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Müllerian Agenesis: Etiology, Diagnosis, and Management

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Mullerian agenesis, a congenital malformation of the genital tract is the second most common cause of primary amenorrhea. Its etiology is poorly understood but it may be associated with renal, skeletal, and other abnormalities. The diagnosis is often made either radiologically or laparoscopically in patients in whom hormonal and karyotypic investigations for primary amenorrhea are normal. Two-dimensional ultrasound is not a reliable method of diagnosis, as exemplified by the two cases presented in this review; however, three-dimensional ultrasound may be a more sensitive diagnostic tool. The management is varied, but we conclude that the treatment of choice should be a nonsurgical approach aimed at creating a neovagina. Because of the implications for reproduction, these patients require psychological support, which should be offered as part of therapy.

Target audience: Gynecologists and Family Physicians

Learning objectives: After completion of this article, the reader will be able to describe the pathophysiology and clinical presentation of müllerian agenesis and to list the other abnormalities associated with this condition and to outline potential treatment options for a patient with müllerian agenesis.

The true prevalence of congenital uterine anomalies in the general population is unknown. Müllerian agenesis, a congenital malformation of the genital tract, is a common cause of primary amenorrhea, second only to gonadal dysgenesis (1). The diagnosis is often made by endoscopy or radiology in women who present with primary amenorrhea, but whose hormone profiles and chromosome analysis are normal. Until recently, the use of two-dimensional sonography was a key to diagnosis. This may, however, be misleading. The use of three-dimensional ultrasonography or magnetic resonance imaging can provide a noninvasive and more accurate means of diagnosing this condition. We report two cases of müllerian agenesis presenting with primary and presumed secondary amenorrhea in which the diagnosis was made at laparoscopy after normal two-dimensional pelvic ultrasound scans.

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CASE REPORTS

The first patient was a 17-year-old nullipara presenting with 6 months of presumed secondary amenorrhea and apareunia. Allegedly, menarche occurred at the age of 15 years followed by regular monthly periods. At the age of 16 years, she had a laparoscopic appendectomy for lower abdominal pain, at which the surgeons described her pelvic organs as normal. On physical examination, her breasts and hair distribution were normal. No hirsutism or acne was noted. The vulva was normal, but the vagina was short, measuring only 1.5 cm in length and 2.5 cm in

width. No cervix was felt. Rectal examination could not reveal any uterus. Two-dimensional abdominal ultrasound showed a juvenile uterus and normal ovaries. Serum hormone levels were normal and her karyotype was 46,XX. At laparoscopy, the patient was found to have normal ovaries and fallopian tubes, but only rudimentary müllerian tissue on both lateral pelvic sidewalls at the brim.

The second patient was a 20-year-old who presented with primary amenorrhea and associated regular monthly lower abdominal and lower back pains of 1 year's duration. She was phenotypically female with normally developed secondary sexual characteristics and external genitalia (she was virgo intacta). Her hormonal profile was normal and the karyotype was 46,XX. Two-dimensional abdominal ultrasound scan showed a prepubescent uterus and ovaries of normal size. At laparoscopy, she was found to have an absent vagina and uterus, but rudiments of müllerian tissues located over the pelvic brim on both sides.

DISCUSSION

The syndrome of congenital absence of the vagina in association with an abnormal or absent uterus was first characterized by Mayer (2), Rokitansky (3), Küster (4), and Hauser and Schreiner (5). In this syndrome, the ovaries are usually normal, although it is not uncommonly associated with renal and/or skeletal anomalies. The syndrome has frequently been referred to as the Mayer-Rokitansky-Küster-Hauser syndrome.

Müllerian anomalies are grouped as class 1 genital abnormalities according to the recommendations of the American Fertility Society (6) for genital tract abnormalities. This class further is subdivided into two types: A, which is characterized by a symmetrical lack of development in the müllerian ducts and B, in which the lack of development is asymmetrical (7). Type B is also associated with ovarian and renal anomalies.

Incidence

The frequency of congenital absence of the vagina and uterus is not entirely clear, although reported incidences vary from 1 in 4,000 to 5,000 female births to 1 in 20,000 hospital admissions. In women presenting with primary amenorrhea, the disorder is fairly common, second only to gonadal dysgenesis as a cause (1).

Etiology

The etiology of müllerian agenesis is unknown. The fetal gonad has the potential to differentiate into either a testis or an ovary (8). The critical factor that signals the bipotential gonad to develop into a testis is a gene called the H-Y antigen, located on the short arm of chromosome Y. The Sertoli cells of the fetal testis produce a substance known as anti-müllerian hormone (also known as müllerian-inhibiting factor or müllerian-inhibiting substance) that causes the müllerian structures to regress *in utero*, so that in the presence of testis, the female internal genital structures will not develop (9). This regression process is thought to be by basement membrane disruption, reorganization of epithelial cells and movement into the mesenchyme (10). For the male embryonic internal genital structures to differentiate into epididymis, vas deferens, seminal vesicles, and ejaculatory ducts, testosterone needs to be present, and unless the fetus is exposed to androgens, the external genitalia will develop as that in phenotypic women.

