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REVIEW PAPER / GYNECOLOGY

Congenital malformations of the female genital organs

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ABSTRACT

Congenital malformations of the female genital organs are rare anomalies and their incidence is estimated to be up to 7% in the general population. Müllerian ducts abnormalities are one of the causes of infertility and occur in approximately 16% of women with recurrent miscarriages. Sex development disorders are diagnosed at different stages of the patient's life depending on the accompanying ailments. Alarming signs of genital malformations include primary amenorrhea or dysmenorrhea, dyspareunia, and periodic abdominal pain.
Keywords: congenital malformations; female genital; uterine septum; mayer-rokitansky-kűster-hauser; androgen insensitivity syndrome syndrome; ohvira syndrome

INTRODUCTION

Congenital malformations of the female genital organs are rare anomalies and their incidence is estimated to be up to 7% in the general population. Müllerian ducts abnormalities are one of the causes of infertility and occur in approximately 16% of women with recurrent miscarriages [1]. Sex development disorders are diagnosed at different stages of the patient's

life depending on the accompanying ailments. Alarming signs of genital malformations include primary amenorrhea or dysmenorrhea, dyspareunia, and periodic abdominal pain.

There are two main classifications of female genital organs defects:

1. European Society of Human Reproducion and Embryology (ESHRE)/European Society for Gynaecological Endoscopy (ESGE) classification (Fig. 1 –3);

Class U0	Correct uterus
Class U1	Dysmorphic uterus: T-shape, child, of another shape
Class U2	Uterus with partial or complete septum
Class U3	Bicornuate uterus partially, completely separated or bicornuate
Class U4	Unicornuate uterus with residual horn or without a residual horn
Class U5	Plastic uterus with residual cavity or without residual cavity
Class U6	Non-classified

Figure 1. Uterine defects distinguished according to the European Society of Human Reproducion and Embryology (ESHRE)/European Society for Gynaecological Endoscopy (ESGE) classification

Class C0	Correct cervix
Class C1	Cervix with septum
Class C2	“Correct” double cervix
Class C3	Unilateral cervix aplasia
Class C4	Cervix aplasia

Figure 2. Cervix defects distinguished according to the European Society of Human Reproducion and Embryology (ESHRE)/European Society for Gynaecological Endoscopy (ESGE) classification

VAGINAL DEFECTS

Class V0	Correct vagina
Class V1	Longitudinal non-closing vaginal septum
Class V2	Longitudinal closing vaginal septum
Class V3	Transverse vaginal septum; obstructed hymen
Class V4	Vaginal aplasia

Figure 3. Vaginal defects distinguished according to the European Society of Human Reproducion and Embryology (ESHRE)/European Society for Gynaecological Endoscopy (ESGE) classification

2. Classification of Müllerian anomalies American Society for Reproductive Medicine (ASRM).

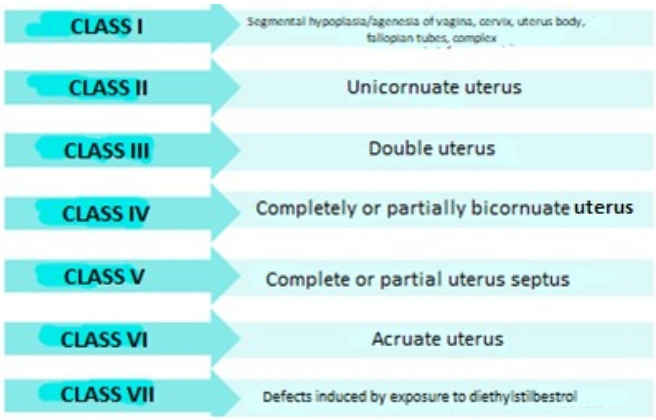

Figure 4. Classification of Müllerian anomalies American Society for Reproductive Medicine (ASRM)

VAGINAL SEPTUM

There are two types of vaginal septum:

1. Transverse — the incidence of this anomaly is estimated at approximately 1:40 000 to 1:84 000 births, so it is a defect that occurs rarely [2]. It is usually located at a height of 2/3 of the upper part of the vagina. A perforated and non-perforated form can be distinguished among the transverse vaginal septum. One of the first alarming symptoms is primary amenorrhea. Importantly, the transverse septum of the vagina is often oligo- or asymptomatic until the first menstrual bleeding occurs. The outflow of

menstrual blood is blocked mechanically, hence very severe, periodic abdominal pain in adolescent girls. Rarely, this defect is recognized as early as in the neonatal period. The main symptom of the disease is then dilation of the uterus and vagina by the accumulating mucous secretion referred to as hydrometrocolpos [2]. The perforated vaginal septum is characterized by less severe adverse symptoms compared to the non-perforated septum. In women with the above-mentioned type of anomaly, menstrual bleeding is prolonged due to the presence of fenestration in the septum compared to healthy women [2];

2. Longitudinal — often diagnosed accidentally during childbirth or during gynecological examination. The main symptom associated with this anomaly is dyspareunia. Often, this defect is so clinically insignificant, asymptomatic and does not bring pain to the patient that its diagnosis occurs accidentally. This anomaly coexists in 25% with the bicornuate uterus [3].

