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Mayer-Rokitansky-Küster-Hauser syndrome – case studies, methods of treatment and the future prospects of human uterus transplantation

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Abstract. – OBJECTIVE: We aimed to present patients with the Mayer-Rokitansky-Küster-Hauser syndrome (MRKH) coming from one center and presenting all the possibilities of its treatment, at the forefront with the uterine transplantation.

PATIENTS AND METHODS: The presented work is an example of different types of MRKH syndrome diagnosed in 25 women who were diagnosed in the Department of Gynecological Endocrinology due to the primary amenorrhea from 01/2001 to 06/2018.

RESULTS: Patients suffering from MRKH syndrome are capable of having genetic offspring but are unable to give birth to their own child, due to an absence of the uterus, blindly terminated vagina, and normal ovaries. Patients suffering from this syndrome have the opportunity to receive treatment in accordance with their current needs. However, there are many medical, technical, and ethical limitations in achieving the most important therapeutic target: uterine transplantation and childbirth.

CONCLUSIONS: Until a few years ago, patients with an absolute uterine factor of infertility, including women with MRKH syndrome, had a real choice of only two equally controversial options giving a chance for motherhood – surrogacy and adoption. However, modern transplantation has shown that a third option – a uterine transplant – exists and is available.

Key Words:
Mayer-Rokitansky-Küster-Hauser syndrome, Uterine factor infertility, Uterus transplantation, Infertility.

Introduction

In 1829, August Mayer, a German anatomist and physiologist, first documented Mayer-Rokitansky-Küster-Hauser syndrome (MRKH), a congenital anomaly caused by agenesis or hypoplasia of the Müllerian duct system in the fifth week of fetal life. Though Mr. Mayer's account is the first of its kind regarding MRKH, similar abnormalities of the female reproductive system have been documented throughout human history. For example, Avicenna (980-1037) and Albucasis (1013-1100) both described the underdevelopment of vagina and uterus in the form of a bicornuate uterus, where the uterus appears to be heart-shaped[1]. In 1838, an Austrian pathologist named Karl von Rokitansky presented further cases of women with absent uteri and vaginal atresia. Though these accounts were documented, they were not under the same scientific scrutiny as today's reviewed publications which started to circulate in the 1900s. The first reviewed publication on MRKH was written in 1910 by Hermann Küster, a German gynecologist, who collected all reported cases available in the world literature pertaining to this disorder[2]. It was only in 1961 that this disorder was first given its name 'Mayer-Rokitansky- Küster syndrome' by the gynaecologist Hauser. Later it was extended to 'Mayer-Rokitansky- Küster-Hauser syndromem' to honour also Hauser's contribution to research of the disease. In the source literature, this disease entity can also be found as Congenital Absence of the Uterus and Vagina, Rokitansky-Philipp syndrome, or *syndroma aplasiae vaginae et uteri congenitum*[3].

Mayer-Rokitansky-Küster-Hauser syndrome is the second most common cause of primary amenorrhea after gonadal dysgenesis characterized by the presence of normal body structure and normal psychophysical development. It also shows the correct genotype (46, XX). The incidence of

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the syndrome has been estimated to be between 1:4000 and 1:5000 live births[4].

Disorders of sex differentiation, due to a teratogenic factor during organogenesis, are believed to be the cause of genital malformations. The extent of emerging defects depends on the type, duration, and period of embryogenesis in which teratogenic factors have acted[1]. Physiologically, upper vagina, cervix, corpus uteri, and oviducts are derived from the Müllerian ducts during embryogenesis[5]. The ovaries develop on the medial surface of the mesonephros, which evolved from Wolffian duct[6].

MRKH has a strong genetic component, so one must also consider genetic factors in its etiopathogenesis. As previously mentioned, researchers in the past hypothesized that the genetic defect may contain incomplete penetration and variable expression may lie at the base of the syndrome[7].

The molecular basis of the syndrome is not fully explained. Theoretically, the abnormalities may be caused by mutations of the Anti-Müllerian hormone (AMH) gene or its receptor[8]. Leydig et al[9] demonstrated that different regions of chromosomes are associated with the MRKH syndrome (1q21.1, 17q12 and 22q11.21). Additionally, candidate genes are LHX1 and HNF1B.

Symptoms

The first symptoms of MRKH syndrome usually appear during puberty in the form of primary amenorrhea in young women, who have normal body structure and psychophysical development. Another frequently reported complaint includes cyclic abdominal pain caused by the accumulation of menstrual blood or dyspareunia and infertility. Due to the common embryological origin, congenital anomalies of the urinary tract may also frequently occur in this syndrome[10].

The classic form of this syndrome, type I, is characterized by either aplasia of the upper part of the vagina, the absence of the uterus and the fallopian tubes, or the presence of rudimentary uterine horns without functional endometrium and residual fallopian tubes. However, normal uteri with functional endometrium may also occur in the MRKH syndrome[11].

Since ovaries are not Müllerian structures, their development and function are usually normal, including preserved ovulation. Ectopic ovaries are common and may be linked to polycystic ovaries[12-14].