Anti-müllerian hormone molecule is a glycoprotein that is translated from two different mRNA transcripts (11). The difference between the two transcripts is that one of them has a greater degree of polyadenylation at its 3′ end. The longer mRNA is most abundant in embryonic testis and it decreases after birth (11). The shorter mRNA is found in the postnatal period, when its action is largely unknown (11). There are several theories about the difference in the translation of the two mRNA transcripts. One of these suggests that the prenatal mRNA, which is the highly polyadenylated transcript, is more stable and less likely to undergo degradation, so it is translated more efficiently into peptide than the postnatal form (11).

The biological activity of anti-müllerian hormone is in the carboxy terminus, but to be active and cause müllerian duct regression it has to be processed proteolytically (12). In the male fetus, the longer anti-müllerian hormone transcript exerts its effects between 8 and 10 weeks of gestation (13), whereas the shorter anti-müllerian hormone persists for several years lasting into infancy.

Although the etiology of müllerian agenesis is currently unknown, several hypotheses have been postulated for the underlying mechanism. The first is an activating mutation of either the gene for the anti-müllerian hormone or the gene for the anti-müllerian hormone receptor, resulting in the inappropriate production of anti-müllerian hormone or the receptor which then acts as if it was bound to the hormone. A

genetic female fetus exposed to anti-müllerian hormone *in utero* during embryogenesis at a time when the müllerian structures are sensitive to anti-müllerian hormone action might develop müllerian duct regression.

The human anti-müllerian hormone receptor gene has recently been cloned (14). The receptor gene is localized in band q13 on chromosome 12. The receptor is similar to the transforming growth factor beta-type II receptor and is expressed in Sertoli cells and the mesenchyme surrounding the fetal müllerian ducts.

Although no activating mutations of the anti-müllerian hormone (AMH) receptor gene have been reported, inactivating mutations of the AMH receptor gene have been associated with persistent müllerian duct syndrome (15). Persistent müllerian syndrome is a disorder in which normally virilized males retain remnants of müllerian structures; in half of them, AMH serum levels and the gene itself are normal, which suggests some type of hormone resistance in the target organ; this resistance is most likely because of mutation in the gene for the AMH receptor (14).

Clinical Presentation

The woman with müllerian agenesis has normal external genitalia and normal functioning ovaries. The phenotype, therefore, is normal with normal secondary sexual characteristics. The degree of malformation of the organs involved in the Mayer-Rokitansky-Küster-Hauser syndrome varies. The fallopian tubes may be normal and the uterus vestigial or vice-versa. Vaginal involvement also varies in extent and degree (16). In approximately one third of cases, there are associated renal abnormalities such as renal agenesis, malrotations, or ectopic kidneys (17). Spinal abnormalities such as asymmetric, fused or wedged vertebrae, or skeletal abnormalities such as absent digits, syndactyly, or hypoplasia of the thenar eminence may also occur. The condition occurs in women with normal 46,XX karyotypes. A strong familial element has been recorded (16).

Müllerian agenesis is usually diagnosed at puberty because of primary amenorrhea. If endometrial tissue is present in the rudimentary uterine horns, the patient may present with primary amenorrhea associated with cyclical lower abdominal pain. Secondary sexual characteristics develop normally and ovarian function after the menarche as assessed by hormone assay and basal body temperature fluctuation is normal also. Some patients describe cyclical breast and mood alterations compatible with ovulation. The main clinical features of the Mayer-Rokitansky-Küster-Hauser syndrome are summarized in Table 1 (18).

In our first case, the patient presented with presumed secondary amenorrhea. Although she claimed to have had regular menses, at examination under anesthesia, she was found to have an almost nonexistent vagina (1.5 cm in length). Regular menstruation was, therefore, impossible in her case. That she declined vaginal examinations and transvaginal ultrasound scans on different occasions may illustrate that she was suspicious of the nature of her problem. Whether this was influenced by family history, culture, or religion is uncertain. There are, however, certain cultures where amenorrhea is socially unacceptable, and such patients, therefore, may run the risk of being socially rejected if they admit to the existence of the problem.