Complications

Lack of menstrual blood outflow results in hematoma in the cavity and cervix. If the surgical intervention is not undertaken quickly enough, then the risk of damage to the fallopian tubes increases significantly, which in the future may lead to fertility problems [4].

Treatment

Treatment of the transverse vaginal septum is based on surgical excision and end-to-end vaginal anastomosis. The procedure is planned when the patient is able to continue treatment with the use of dilators after the surgery. Dilators prevent secondary vaginal narrowing after surgery. The publications also present a method with leaving the catheter 22 after surgery and the use of cream with estrogens, which allows proper healing of the postoperative wound and reduces the risk of postoperative vaginal stenosis. Other methods of surgical removal of the septum include laparoscopic resection and abdominal-vaginal access surgery [4].

NON-PERFORATED HYMEN

This defect occurs with a frequency of about 1 in 1000 women's births [5]. The fetal malformation of the non-perforated hymen is largely manifested only during adolescence in girls. In newborns, the absence of hymen perforation is so oligosymptomatic that this anomaly is rarely diagnosed during this period of life.

Symptoms

Diagnostics of the defect consists in a carefully collected medical history and ultrasound imaging of retained menstrual blood, most often in the uterine cavity and vagina. This can also be seen in the uterine cavity.

The main symptoms reported by young patients are periodic abdominal pain and primary amenorrhea. During the gynecological examination, an organized, mobile at palpation mass and a bruised hymen are noticeable.

Compression of accumulated menstrual blood can lead to problems with urination. In extreme cases, it is possible to develop hydronephrosis and urinary retention leading to acute kidney injury. Other reported symptoms include back pain and constipation problems [5].

Treatment

Treatment involves in-patient surgical incision of the hymen, due to the risk of iatrogenic infection. The following methods of treatment of non-perforated hymen are described in the literature: hymenotomy using electrocoagulation or CO2 laser, possible with a cross or annular incision [5].

CONGENITAL UTERINE DEFECTS

Uterine defects are divided into congenital and acquired. According to studies, congenital uterine defects are the cause of from 7% to 28% of recurrent pregnancy losses [6]. There is a partial septum and a complete septum of the uterus. The screening test is a 2D ultrasound, and in the case of suspected uterine defects, a 3D ultrasound is used. Not only the cavity but also the fundus of the uterus should be assessed in detail. Sonohisterography, hysteroscopy, and laparoscopy are also useful, while magnetic resonance imaging is the gold standard in the diagnosis of genital malformations. A patient with U2 and U5 defects should be diagnosed for concomitant urinary tract defects. One of the more common concomitant defects is renal agenesis, which increases the risk of developing pregnancy-induced hypertension and preeclampsia [6].

UTERINE SEPTUM

The most common cause of approximately 6%-16% among uterine malformations leading to recurrent pregnancy loss is the presence of a septum resulting from a partial or complete lack of resorption of the medial septum between the two ducts before week 20 [6].

The definition of the uterine septum according to the ESHRE classification, as muscular incision depth > 50% differs from the definition according to the ASRM classification. In order to unify the definition of the uterine septum, the Congenital Uterine Malformation by Experts (CUME) group defined the uterine septum as the presence of an incision to a depth of > 10 mm [7]. In addition, this defect should be differentiated with the arcuate uterus, the definition of which is based on the diagnosis of a uterine fundus depression of 1 to 1.5 centimeters.

The presence of a uterine septum, although asymptomatic on a daily basis, is associated with fertility problems. Patients are at increased risk of preterm birth and even pregnancy loss [8]. In this group, more frequent intrauterine limitations of fetal growth and premature separation of the placenta [7] were observed.

Treatment

The gold standard in treatment is hysteroscopic electroresection of the uterine septum. Recent controversial research among women with a history of recurrent pregnancy loss or primary infertility, defined as inability to conceive during the last 12 months, has not shown that the procedure in this group of women increased the number of live births compared to the expectant management. There were also no significant differences in the duration of pregnancy and preterm delivery in women after hysteroscopic electroresection of the uterine septum compared to women who did not undergo this procedure. Removal of the septum reduces the risk of abnormal positioning of the fetus, but does not reduce the risk of pregnancy loss or premature birth [8, 9]. However, in the light of the insufficiently large group of respondents in the above-mentioned study and other limitations, it was decided to maintain hysteroscopic septal resection as the preferred method of treatment in women with a history of obstetric failure who plan a pregnancy [7].

BICORNUATE UTERUS

Similar consequences for abnormal development of pregnancy may coexist as a result of the presence of a bicornuate uterus. The aforementioned uterine anomaly is usually asymptomatic and diagnosed only during pregnancy due to obstetric complications [3]. A pregnant woman with a bicornuate uterus should be monitored due to the proven higher risk of pregnancy loss in the first and second trimester, low birth weight of the newborn or premature birth even before the 28^{th} week of pregnancy [3].