The genetic and phenotypic gender of patients suffering from the MRKH syndrome is female, characterized by correct proportions and body structure, proper hair, correct formation of the labia minora, labia majora, clitoris, as well as the correct development of the mammary glands[10]. The results of hormonal tests also do not deviate from the norm. However, in the gynecological examination abnormalities could be found, including varying lengths, blindly terminated vaginal recess, or the complete absence of vagina. Additionally, the urethral fossa and/or the urethra itself are significantly widened[1]. Throughout the examination, patients may lack complete uterus, rudimentary uterine horns, rudimentary fallopian tube, and ovaries.

Type II form of MRKH syndrome contains urinary system defects, such as ectopic kidney, renal agenesis, horseshoe kidney, abnormalities of collecting ducts (or bladder eversion), and skeletal anomalies (most frequently comprising the spine). According to Oppelt et al[15] in 11% of cases, defects of skeletal system occurred in the form of scoliosis.

A rare disorder known as MURCS, first described by Duncan et al[16] in 1979, involves Müllerian agenesis, Unilateral Renal Aplasia, and Cervicothoracic Somite Dysplasia. MURCS may additionally include other urinary system defects, such as malformations of the musculoskeletal and/or cardiovascular system. According to Oppelt et al[15] 47% of women had a typical MRKH syndrome, 21% had atypical and 32% had MURCS.

The diagnosis of the syndrome can be made on the basis of an interview, gynecological examination, imaging studies, and laparoscopy[17]. Magnetic resonance imaging (MRI) of the pelvis is the examination of choice for the assessment of the uterus and ovaries in women with MRKH. Hall-Craggs et al[11] examined a group of 66 women and found rudimentary uterus in 92% of cases, with 27 patients having ectopic ovaries, as well as inability to reveal the vagina in 22 cases. Among 44 patients with visible vagina, the average length was measured to be 2 cm (ranging from 1-6,5 cm)[11]. When numerous defects are suspected, the diagnostics should be expanded, and could include ultrasound examination of the abdominal and retroperitoneal space, urography, X-ray of the spine, ultrasonic cardiography, morphology, saturation, and neurological examination[18].

MRKH syndrome may be accompanied by other congenital malformations or tumors, such as bilateral hypoplasia of the proximal femur[19], hearing defects in the form of stapes immobilization or sensory deafness, finger defects, such

as syndactyly or polydactyly, occurrence of syndromes, such as Dandy-Walker syndrome, Meckel-Gruber, Bardet-Biedl, Holt-Oramm, McKusick-Kaufman[20] or Goldenhar's syndrome[21]. MRKH syndrome can also coexist with neoplastic changes, such as mature teratoma, adenomyosis, ovarian adenocarcinoma or blood diseases[7,22,23].

Methods of Treatment

Treatment of MRKH includes surgical treatment. Its purpose is not only to allow physiological intercourse *via* creation between the uterus and the vagina, but also to provide sexual satisfaction.

Depending on the initial anatomical conditions, treatment of vaginal agenesis is divided into surgical and non-surgical modalitalies[24]. Non-surgical techniques consist of dilating the vagina with appropriate dilators. Additionally, through appropriate stretching exercises, it is possible to form a functional vagina, even from a small opening. The best-known modality is Frank's method, which consists of placing a special dilator into the vaginal vestibule area[25]. Another method known for increasing the patient's comfort was created by Ingram et al[26], who constructed a stool with an appropriate dilator in the seat. This dilator is placed by the patient in the vaginal vestibule opening, and by using the patient's body weight, it models and stretches the area to deepen the opening (Tampa, FL, USA). The dilators themselves differ in terms of shape, size, and material. The effectiveness of non-surgical treatment of vaginal agenesis is estimated at 75-90%[24].

According to the guidelines of the American Congress of Obstetricians and Gynecologists, surgical reconstructive procedures are recommended for patients in whom non-surgical procedure did not bring the desired effect or was not considered due to anatomical conditions. Surgical vaginal creation or its correction should be proposed to patients who have reached emotional maturity and have already attempted sexual intercourse or declared readiness for it[27].

There are many surgical methods of creating a functional vagina. The main problem in this type of surgery is the selection of the right material for vaginal reconstruction itself. The first surgical vaginal creation occurred in 1832 by Amussat, while the first transplanted skin piece for vaginoplasty was performed in 1872 by Bastu et al[28]. However, this material was unsatisfactory due to the occurrence of hair and dryness of the vagina. In subsequent years, different materials were used for vaginal reconstruction. At first, fragments of the small intestine were used (Baldwin). However, through time, fragments from varying areas of the body were used, including but not limited to sigmoid colonic fragments (Wagner, Ruge), fetal membranes, flat skin of the labia majora, and the peritoneum from the rectovaginal pouch.

An entirely different method of surgical procedure was the creation of a vagina from the rectum. The first such operation was performed in 1882 by Snigerow. In 1909, Popov modified this method by dissecting the final part of the rectum from the external anal sphincter and sewing it to the vulva[29]. In subsequent years, there were attempts to use other materials such as mucosal fragments, artificial recombinant skin or biomaterial meshes, and biologic mesh which was widely used as a skin substitute in various reconstructive operations[30]. However, despite the existence of at least several alternative methods of vaginoplasty, there is still no effective and recommended technique[28].