Diagnosis

This is often made after radiological (ultrasound or MRI) or endoscopic examination. General physical examination commonly reveals a normal phenotypic woman with well-developed secondary sexual characteristics. However, vaginal examination may either reveal a short or absent vagina. When examined rectally, findings may be difficult to interpret (as was demonstrated in one of our cases). Where the patient presents with cyclical abdominal pain, it may be necessary to relate this pain with the ovarian cycle. Such pain may be Mittelschmerz or pain from retained menstruation in the rudimentary uterine horns. A monthly record of basal body temperature with a biphasic pattern and the timing of the pain will be helpful. Weekly serum progesterone assays can also be used to document ovulation and the timing of the pain. The karyotype is always 46,XX.

The main differential diagnosis of müllerian agenesis is testicular feminization syndrome. The karyotype in this condition is, however, 46,XY. In addition, the hormone profile in müllerian agenesis will

TABLE 1 **Principal clinical features of the Mayer-Rokitansky-Küster-Hauser syndrome**

Primary amenorrhea associated with congenital absence of the vagina
46,XX karyotype
Variable uterine development
Normal ovarian function and normal ovulation
Normal female breast development, body proportions, and body hair
Frequent association of renal, skeletal, and other congenital anomalies

be typically that of a woman. Failure to obtain a karyotype, therefore, may miss the diagnosis of testicular feminization syndrome with the resultant retention of testes that could become malignant later in life (19).

Urinary tract abnormalities must be excluded because they may be associated with müllerian agenesis. This should be done by ultrasound scan, MRI, CT scan, or intravenous urogram. The presence of a single kidney may influence the means of creating a neovagina (20, 21). Approximately 10 percent of patients with müllerian agenesis have anomalies of the urinary tract (19), 3 to 5 percent have anomalies involving the vertebral column (19) and very rarely serious defects in the bones of the extremities. Radiological studies to exclude such skeletal anomalies may be indicated.

In evaluating patients with suspected müllerian agenesis, the first investigation should be pelvic and renal tract ultrasonography because of it simplicity and low cost. If the ultrasonographic findings are indeterminate or incomplete, an MRI should be performed, as the information is much more precise (22). Until recently, laparoscopy was considered necessary for the definitive diagnosis of this condition, because failure of ultrasonography to clearly identify the uterus or müllerian rudiments or ovaries does not necessarily imply their absence. Laparoscopy, on the other hand, will define the precise anatomical location and abnormalities of the uterus and the ovaries. Several studies (22, 23) have suggested that MRI is advantageous to laparoscopy in diagnosing müllerian agenesis because it is noninvasive. It also may be less expensive inasmuch as hospitalization and anesthesia are not necessary. Compared with ultrasonography, MRI gives equally good images of superficial and deep planes, and unlike ultrasound, the images are not affected by the patient's size (24). The disadvantages of an MRI include cost and discomfort, especially because the procedure lasts longer and requires immobility and magnetic insulation.

Three-dimensional ultrasonography, which has recently been introduced into clinical practice, also provides accurate diagnosis of congenital uterine anomalies (25). The technique is noninvasive, provides quantitative information, and can reconstruct a three-dimensional view of the pelvic organs, which hitherto was impossible with traditional two-dimensional techniques (26). The disadvantage is that the technique is currently confined to a few specialized centers.

In our first case, the patient had two transabdominal ultrasound scans that showed a juvenile uterus on both occasions, whereas in the second case, one transabdominal ultrasound again showed a prepubescent uterus. However, when diagnostic laparoscopy was done, there was, in fact, no uterus in the pelvis.

Treatment

Treatment is usually delayed until the patient is ready to start sexual activity, even when the diagnosis is made during adolescence (27). It may be either surgical or nonsurgical, but the chosen method needs to be individualized depending on the patient's needs, motivation, and the options available.

Nonsurgical. The most commonly used nonsurgical procedure is Frank's dilator method. This method was first described in the 1930s and has since been widely used. The procedure involves the application of progressively increasing sizes of vaginal dilators, from 1.3 cm in diameter and 10 to 12 cm in length to 2.5 cm in diameter and 10 to 12 cm in length. The patients start with the smallest dilator and apply pressure to the vaginal dimple for periods of 20 minutes three times a day. The dilators of increasing sizes are then gradually introduced until the largest dilator has been used for 1 month. Sexual intercourse may then be attempted (28). The whole process usually takes from 6 to 8 weeks. The success rate as defined by normal sexual function is 76 percent (28).

In 1981, Ingram (29) described a variation of the Frank's dilator method. The Frank's method had the disadvantages of being very tiring and causing finger and hand fatigue. Ingram designed a bicycle stool that enabled the application of constant perineal pressure to special dilators. The dilator is placed underneath the patient's clothing and held in place by athletic compression shorts. The patient then sits on the stool for variable periods of time for a total of up to 2 hours a day. Some degree of discomfort is necessary to develop the vaginal barrel effectively. The aim of this procedure is to lengthen the vaginal canal first and then increase its width. Some clinicians use estrogen creams in conjunction with the dilators to give the neovagina a normal vaginal epithelial character. Today, this approach is preferred to surgery.

