Abstract

The Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome, also known as Müllerian agenesis or aplasia, is a congenital disease manifested by the aplasia of the uterus and the upper 2/3 of the vagina; its incidence is 1 in 4,000–5,000 female live births. We can distinguish 2 types of the MRKH syndrome: type I, which is characterized by an isolated absence of 2/3 of the vagina and uterus; and type II or MURCS (Mullerian duct aplasia, unilateral renal agenesis and cervicothoracic somite anomalies), which is also associated with other symptoms. The treatment of the MRKH syndrome patients aims at creating a neovagina and enabling sexual intercourse. Non-surgical techniques are the first-choice methods, and more than 90% of patients notice an anatomical and functional improvement if they are well-prepared emotionally. If non-surgical treatment does not bring about the expected results, a surgical procedure remains an option. The surgical method is mainly determined by the surgeon’s experience. There are a few types of operations, though none of them seems superior to others. The next challenge is to provide these patients with a chance to become parents. Nowadays, a uterine transplant, a surrogate or adoption are the available solutions. An interdisciplinary approach is required, and the treatment should consist of medical and psychological support. This review presents the current knowledge about the MRKH syndrome with regard to the current methods of non-surgical and surgical treatment as well as a summary of the associated psychological problems.

Key words: MRKH syndrome, treatment, surgical, psychological aspects
Definition and epidemiology

The Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome is a disorder of congenital anomalies that affects about 1:4,000–1:5,000 live-born girls.12 This syndrome is characterized by a missing or hypoplastic uterus, the upper 2/3 of the vagina missing, the proper development of external genitalia, properly functioning ovaries, and the appropriate karyotype for women – 46,XX.3

Etiopathogenesis

The etiology of the MRKH syndrome still remains unknown,4,5 though family cases have been described, suggesting that the MRKH syndrome may be an inherited disorder. Most of the current research suggests autosomal dominant inheritance, or a multifactorial or polygenic etiology of the MRKH syndrome.6 From the genetic point of view, 2 locations have been studied extensively. Among the suspected contributors to the MRKH syndrome are mutations in the homeobox genes. The homeobox genes are a large family of 39 genes, which can be divided into 4 classes: Hoxa, Hoxb, Hoxc, and Hoxd.7 The most important genes seem to be Hoxa10, Hoxa11 and Hoxa13; they are located in the area which is directly responsible for the development of the uterus, cervix and vagina. Hoxa 10 is expressed in the developing uterus, Hoxa 11 in the lower uterine segment and cervix, and finally, Hoxa 13 is expressed in the vagina.8 Another interesting genetic abnormality was described in the WNT4 gene locus. The WNT4 gene inhibits steroidogenic enzymes like 3β-hydroxysteroid dehydrogenase and 17α-hydroxylase, making the MRKH syndrome patients exhibit hyperandrogenism. A study conducted by Biason-Lauber et al., comprising the genetic analysis of an 18-year-old patient with the MRKH syndrome, confirmed the mutation of the WNT4 gene in the woman.9 On the contrary, Philibert et al. examined 28 adolescent girls with the MRKH syndrome, 27 of whom – without hyperandrogenism – had no WNT4 mutation.10

Clinical manifestation

Historically, 2 types of the MRKH syndrome have been distinguished: type I is characterized by an isolated absence of 2/3 of the vagina and uterus, whereas type II (MURCS – Müllerian duct aplasia, unilateral renal agenesis and cervicothoracic somite anomalies) is also associated with other symptoms, such as cardiac, urological and otological malformations.11–14 The associated malformations can be found in nearly 50% of patients with the MRKH syndrome; in 1/3 of cases, renal anomalies are detected, such as horseshoe kidney, or ectopic or bilateral ureteropelvic junction obstruction.15 In some situations, the term GRES (Genital, Renal, Ear, Skeletal) syndrome may be more appropriate.16 According to Deng et al., the spectrum of types I and II of the MRKH syndrome varies across different races and geographical locations; in their recent study, MURCS occurred in only 3% of cases.17

The MRKH syndrome often remains unrecognized until primary amenorrhea is observed; then, the diagnosis of the situation is extended. It is important to emphasize that the MRKH syndrome is the 2nd most common reason for the total absence of menstruation.18 Many patients have small remnants of endometrial tissue located in the muscular buds, which can lead to cyclical pelvic pain, sometimes requiring surgical or pharmacological management.19,20 Lately, there has been reported an increasing number of leiomyomas and fibroids, developing in the Müllerian remnant tissues or in the rudimentary uterus, which also may cause lower abdominal pain.21–23