Amongst surgical procedures, divisions occur in vaginoplasty using the McIndoe method, Vecchietti surgery, or Fanky's preparatory procedure. McIndoe vaginoplasty is a common surgical treatment for MRKH, creating a vaginal tunnel of 10-12 cm in length in place of atresia with the addition of a plastic prosthesis, which is then covered with a skin patch taken from the patient's thigh or anterior abdominal wall area[1]. The main disadvantages of this method are vaginal dryness, the conical shape of its canal, and the presence of hair.

Currently, the most common method of surgical vaginal creation is the Vecchietti method. Originally, it was a largely invasive procedure, dissecting the recto-vesical area, placing two sutures over the abdominal wall, which then passed through the pelvic diaphragm and then pulled the vaginal cavity of the perineum to extend the olive. Afterwards, the olive was successively pulled up, 1-1.5 cm every day in the postoperative period[31]. It is now less invasive, as laparotomy has been largely replaced by laparoscopy. Another surgical treatment for MRKH syndrome is Franky's treatment. It is both safe and non-invasive, consisting of placing Hegar's dilator into the vaginal vestibule and systematically applying pressure to the area[1].

Although there are no indications for routine vaginal cytological testing in patients with MRKH syndrome after vaginal reconstruction surgery, the occurrence of squamous cell carcinoma in FIGO III was recorded in the literature.

For example, a 48-year-old woman with MRKH syndrome treated surgically 28 years ago *via* Vecchietti vaginoplasty was found to later have SCC. Although carcinomas are relatively rare after surgical vaginal creation, it is crucial to regularly test patients. If positive, radical operations are possible, but there is no long-term, prognostic data that currently exists for these patients[32].

Equally important to treatment is proper post-surgical rehabilitation, consisting of constant widening and elongation of the newly created vagina. In the early postoperative period, vaginal modeling should be performed by medical personnel, then, by the patient herself.

It should not be forgotten that psychological treatment must be available for both the individual and her family when treating MRKH syndrome. Patient education is imperative, as this disease and its treatment encompasses an individual's entire life. Its defects can significantly impact patient's sexuality through performance of social roles, self-perception, and self-acceptance[33].

The next stage of treatment of women with MRKH syndrome should include sexological care of the patient and her partner. An important problem for both patients and her partner(s) revolve around intercourse post-treatment. Patients and partner(s) often fear damaging a newly created vagina, dyspareunia, and increased vaginal dryness.

Infertility is a common concern for patients as well. Patients with MRKH syndrome have properly functioning ovaries and a hypothalamus-pituitary gland-ovary axis. From the hormonal and physiological point of view, these women are therefore capable of reproduction and may have genetic offspring but cannot give live birth to offspring herself. An option for such patients is adoption or hiring a surrogate mother. However, in many countries, surrogate motherhood is not allowed for ethical, legal or religious reasons. Fortunately, uterine transplant remains an option in these patients.

Uterine Transplantation

The first attempts to transplant a human uterus from a multi-organ donor were described in 2013 in Turkey. However, these efforts were unsuccessful resulting in progressive uterine necrosis in the first months after transplantation and, as a consequence, its removal after 3 months[34]. In the following years, various attempts were made to improve the techniques of vascular transplantation. At first, the causes of failure were attributed to blood clots in vessels created using the microvascular anastomosis technique of an organ taken from a living donor[35]. To overcome this obstacle, it was decided to transplant the uterus in one block with the subrenal aorta, inferior vena cava, and both the common and internal iliac arteries, as well as the arterial and venous vessels of the uterus in both human and animal models[36].

The first successful uterine transplant was documented in 2014 when the work of Swedish specialists[37] on live birth after uterine transplantation in 2013 was published. The recipient of the organ was a 21-year-old patient with an atypical MRKH syndrome accompanied by kidney agenesis. She was repeatedly informed about the possibility of removal of the transplanted uterus due to organ rejection, complications associated with caesarean section, side effects of immunosuppression, and information regarding the removal of the transplanted uterus after a maximum of two successful pregnancies. The donor, whose blood was compatible with the recipient's blood, was a 61-year-old woman who had two natural births, both in the 41st week of pregnancy. The donor also went through menopause seven years before transplantation. The resumption of ovarian function was achieved by using oral contraception for 3 months in a continuous system (ethinylestradiol: 30-40 μg and levonorgestrel: 50-125 μg)[37].

The patient underwent an assisted reproduction procedure with ovarian stimulation from 18 to 6 months before transplantation. Three full cycles of stimulation using buserelin, a human menopausal gonadotropin and recombinant follicle-stimulating hormone (FSH), at appropriate doses and days of the cycle were performed. Ovulation was induced by using recombinant human choriogonadotropin[37]. Under the control of ultrasonography, oocytes were taken and fertilized by intracytoplasmic sperm injection. The transfer of a single embryo was carried out a year after transplantation of the uterus, in the natural cycle, using a soft catheter and an ultrasound as a guide.

Embryo transfer techniques have an advantage over the natural method, because they avoid complications and side effects, such as ectopic pregnancy, pelvic inflammatory disease or infertility of tubal origin[38]. Therefore, most authors[35,39-41] believe that the fallopian tubes should not be routinely transplanted with the uterus.