Surgical. The most commonly used surgical method to correct the inadequate vagina is the Abbe-McIndoe technique, described by McIndoe in the 1950s (30). It involves the construction of a vaginal cavity at the site of the vaginal dimple by making an H-shaped incision in the space between the urethral opening and the posterior fourchette. The fascial plane is then separated and the neovagina epithelialized with a skin graft obtained from the gluteal

region. The most important aspect of the procedure is the continuous prolonged dilatation of the vaginal cavity during healing to prevent contracture of the opening (30), and this is achieved by a form or a stent, that stays *in situ* for 7 to 10 days after surgery. After that, the form is replaced by a new one that stays *in situ* for another 6 weeks except during urination, defecation, and routine cleaning. After 6 weeks, the form is only used at night for the next 12 months (30). The form is then used only occasionally until coitus occurs. The artificial vaginal acquires the same physiological characteristics as the normal vagina. The graft will acquire stratified squamous epithelium with cornification and production of glycogen that varies cyclically with the estrogen production of the ovary similar to normal vaginal tissue (28).

Modifications of the McIndoe procedure use different materials such as human amnion, peritoneum, segments of colon, gracilis or rectus abdominis muscles, myocutaneous flaps, and synthetic materials to replace the skin graft (31).

The Vecchietti operation is a mixture of the surgical and nonsurgical methods of creating a neovagina. It has been performed frequently in Europe over the last 20 years (27). It involves the use of a traction device that is connected to two threads, which pass through the abdominal wall and the potential neovaginal space and are connected to an acrylic olive. The olive is placed in the vaginal dimple, where it applies progressive continuous pressure. Initially, this procedure was performed at laparotomy, but a modification of the operation has been proposed using laparoscopy. Perforations of the bladder and rectum with this modification have been minimized.

Psychotherapy

It is very important to manage psychological symptoms in women with müllerian agenesis. A young woman who discovers that she has a congenital malformation involving her reproductive organs may develop extreme anxiety about her femininity and a distortion of her physical image that can affect her self-esteem. It is recommended that the patient and her family attend counseling throughout treatment. The psychological adjustment and general attitude are also very important in deciding what procedure should be used and when it should be done (27).

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SURVEY ALERT

1998 Practice Guidelines for the Management of Patients Undergoing Spinal or Epidural Anesthesia in Association With Use of Perioperative Low Molecular Weight Heparin

In 1997, the Food and Drug Administration (FDA) issued a public health advisory and requested manufacturers of low molecular weight heparin (LMWH) to include in their label a black-box warning of the complication of spinal hematoma. The FDA approached the American Society of Regional Anesthesia (ASRA) for assistance in developing practice guidelines. In response, the ASRA convened a consensus conference on Neuraxial Block and Anticoagulation on May 2, 1998. A supplement to *Regional Anesthesia and Pain Medicine* (1998;23(Suppl 2)) includes 10 articles relating to the subject of anticoagulation and neuroaxial block particularly as it relates to the use of: low molecular weight heparin, oral anticoagulants, antiplatelet agents, fibrinolytics/thrombolytics, standard heparin, and recommendations of monitoring adverse drug events. Regional anesthesia can be administered safely to patients receiving LMWH prophylaxis, if the following guidelines are considered:

1. Monitoring of anti-Xa level is not recommended because anti-Xa is not predictive of the risk of bleeding.
2. A combination of antiplatelet or anticoagulant medication administered in combination with LMWH may increase the risk of spinal hematoma.
3. Patients on preoperative LMWH can be assumed to have altered coagulation. A single dose of spinal anesthetic may be the safest neuroaxial technique in patients receiving preoperative LMWH. In these patients, neuroaxial technique should occur at least 10 to 12 hours after the LMWH dose. Whereas patients receiving higher doses of LMWH (e.g., 1 mg/kg of enoxaparin twice daily) will require longer delays (24 hours). Neuroaxial techniques should be avoided in patients administered a dose of LMWH 2 hours preoperatively.
4. Patients with postoperative initiation of LMWH thrombophylaxis may safely undergo single-dose, continuous catheter technique. It is recommended that in-dwelling catheters be removed before the initiation of LMWH thrombophylaxis.

The ASRA believes that it is impossible to devise guidelines that will completely eliminate the risk of spinal hematoma. It is strongly recommended that all obstetrician/gynecologists become conversant with their anesthesiologists of these recommendations.

RECOMMENDED READING

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