Diagnostic tools

Women with a diagnosis of the MRKH syndrome present with 46,XX karyotypes and normal external genitalia. They develop secondary sexual characteristics due to functional ovaries.24–26 The levels of the follicle-stimulating hormone (FSH) and the lutenizing hormone (LH) are appropriate to their age and to the phase of their menstrual cycle.3 The first suspicion of the MRKH syndrome is based on a medical interview (primary amenorrhea) as well as on a clinical examination revealing the absence of the vagina and a non-palpable uterus. To confirm the initial diagnosis, various diagnostic techniques may be used.27

A highly available method, routinely used in diagnostics, is ultrasound examination. It easily shows the upper level of the vagina as well as the presence or absence of the uterus. Furthermore, it simultaneously allows the assessment of the kidneys and bladder for coexistent abnormalities.18 In many cases, ultrasonography (USG) findings are incomplete or inconclusive, especially when it comes to differentiation between types I and II of the MRKH syndrome.28

Magnetic resonance imaging (MRI) is the gold standard in the process of diagnosing the MRKH syndrome patients. This technique is more sensitive than USG in detecting rudimentary Müllerian structures, which can be found in 90% of patients with the MRKH syndrome.29,30 In a recent study by Wang et al., MRI was crucial in exploring the location of the ovaries, as in 28% of cases, they were abnormally located.31 Such knowledge is important in the process of surgical planning and infertility treatment. Additionally, MRI can visualize the associated congenital anomalies, especially in the urinary tract.18
Differential diagnosis

Symptoms that are most similar to the MRKH phenotype are present in the androgen insensitivity syndrome. In both situations, primary amenorrhea, a shortened vagina, and an absent cervix are observed. In patients with the androgen insensitivity syndrome, the gonads are testes. The differentiating symptoms are the androgen insensitivity syndrome patients’ serum testosterone levels within the male range and karyotype 46,XY. The most common genetic etiology of pubertal delay and primary amenorrhea is the Turner syndrome, with 45,X karyotype and an elevated FSH level. The final diagnosis of the Turner syndrome is based on the karyotype analysis. Typical clinical signs include a short and webbed neck, a low hairline at the nape of the neck, a short stature, a shield chest, and delayed puberty due to hypogonadism. Another disease with a similar clinical appearance is CYP17A1 deficiency – congenital adrenal hyperplasia due to 17α-hydroxylase deficiency. CYP17A1 is a gene that is necessary for the synthesis of sex steroids and cortisol. Additionally, hypertension and hypokalemia are observed. Females affected by these symptoms will have the uterus and vagina, but males will usually have female external genitalia, a blind vagina and intra-abdominal testes. In CYP17A1 deficiency, reduced sex steroids and elevated gonadotropin and progesterone levels as well as mineralocorticoid hypertension are pathognomonic (Table 1).

Management

The main goal of the MRKH treatment is to create an appropriate vaginal cavity in order to facilitate sexual intercourse. Throughout the years, a lot of non-surgical and surgical interventions have been developed. Currently, the best management method remains controversial due to the lack of longitudinal studies and prospective evaluation of the interventions undertaken. Moreover, there is no general unified definition of successful neovagina formation. Studies focus on the anatomical length or functionality which enables satisfactory intercourse. The lack of guidelines leaves the choice of treatment to the surgeon; it depends on the surgeon’s expertise and previous surgical attempts as well as on the patient’s genital configuration.

Psychological aspects

Apart from the most common physiological symptoms, the MRKH syndrome patients are very often afflicted with various psychological problems. They suffer from disturbances in perceiving their sex, body, and social or sexual role as a woman. Heller-Boersma et al. point to the fact that the MRKH syndrome may contribute to various, often extreme, emotional behaviors, ranging from positive ones – like a high level of motivation for treatment – to negative ones like depression, anxiety, shock, the feeling of isolation, shame, and even suicidal tendencies. In 2012, Gupta and Kharb described the first case of suicide related to the MRKH syndrome. The woman was in a state of despair due to her illness. She came to the point where she did not care about hygiene and stopped bathing, thus causing infective dermatitis. Then, as a result of the additional stress, she committed a suicide. The American College of Obstetricians and Gynecologists (ACOG) indicates that the role of support groups for patients with the MRKH syndrome is crucial. What is also emphasized by ACOG is the importance of the psychological aspect in the whole process of healing. Studies have revealed that the best indicator of the emotional acceptance of the diagnosis is the relationship between parents or caretakers and the patient as well as the patient’s ability to share their feelings with their family and friends. Beisert et al. analyzed 31 MRKH patients in comparison with 31 healthy women. They observed partly similar sexual development, whereby the MRKH patients exhibited dyadic sexual activity. It was speculated that this was not only due to the defective biological condition, but was also a psychological consequence of the disease. To our knowledge, there are no studies that have indicated patients affected by the MRKH syndrome deciding to change their gender or having gender dysphoria. Nevertheless, many studies have revealed the patients’ doubts about their female identity, and a sense of being defective and incomplete. Some women believed that