Transplantation of the uterus consists of its removal along with long vascular bundles from the organ donor and its transplantation to the previously prepared appropriate anatomical area of the recip-

ient. The complexity of the procedure results from the necessity of wide dissection of distal parts of internal arteries and internal iliac veins (Figure 1).

The patient received appropriate intravenous immunosuppressive therapy before the procedure, and then, immunosuppression was continued with oral drugs. The patient remained compliant throughout the entire pregnancy, under strict control of high-risk pregnancy and transplantologists.

The first spontaneous menstruation after transplantation occurred in the patient after 43 days and lasted 4 days[37]. Menstrual cycles occurred regularly, every 26-36 days. Serial ultrasound examinations of blood flow in the uterine arteries did not show any abnormalities. Before the embryo was transferred, patient underwent 3 episodes of benign transplant rejection, which was successfully prevented by using appropriate doses of corticosteroids.

After the *in vitro* fertilization procedure (IVF), before transplantation, one cryopreserved embryo was obtained from one oocyte in the first cycle, four embryos from nine oocytes in the second cycle, and six embryos from eight oocytes in the third cycle. A year after the transplantation of the uterus, one embryo was transferred in the early luteal phase of the menstrual cycle. The patient was prescribed daily intake of acetylsalicylic acid, folic acid, and intravaginal lutein. Pregnancy progression was normal, with 3 exacerbations that had no effect on it. At the end of 31 weeks of pregnancy, the patient was hospitalized with symptoms of pre-eclampsia. Despite the inclusion of appropriate treatment, the patient gave birth by caesarean section at 31 weeks and 5 days of gestation to newborn with body weight of 1771 g, length of 40 cm, and Apgar score of 9/9/10 points. The patient was discharged home on the third day after caesarean section in good general condition.

While natural labor is encouraged, caesarean section seems to be a better solution with uterine transplantation as it provides greater control over birthing and the ability to perform elective hysterectomy[41]. An alternative option is to discontinue the administration of immunosuppressive drugs and to allow for slow atrophy of the transplanted organ. Theoretically, caesarean section is also associated with an increased risk of incorrect placentation, but studies on animal models have not confirmed its existence in practice[41].

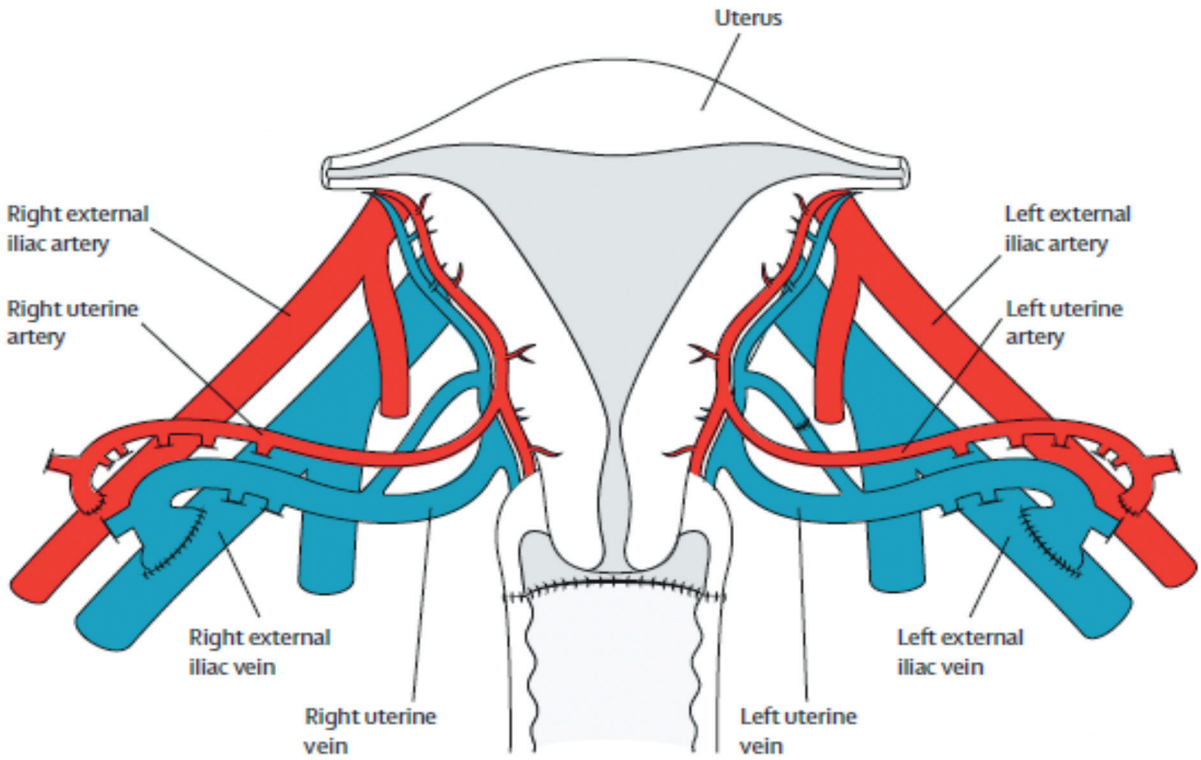

Figure 1. Vascular diagram of the grafted uterus - based on Brännström et al[37].

