited. Magnetic resonance imaging (MRI) provides a more sensitive and specific means of diagnosis than ultrasonography. The multiplanar capabilities and high soft-tissue resolution allow an accurate evaluation of the uterine aplasia with clear visualisation of the rudimentary horns and ovaries. Uterine aplasia is best characterised on sagittal images, vaginal aplasia on transverse images. MRI can also be used to identify the presence of an endometrial line in a hypoplastic uterus and to search for associated renal and skeletal malformations. Unlike ultrasound, the images are not affected by body size. MRI has replaced laparoscopy for complete anatomical evaluation in MRKH syndrome and is considered the gold standard for diagnosis of müllerian abnormalities.

An endocrine profile and karyotyping may be helpful in ruling out CAIS, although the condition may be identified clinically from the absence of axillary and pubic hair. Absence of ovaries and müllerian structures on ultrasound will also support the diagnosis of CAIS. Other investigations that may be necessary are intravenous urography, spine and limb X-rays, echocardiography and audiograms.

Management

Psychological support
The diagnosis of MRKH syndrome can be devastating for any woman, especially an adolescent, due to the psychological, social and reproductive implications. The diagnosis must be disclosed sensitively. The way the diagnosis is explained may have a lasting negative impact on the woman’s psychological status and self-esteem. Extensive counselling and psychological support is important at the time of diagnosis and later in life. Group-based interventions and cognitive behavioural therapy have been found to be effective.

Creation of a neovagina
A functional vagina should enable a woman to have comfortable sexual intercourse: this usually equates to being able to accept the largest conventional dilator or to a vaginal length of approximately 7 cm. The timing of treatment should be individualised and treatment may be postponed until the woman is considering becoming sexually active and is emotionally able to cope with treatment. Psychological preparation plays a vital role in management.

Non-surgical treatment
The non-operative approach to creating a functional vagina is by using vaginal dilators. This was first described by Frank in 1938 with the use of Pyrex® tubes of gradually increasing sizes. These dilators are held in place for 20–30 minutes, two or three times a day, in order to stretch the vaginal epithelium into the potential space between the bladder and rectum. Success rates of up to 81–88% are reported for this method. In 1981, Ingram modified Frank’s technique by using a bicycle seat mounted on a stool to facilitate perineal pressure. A success rate of 91% is reported using Ingram’s method. Plastic vaginal dilators are offered as the first-line therapy. The advantages are low morbidity, creation of a more physiological vaginal milieu and that there is no scarring. With appropriate support from a dedicated and fully trained nurse, success rates are high and the initial discomfort can be overcome with a combination of anaesthetic lubricating jelly and simple analgesics taken half an hour before commencing the dilatation.

Surgical treatment
Surgery is undertaken if non-surgical methods fail or if the woman chooses a surgical option at the outset. Surgical treatment has evolved over the years, with many procedures being only of historical interest due to the serious risks and complications. The McIndoe procedure, sigmoid vaginoplasty and Williams’ vulvovaginoplasty are among these outdated procedures; with the availability of safer, more effective and simpler laparoscopic procedures, the British Society for Paediatric and Adolescent Gynaecology
recommends that they are not performed in the UK. These outdated procedures are described below to highlight the progress made in the surgical management of this uncommon syndrome.

The two most popular techniques for vaginoplasty practised in Europe are now the Vecchietti and Davydov procedures (described below). Both were originally described as being open techniques but with advances in minimal access surgery, laparoscopic modifications have become popular.

**McIndoe procedure**
This involves creation of neovaginal space between the bladder and rectum and lining this space with a split-thickness skin graft placed over a mould, which is then inserted into the neovagina. The woman has to wear the mould for 3 months and is advised to use a dilator regularly. The main disadvantages of this technique are potential vaginal stenosis, perforation of the bladder and rectum, graft failure and unsightly scarring at the graft site.

**Sigmoid vaginoplasty**
In this procedure one end of a resected sigmoid segment is pulled down with its vascular pedicle to the introitus to form a new vagina and the other end is closed to create a blind pouch. Potential disadvantages are chronic vaginal discharge, foul odour, stenosis at the anastomotic site and the risk of developing adenocarcinoma in the graft.

**Williams vulvovaginoplasty**
A horseshoe-shaped incision is made on the perineum and skin flaps from the labia majora are used to create a pouch horizontal to the perineum. Although technically simpler than the other two techniques, this method became less popular due to the short length and unusual angle for coitus of the resulting pouch.

**Vecchietti procedure**
The principle is to create a neovagina by gradual stretching of the vaginal skin. This is one of the most popular techniques for surgical creation of a vagina and it is performed in certain centres in the UK. The procedure involves placing an olive-shaped bead onto the vaginal dimple, which is pulled up gradually by threads that run through the olive from the perineum into the pelvis subperitoneally, across the vesicorectal space and out through the abdomen, where they are attached to a traction device placed suprapubically. Gradually increasing traction is applied to produce 1.0–1.5 cm of invagination per day. It takes 7–9 days to create the neovagina. The dilating olive and the traction device are removed once the neovagina is at least 7–8 cm long. Once the neovagina is created it is maintained by using vaginal dilators or by regular sexual activity. The traction can be completed as an outpatient.

reported anatomical success in 98% and functional success in 97% of 110 women who underwent this procedure. Potential complications are visceral damage during laparoscopy and an increased risk of stress urinary incontinence.

**Davydov procedure**
A neovagina is created using the woman’s own peritoneum as lining. The procedure involves dissection of rectovesical space, abdominal mobilisation of the peritoneum to create vaginal fornices and attachment of the peritoneum to the introitus. Postoperatively a vaginal mould is inserted for 6 weeks and regular vaginal dilators are used until commencement of regular sexual activity. Good anatomical and functional success is reported with this procedure. No major complications are reported other than growth of granulation tissue at the vaginal vault. The laparoscopic approach has the added benefit of clear visualisation of the anatomy, a shorter hospital stay and less postoperative pain.

**Fertility options**
The inability to reproduce is one of the most emotionally detrimental aspects of MRKH syndrome. As the ovaries function normally, in vitro fertilisation and surrogacy are possible ways of producing genetically related offspring using the woman’s own eggs. Transvaginal egg retrieval is challenging in some cases where there is an artificially created vagina and abnormally positioned ovaries. Transabdominal or, rarely, laparoscopic egg retrieval may be necessary. There is also concern about transmitting the same congenital abnormality to the offspring. In a study of 58 women with MRKH syndrome undergoing fertility treatment with gestational surrogates, none of the 17 female children born had MRKH syndrome. Adoption is another option.

**Future prospects**
Uterine transplantation may hold hope for these women in the future, as studies in animals have been promising. One attempted uterine transplantation in humans has been reported but was unsuccessful. Research is focusing on such novel therapies and the genetic aetiology and pattern of inheritance of MRKH syndrome.

**Conclusion**
MRKH syndrome is a spectrum of congenital abnormalities of the vagina and the uterus with varying anatomical presentation in a phenotypically and genotypically normal female. Management includes psychological support and the creation of a neovagina for sexual function. As this condition is relatively rare, centralising the care of such women in centres...
of expertise may improve patient care and help with future research into aetiology and management.

References