### Table 1. Differential diagnosis of the Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Karyotype</th>
<th>Menstruation</th>
<th>Female internal reproductive organs</th>
<th>Laboratory findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRKH syndrome</td>
<td>46,XX</td>
<td>primary amenorrhea</td>
<td>– lack/hypoplasia of the uterus – lack of the upper ⅔ of the vagina – normal ovaries</td>
<td>↑ testosterone</td>
</tr>
<tr>
<td>Androgen insensitivity syndrome</td>
<td>46,XY</td>
<td>primary amenorrhea</td>
<td>– a shortened vagina – lack of the cervix – testes</td>
<td>↑ FSH</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>45,X</td>
<td>primary amenorrhea</td>
<td>hypogonadism</td>
<td>↑/N FSH</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>46,XY</td>
<td>irregular menstruation</td>
<td>presence of the vagina and uterus</td>
<td>↑ FSH ↓ estrogen</td>
</tr>
</tbody>
</table>

FSH – follicle-stimulating hormone; N – normal.
Non-surgical treatment

According to the ACOG recommendations, the first-choice treatment should begin with non-surgical methods. A multicenter study conducted by Cheikhelard et al. showed that surgery was not superior to non-surgical methods based on dilation. First described by Frank, the use of dilators of increasing sizes still remains one of the most popular first-line treatment methods as well as the one used after surgical procedures for maintaining the vaginal cavity. In 1981, Ingram modified Frank’s technique to avoid some inconveniences by installing a dilator on a bicycle seat, allowing the patient to perform other activities during the sessions. Dilators of increasing sizes are placed inside the vaginal dimple and intermittent, progressive, manual pressure is used to create a vaginal cavity. Dilators are supposed to be used 3 times a day for 15–20 min. Both methods are minimally invasive and cost-effective procedures, with a low complication rate, allowing a vagina to be created from normal vaginal tissue. Non-surgical options are reserved for those patients who are motivated and psychologically mature, because the success rate depends mainly on the patient’s compliance. According to Edmonds et al., more than 90% of patients will respond to a non-surgical procedure using vaginal dilators with both the anatomical (a neovagina greater than 6 cm in length) and functional success. According to a recent study by Both et al., women with a neovagina after dilation showed a weaker vaginal blood flow response after sexual stimulation, which may be related to lesser innervation and vascularization as compared to a natal vagina. Despite such findings, patients with the MRKH syndrome did not differ in the level of subjective sexual arousal and satisfaction from the control group. Ketheeswaran et al. found that adjuvant treatment, such as estriol cream, nitrous oxide and oxygen, diazepam, lidocaine ointment, paracetamol, and naproxen, can improve outcomes in women who used vaginal dilators. The adjuvants minimize discomfort and anxiety during progressive dilation. The success rate depends on the patient’s compliance and attitude; therefore, multidisciplinary care involving social workers, trained nurses, psychologists, and physicians play a key role.