Discussion

The present work is an example of different types of MRKH syndrome diagnosed in 25 women who from 01/2001 to 06/2018 were diagnosed by the Department of Gynecological Endocrinology due to primary amenorrhea, as well as treatment options adapted to their current needs (Table I).

The main reason for hospitalization of patients and the most frequently reported symptom reported was primary amenorrhea. Three patients underwent surgery according to the Vecchietti method at 21, 19, and 19 years of age, respectively. The age range for first-time patients was between 17 and 24 years. One of the hospitalized patients at 27 years of age, who was diagnosed with MRKH syndrome several years earlier, was referred to the ward for a different reason. In the presented group, 22 women never had their first menstrual period. One patient reported single uterine bleeding at the age of 18.

In some cases, the MRKH syndrome may be accompanied by other typical diseases and congenital malformations requiring correction in early childhood or immediately after birth. In the presented group of patients, there were isolated cases of cleft lip and cleft palate surgery, anorectal outlet obstruction, hypoacusis, and urethroplasty. Apart from that, one patient was diagnosed with retrognathism, two were diagnosed with scoliosis, other two patients with polydactyl and sindactilia, and one patient with cubitus valgus. In one patient with diagnosed MURCS, the occurrence of congenital malformations, Klippel-Feil syndrome and Arnold-Chiari type I syndrome has been documented. Two patients underwent appendectomy in childhood, one tonsillectomy, and one removal of right breast fibroadenoma. Other less common conditions in the test group included hypothyroidism, cholecystitis, epilepsy, and Gilbert's syndrome. Two patients reported hyperprolactinemia, five patients reported acne, and other five reported hirsutism.

In order to diagnose MRKH syndrome, gynecological examination, ultrasound examination, pelvic magnetic resonance imaging (MRI), and laparoscopy are used. It is also recommended to perform urography due to frequent defects of the urinary tract. The research can be supported by the results of cytogenetic karyotype testing. To complete the diagnosis, basic laboratory and hormonal tests should not be disregarded.

The principle of the syndrome is the lack of the development of structures arising from Müller's perimeter conductors. In the gynecological examination, all patients had well-developed female external genitalia. In three cases from the presented group of patients, a complete lack of vagina was reported after the gynecological examination. In the remaining patients, a blind-ending vagina of different length was reported, without revealing the cervix. The length of the vagina or its opening was from 0,5-1 cm in four patients, and up to 10 cm in one patient. In other cases, the length was 1,5 cm, 2 cm, 3 cm, 4 cm, 5 cm, 6 cm, and 8 cm. In each case, the uterus was described as nonpalpable or absent. Apart from one patient, the appendages were not palpable. Breast development, assessed by the Tanner scale, was reported as Tanner V in 21 patients, Tanner I in one of the patients, and Tanner IV in another patient.

The ultrasound image of the reproductive organ of a patient with MRKH syndrome is also characteristic. It allows to describe the uterus as residual or as in the form of a solid band, with no visible endometrium. The ultrasound examination is performed depending on the condition, using either transvaginal or transperineal, abdominal or transrectal access. In the presented group, where the ultrasound examination was performed, the uterus was not visible in 14 cases, and appeared as a solid tissue band or was described as a residual uterus in eight cases.

Ovaries in patients with MRKH syndrome also tend to be normal. In 5 presented patients, polycystic ovarian structures were observed in an ultrasound image. In the remaining 12 patients, ovaries were described as normal bilaterally, with correct echogenicity, structure and volume, and with visible normal follicles at various stages of development. The ovaries were not revealed in two patients. In additional two patients, the right ovary was not visible, and in another patient the same was true for left ovary.

In order to exclude associated congenital malformations and to supplement the ultrasound examination, it is recommended to perform MRI of the pelvis minor. This type of MRI is performed during hospitalization, and in 7 cases it was identified the presence of tissues that could correspond to fragments of an abnormally developed uterus; uterine dysgenesis; a structure showing signals and a layered structure typical of the uterus and likely corresponding to the hypoplastic uterus; a narrow band with a tissue signal that may conform to a uterus, a vestigial organ or agenesis; banded tissue structure that corresponds to the undeveloped uterine band. In two cases the cor-

Table I. Different types of MRKH syndrome and treatment options adapted to their needs.

No.	Patient name and age	Present history	Concomitant illness	Anthropometric examination	Gynaecological examination	Gynecologic ultrasonography - conclusions	MRI pelvis minor - conclusions	Urography with an ionic contrast media	Laboratory examination
1	S. D.; 18	Primary amenorrhea, atresia of the hymen	Acne, cleft lip and palate. Additional lumbar vertebrae. Left-sided scoliosis with rotation. Slightly enlarged left lobe of the liver.			TAS. In the uterus projection, a solid structure with dimensions 16x7 mm. The ovaries on both sides seems to be correct.	In connection with the bladder, a banded area of about 5mm thick can be found which may correspond to an abnormally developed uterus. Ovaries correct.	Pelvicalyceal system of the right kidney in the form of bipartite pelvis	Insulin resistance, hyperinsulinemia, macroprolactinemia, hyperandrogenemia, glucose intolerance
2	S. E.; 18	Primary amenorrhea. hyperprolactinaemia	Congenital atrophy of the anus (after plastic surgery). Alignment of physiological cervical lordosis, minor degenerative changes on the rear edges of cervical vertebrae.	Height: 152 cm, Weight: 41 kg, BMI: 17,75	No vagina	TAS. Corpus uteri is not shown. In the uterus projection, a solid structure with dimensions 16x7 mm. The ovaries on both sides seems to be correct.		In the bladder visible bulge of the bladder wall with a wide pedicle, on the left side at the level of the femoral head	Insulin resistance
3	K. B.; 22	Amenorhoea paraprimaria – single bleeding from the genital tract in the age of 18	Acne	Height: 164 cm, Weight: 48 kg, BMI: 17,85	Vaginal cavity 5 cm lenght, blindly terminated vagina	TVS. The uterus is not shown. The ovaries on both sides correct.		No change	Hyperandrogenemia
4	S. A.; 17	Primary amenorrhea, Hyperandrogenism	Hirsutism, left scoliosis of the borderline of the cervical and thoracic vertebral column from C7, narrowing of the C6-C7 intervertebral space, overly developed transverse processes of the C7 shaft on both sides	Height: 166 cm, Weight: 73 kg, BMI: 26,49	Vaginal atresia, blindly terminated vagina	TAS. Corpus uteri is not shown. The correct structure of the ovaries on both sides.	Dysgenesis of the uterus, ovaries on both sides of the normal structure	No change	Insulin resistance, hyperinsulinemia, hyperandrogenemia,

Table continued

Table I ***(Continued).*** Different types of MRKH syndrome and treatment options adapted to their needs.

No.	Patient name and age	Present history	Concomitant illness	Anthropometric examination	Gynaecological examination	MRI pelvis minor - conclusions	MRI pelvis minor - conclusions	Urography with an ionic contrast media	Laboratory examination
5	K. M.; 21	Primary amenorrhea	Hirsutism, Gilbert's syndrome	Height: 165 cm, Weight: 44 kg, BMI: 16,16	Blindly terminated vagina of 3 cm lenght, the uterus not palpable	TAS. In the uterus projection, a solid structure with dimensions 22x20 mm. The ovaries on both sides are correct.	The correct image of the ovaries. The typical vaginal image is not shown. Corpus uteri absent.	Movable kidneys on both sides.	Hyperandrogenemia, hyperprolaktynemia, yperbilirubinemia
6	M. D.; 18	Primary amenorrhea		Height 158 cm, Weight 52 kg, BMI: 20,83	Blindly terminated vagina of 3 cm lenght, the uterus and ovaries not palpable	TAS. The ovaries on both sides with no changes. Residual uterus.		Minor and major calices and right renal pelvis slightly widened in comparison to the opposite side. In the standing position lowering the height of both kidneys.	Insulin resistance, hyperandrogenemia,
7	D. E.; 21	Primary amenorrhea. Vecchietti vaginal surgery in 2001			Vaginal cavity of 2 cm lenght			Agenesis of the right kidney	
8	J. A.; 18	Primary amenorrhea	Tonsillectomy. Surgery due to hearing loss	Height: 160 cm, Weight: 60 kg, BMI: 23,34	Vaginal cavity up to 1 cm, the uterus not palpable	TAS.The uterus and right ovary is not shown, left ovary 35x22 mm		Ectopic left kidney in the lesser pelvis, right kidney with malrotation without sign of retention	

Table continued

Table I ***(Continued).*** Different types of MRKH syndrome and treatment options adapted to their needs.

No.	Patient name and age	Present history	Concomitant illness	Anthropometric examination	Gynaecological examination	MRI pelvis minor - conclusions	MRI pelvis minor - conclusions	Urography with an ionic contrast media	Laboratory examination
9	K. M.; 20	Amenorhoea primaria	Hirsutism, acne, epilepsy	Height: 162 cm, Weight: 47 kg, BMI: 17,91	Vaginal canal of 1cm depth. Per rectum: the uterus not palpable, left ovaries enlarged, right with no changes,	TAS. Corpus uteri is not shown, the ovaries on both sides with no changes		No change	Hyperandrogenemia
10	L. M.; 23	Primary amenorrhea	Hyperprolactinaemia,	Height: 170 cm, Weight: 58 kg, BMI: 20,07	The vagina of 10 cm lenght, blindly terminated	TAS. In place of the uterine tissue structure 31x14 mm. The endometrium is not shown. Ovaries on both sides of the structure PCO	Structures that may conform to the uterus are not shown. The vagina is fragmentarily visible. Both ovaries with nu-merous vesicles.	No change	Hyperprolactinemia
11	F. M.; 21	Amenorhoea primaria Vecchietti vaginal surgery in 2010	Cholecystolithiasis	Height: 158 cm, Weight: 67 kg, BMI: 26,84	Blindly terminated vaginal canal 1,5 cm. The uterus and ovaries not palpable	TAS. The uterus and ovaries are not shown.	Both ovaries located atypically. A structure of about 2 cm in size - probably the hypoplastic uterus - has been seen.	Right kidney with uneven renal contours, lobed kidney	Hyperprolactinemia, hyperandrogenemia
12	K. E.; 17	Amenorrhea primaria	Frequent infections of the urinary tract, hirsutism, hypothyroidism, stretch marks on the coatings	Height: 154 cm, Weight: 92 kg, BMI: 38,79	At the entrance to the vagina solid connective tissue, the uterus and ovaries not palpable	TAS. The uterus is not shown. In the projection of the left ovarie with dimensions of 21x9 mm, volume 1 ml - small follicles about 1-2 mm in diameter. The left ovary is not visible.	A visible band of unformed uterus. On the left side visible correct ovarian tissue. On the right side, structures suggesting the presence of ovarian tissue are not found.	Suspicion of a bipartite pelvis	Insulin resistance, hyperprolactinemia, hyperandrogenemia

Table continued

Table I ***(Continued).*** Different types of MRKH syndrome and treatment options adapted to their needs.