Surgical treatment

Surgical methods should be reserved for patients depreating the dilation technique as well as for those after unsuccessful non-surgical management. There are a number of surgical techniques used to create an artificial vagina. Intestinal vaginoplasty was first described in 1892 by Sneuguireff, and today utilizes the sigmoid colon in the creation of a neovagina. This technique requires both a perineal approach and laparotomy, demanding the cooperation of a pediatric surgeon and a gynecologist. The sigmoid colon is widely used as a graft due to its larger diameter and close proximity to the perineum. Historically, the ileum, cecum and jejunum segments were used, but due to high morbidity and mortality, the procedure was abandoned. Sigmoid colon tissue, 10–12 cm in length, with its own blood supply, is distended toward the introitus, and then connected with the created cavity. There are a number of advantages of this method, e.g., no dilators are required after the surgery and lubrication is satisfactory. In a recent study by Özkan et al., 43 cases of sigmoid vaginoplasty were reviewed and the overall success was reported, both anatomical (the mean length of a neovagina was 11.7 ±1.2 cm) and functional (97% of patients rated their sexual intercourse as satisfactory). The most concerning flaws are excessive odorous secretion in the beginning, donor site morbidity, defection problems, postoperative ileus, anastomotic leaks, the development of inflammatory bowel disease, ulcerative colitis, diversion colitis, potential neoplasia and carcinoma in the grafts, neovaginal prolapse, and stenosis. The laparoscopic modification has been gaining more and more popularity, with fewer postoperative pelvic adhesions, less intraoperative blood loss, a better cosmetic effect, a shorter hospital stay, and faster recovery. Nevertheless, it should be performed only by experienced laparoscopic surgeons. Robotic approaches are also evolving, but due to high costs, they still remain limited. In the upcoming era of the uterus transplantation, while choosing the method for neovagina creation, performing such transplantation in the future should be taken into consideration. Gauthier et al. raise concerns about sigmoid coloplasty and suggests that this type of surgery should be avoided in neovagina creation. An increased risk of adhesions, damage to a neovagina and contamination from bowel mucosa can put a uterine transplant at risk and lead to the failure of the procedure. One of the most popular types of surgery is the laparoscopic Vecchietti vaginoplasty, first described in 1965 as a laparotomy. This technique is based on progressive passive traction through the external pelvic wall on the retrohymenal fovea with the use of an acrylic “olive”. This method preserves natural vaginal tissue, and avoids stenosis complications and excessive mucus production. As compared to other surgical interventions, the Vecchietti procedure boasts the shortest operative time. Some alternatives to Vecchietti’s procedure have been proposed, using balloons or a Foley catheter instead of acrylic olives, or applying a different approach, avoiding vesicorectal tunneling – a safer, shorter, more effective, and less traumatic procedure, with a very low complication rate.

Another type of surgery relies on creating a neovaginal space between the rectum and the bladder by inserting...
an inlay graft. McIndoe’s approach requires perineal access, avoiding an abdominal incision. A cavity is created between the urethra and the rectum, and a skin graft, usually acquired from the buttock area, is used. McIndoe modifications with different types of grafts have been proposed, e.g., with split-thickness skin grafts and full-thickness skin grafts, an amnion, autologous vaginal tissue cultured in vitro, and artificial grafts. Injury to the neighboring organs, such as the rectum and bladder, are the most serious complications. Skin grafts are often problematic because of inadequate lubrication, resulting in dyspareunia, a high rate of stenosis and excessive hair growth. External visible scars from the graft harvest sites – the buttock, groin or thigh – can also cause the patient’s discomfort. Graft methods require the postoperative use of molds in order to prevent possible graft contraction and stenosis. The molds need to be carefully changed to avoid the shearing of the graft, as the secondary healing of lesions is connected with unfavorable long-term results. According to McQuillan and Grover, graft techniques require the longest hospital stay after the surgery. Squamous papillomas in the skin graft have been reported in a neovagina, hence there are some concerns about their malignant transformation.

The Davydov procedure, designed as an abdominal approach, is nowadays widely performed laparoscopically. After dissecting the retrovesical space, the peritoneum is mobilized and an attachment with the neovaginal introitus is created. Postoperative dilation is required to avoid vaginal collapse before epithelialization is complete. Still, perineal vaginoplasty is accompanied by a greater number of intra- and postoperative complications, and more frequent rectal injuries than other vaginoplasty techniques.

Another form is Williams vaginoplasty, later modified by Creatas, where a neovaginal pouch is created with a deep incision extending from the labia majora to the peritoneum, further expanded by dilators or sexual intercourse. A study on 178 women reported a 96% anatomical success rate and a 94% functional success rate. Wound infection, hematomas and excessive hair growth may complicate the procedure.

The gold standard treatment for the MRKH syndrome has yet to be established, because it is extremely difficult to compare the results of different techniques without prospective long-term studies.

Reproductive challenges

Every woman affected by the MRKH syndrome has no reproductive ability, which is one of the main problems for these patients. The possibility of having children is limited to a uterine transplant, or an in vitro method using a surrogate or adoption. In a study on 50 MRKH syndrome women, after reconstructive surgery, nearly 2/3 of the study group were interested in uterus transplantation. Uterine transplantation can be a real solution in the future for patients with the MRKH syndrome, especially with the latest report of the first live birth after a uterus transplant in the USA in an MRKH syndrome patient. Currently, there are 7 ongoing clinical trials concerning uterine transplantation in the MRKH syndrome patients.

Summary

The MRKH syndrome is certainly a disease that requires an interdisciplinary approach. The congenital defects occurring in the patient modify her own image as a sexual person, but should not necessarily be regarded as impairing sexual satisfaction, since it is affected by many more factors. In recent years, numerous methods of MRKH management for patients have been developed. However, in fact there is no ideal method for all patients. Optimal care for such patients includes both therapeutic and psychological support.

References


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