No.	Patient name and age	Present history	Concomitant illness	Anthropometric examination	Gynaecological examination	MRI pelvis minor - conclusions	MRI pelvis minor - conclusions	Urography with an ionic contrast media	Laboratory examination
13	K. M.; 24	Amenorrhea primaria	Acne	Height: 152 cm, Weight: 52 kg, BMI: 22,51	The vagina of 8 cm lenght, blindly terminated, the uterus is not palpable	TAS. The uterus is not visible. The ovaries on both sides are correct.		No change	Hyperandrogenemia
14	S. J.; 24	Amenorrhea primaria	Appendectomy, removal of right breast fibroadenoma, nephrolithiasis	Height: 171 cm, Weight: 54 kg, BMI: 18,47	The vagina of 3 cm lenght, blindly terminated, the uterus and ovaries are not palpable	TAS. Corpus uteri 27x21 mm. Endometrium 6 mm. Structure of the cervix is not shown. PCO image in the ultrasound examination.	As in the ultrasonography examination	No change	
15	C. D.; 22	Amenorrhoea primaria	Hirsutism	Height: 156 cm, Weight: 52 kg, BMI: 21,37	The vagina of 5 cm lenght, blindly terminated, the uterus and ovaries are not palpable	TAS. The uterus was not visible. In the ovarian projection fragments of banded tissues with follicles up to 3mm			
16	Ch. M.; 18	Amenorrhoea primaria	Retrognatism, cubitus valgus	Height: 153 cm, Weight: 53 kg, BMI: 22,64	No cervix, the ovaries are not palpable	TAS. The uterus is not visible. The ovaries on both sides are correct.		No change	Hyperandrogenemia
17	B. A.; 22		Hypothyroidism	Height: 176 cm, Weight: 60 kg, BMI: 19,37	The vagina of 5 cm lenght, blindly terminated, the uterus and ovaries are not palpable	TAS. The uterus is not visible. The ovaries on both sides with no follicles.			

Table continued

Table I ***(Continued).*** Different types of MRKH syndrome and treatment options adapted to their needs.

No.	Patient name and age	Present history	Concomitant illness	Anthropometric examination	Gynaecological examination	MRI pelvis minor - conclusions	MRI pelvis minor - conclusions	Urography with an ionic contrast media	Laboratory examination
18	N. A.; 27	Amenorrhoea primaria.Operated in 1997 by Vecchietti method		Height: 160 cm, Weight: 70 kg, BMI : 27,34	The vagina of 6 cm lenght, blindly terminated, the uterus not palpable, the ovaries on both sides with no changes	TAS. The uterus is not visible. The policystic struture ovaries.			
19	T. M.; 20	Amenorrhoea primaria.	Appendectomy	Height 160 cm, Weight 58 kg, BMI: 22,66	The vagina of cm lenght, the uterus and ovaries are not palpable	TAS. No uterus. PCO image in the ultrasound examination		Pelvicalyceal system slightly widened	
20	N. N.; 18	Amenorrhoea primaria		Height: 159 cm, Weight: 56 cm, BMI: 22,15	The vagina of 0,5 cm lenght, blindly terminated, the uterus and ovaries are not palpable	The uterus was not visible. Ovaries correct with a few follicles		No change	
21	P. K.; 19	Amenorrhoea primaria	Polidactylia. Syndactylia. Hyperprolactinaemia. Hashimoto disease. Acne	Height 164 cm, Weight 87 kg, BMI: 32,35	Blindly terminated vagina with small entrance, the uterus and ovaries are not palpable	Residual uterus 22x8 mm. Ovaries are correct on both sides.		No change	
22	MURCS, 18		Kliipel - Feil syndrome. Arnold-Chiari syndrome type I. Polidactylia. Plastic surgery of the ureters	Height 156 cm, Weight 66 kg, BMI: 27,12	Hypertrophy of the labia. The ovaries and the uterus are not palpable. Hypoplastic nails			Ectopic left kidney. Lack of right kidney.	Hyperandrogenemia, hyperinsulinemia

Table continued

Table I *(Continued)*. Different types of MRKH syndrome and treatment options adapted to their needs.

No.	Patient name and age	Present history	Concomitant illness	Concomitant illness	Gynaecological examination	MRI pelvis minor - conclusions	MRI pelvis minor - conclusions	Urography with an ionic contrast media	Laboratory examination
23	K. M.; 19	Amenorrhea primaria	Acne	Height: 168 cm, Weight: 50 kg, BMI: 17,72	Blindly terminated vaginal recess of 1,5 cm lenght, the terus and ovaries are not plapable	TVS+TAS. The uterus is not shown. The ovaries on both sides are not shown, in the ovaries' projection no pathological changes	in the vaginal and uterine projection visible residual organs or agenesis. Left ovary correct. Right ovary with an unusual location.	Ectopic right kidney. Malformated and incorrectly developed but non-enlarged diyears olded pelvicalyceal system of the right kidney.	
24	C. J.; 18	Primary amenorrhea, defect of the sexual organ		Height: 156 cm, Weight: 48 kg, BMI: 19,7	Blindly terminated vagina of 3 cm lenght. Per rectum on the right side there is palpable structure of 2 cm lenght not communicated with vagina.	TAS. Endometrium in the corpus uteri on the right side 8 mm, on the left side 10 mm. Right ovary with proper structure with corpus luteum. Left ovary of the correct structure with a few small follicles. In rectovaginal pouch a mediocre amount of free liquid - pouch 19mm	On the right side there is visible the corpus uteri, with endometrium up to 8mm wide. On the left side, there is visible the second corpus uteri with endometrium up to 10mm wide. The ovaries on the right and left side are correct. The vagina is visible fragmentarily at a lenght of about 2.5 cm, blindly terminated.	Correct shape, size and positions of both kidneys.	Insulin resistance, hyperinsulinemia, hyperandrogenemia
25	K. S.; 26	Primary amenorrhea	Obesity	Height: 163 cm, Weight: 83 kg, BMI: 31,23	A blindly terminated vagina of 4 cm lenght. In the long axis of the vagina, a creature that may correspond to the hypoplastic uterus. The ovaries not palpable	TRS. Hipoplastic vagina, 3-4 cm long. Between the bladder and the rectum, a 20x13 mm creation with echogenicity corresponding to the myometrium. The ovaries are correct on both sides			Insulin resistance, hyperinsulinemia, hyperandrogenemia

pus uteri were described as absent and in another two as hypoplastic with marked endometrium.

In the vaginal projection, the organ was described as residual or as partially developed. The size, structure, and location of the ovaries and the texture of their tissue were described as correct in all cases except for two, one where the polycystic ovaries were described, and another where an unusual location of the ovaries was noted. In one patient, there were no structures suggesting the presence of ovarian tissue on the right side. In one of the cases, the presence of an enlarged urethra was described.

Bearing in mind the frequent occurrence of congenital defects of the urinary system in the MRKH syndrome, 20 patients were given urography with an ionic contrast media. In 10 cases, the result of this study was no lesion. In three patients, dilated pelvicalyceal system was described, and in the next three, ectopic position of one kidney in the smaller pelvis was observed. Agenesis of the right kidney was diagnosed in two cases. Similarly, in two cases the occurrence or suspicion of a bipartite pelvis was described. Additionally, isolated cases of the kidney with malrotation and with no signs of urine retention, kidneys with uneven renal contours, lobed distorted kidney, and incorrectly developed but non-enlarged dilated pelvicalyceal system were described.

The results of laboratory tests revealed the occurrence of hyperandrogenemia in the studied group of 10 patients, carbohydrate metabolism disorders in the form of insulin resistance or hyperinsulinemia in 6 patients, hyperprolactinemia in 3 patients, and hypercortisolemia in one patient.

As mentioned above, this syndrome is characterized by the presence of the correct female karyotype 46, XX. In the majority of patients who underwent a cytogenetic examination, a result confirming the presence of a normal karyotype was observed. In the case of one patient the results were 46, XX with interstitial duplication in chromosome 5dup5q35.1.

The patient's family history was not significant, except for the one who reported the occurrence of menstrual disorders or absence of menstruation in her aunt.

All hospitalized patients were offered a consultation with a clinical psychologist.

Conclusions

The MRKH syndrome is a typical example of a total uterine infertility factor. Patients suffering from this syndrome are capable of having genetic offspring but are unable to give birth. Therefore, they become ideal candidates for transplantation of the uterus.

Successful human uterine transplantation was carried out 12 times prior to 2016[42]. In ten cases, the organ was obtained from a deceased donor, and in another two cases from a living donor. In the first case, the uterus was transplanted from an unrelated woman of postmenopausal age[37], and the second donor was the mother of the patient[42]. Both cases led to the birth of a healthy baby. In the same year, the team of Swedish professor Brännström issued a report of the next five live births[43]. Up until 2017, a total of 25 uterine transplant procedures have been published, mainly from living donors, in leading centres of Czech Republic, China, India, Brazil, France, Germany, Serbia, United States, Sweden, and Turkey[44]. This data also included one twin transplantation and one robot-assisted laparoscopy[45]. According to the latest reports from 2018, the number of registered uterine transplants exceeded 37[45,46]. Moreover, more countries have declared their willingness to pursue with further attempts.

Until a few years ago, patients with an absolute uterine factor of infertility, including women with MRKH syndrome, had only two equally controversial options for motherhood – either surrogacy or adoption. However, modern transplantation has shown that a third option – uterine transplantation – exists, is viable, and available for patient use. In the future, additional information about the prognosis and success of uterine transplantation is expected, and long-term effects should also be studied in further detail.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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