Treatment of bicornuate uterus

Abdominal metroplasty with the Strassman method results in a reduced risk of fetal loss. An alternative to this method is a laparoscopic modification of the Strassman method. Surgical treatment is recommended for women with a history of pregnancy loss [10]. The recommended method of termination of pregnancy is caesarean section due to the significant risk of rupture of the uterus [11]. Yes, Strassman metroplasty increases the chances of maintaining pregnancy by changing the morphology of the uterus, but the patient should be informed about possible late complications of the procedure occurring during the intra-natal period. These include, but are not limited to, an increased risk of anterior or ingrown placenta, as well as life-threatening haemorrhage due to abnormal systolic function and impaired response to vasoconstrictors [11].

UNICORNUATE UTERUS

Unicornuate uterus belongs to only 10% of all uterine defects. It is possible to have a second horn in residual form without a uterine cavity present. Another example of the anomaly is the presence of a residual horn with an active endometrium that does not communicate with the uterine cavity. The consequence of this is painful menstruation and hematoma due to lack of menstrual blood outflow as opposed to the presence of a unicornuate uterus without a residual horn, which is usually asymptomatic. Studies also indicate a higher risk of developing pelvic endometriosis in women with a unicornuate uterus with a residual horn compared to women with a uterus without a functional horn. In the given research groups, there were no differences in the incidence of adenomyosis, although it occurs much more often in patients with a unicornuate uterus compared to women with a properly shaped uterus [12].

Also in this case, the pregnancy of women with a unicornuate uterus is eligible for high-risk pregnancies, due to significantly more frequent miscarriages and a lower rate of live births. Childbirth before the 37th week of pregnancy and termination of pregnancy by caesarean section due to abnormal positioning of the fetus are also more often observed. In addition, the risk of postpartum hemorrhage is higher due to the more frequent occurrence of ingrown placenta [13].

Treatment

Treatment of the uterine anomaly described requires laparoscopic resection of the residual horn. The procedure reduces the risk of an ectopic pregnancy developing first in the

residual horn, which can lead to rupture and life-threatening hemorrhage. A reduced risk of developing adenomyosis after the procedure [12] has also been proven.

DOUBLE UTERUS

The incidence of this defect ranges from 0.3% to 5% in the population. In this group of women, two cervices and an elongated vaginal septum are more common [14]. Double uterus with unilateral obstructed vagina and renal anomaly occurring on the same, usually left side, is referred to as Herlyn-Werner-Wunderlich syndrome or OHVIRA (Obstructed hemivagina and ipsilateral renal anomaly). This is a rare congenital malformation of the Müller ducts. Approximately 92% of cases have renal agenesis, while about 8% have polycystic dysplasia of the kidney [15]. Like other uterine anomalies, it manifests itself in adolescence with severe abdominal pain due to blockage of menstrual blood outflow in the uterine cavity and vagina. Before puberty, girls may report a feeling of a tumor in the vagina and a problem of urinary incontinence. Among patients with OHVIRA syndrome, we can distinguish two types of the disease due to the degree of obstructed hemivagina. Patients with complete vaginal obstruction are at increased risk of developing peritoneal hematoma and fallopian hematoma. On the other hand, in patients with incomplete obstructed hemivagina, symptoms often appear only a few years after the first menstrual period. The complaints reported at that time concern abnormal, often purulent vaginal discharge and symptoms of ascending infection [16]. There is evidence of an increased risk of cancer in patients with OHVIRA syndrome. A higher incidence of adenocarcinoma of the obstructed cervix and clear cell carcinoma of the obstructed part of the vagina has been demonstrated. Magnetic resonance imaging remains the gold standard in diagnostics, as in other defects.

MAYER-ROKITANSKY-KŰSTER-HAUSER SYNDROME

Müllerian duct agenesis occurs at a frequency of 1:5000 live births of women [17]. It is characterized by vaginal and uterine agenesis in women with normal karyotype 46 XX and female phenotype and developed secondary features.

Symptoms

In most cases, the syndrome remains asymptomatic until puberty due to primary amenorrhea despite properly developing secondary features due to retained ovarian function. The ovarian location is atypical, usually lateral due to the absence of the fallopian tubes. Sick women do not only have psychological problems due to problems with gender identification. They also struggle with dyspareunia due to impossible vaginal penetration.
Mayer-Rokitansky-Küster-Hauser syndrome can be classified as:

a) Type 1 classic — isolated uterine and upper vaginal aplasia or residual vagina. The cause of cyclic abdominal pain may be aplastic uterine buds with an active endometrium, which occur in some cases. The residual uterus is subject to pathological processes that may lead to the development of fibroids and adenomyosis and endometriosis;
b) Non-classical type 2 — is associated with extra-genital symptoms. The most common defects are those involving the kidneys, among which unilateral renal agenesis and the less common horseshoe kidney, single kidney and double kidney, are distinguished. Accompanying defects of the skeletal system are ribs aplasia, hemispheric vertebrae and Klippel-Feil syndrome manifested mainly by cervix shortening [17]. Defects of clinical importance are heart anomalies, which include mitral valve regurgitation, pulmonary valve stenosis, atrial septal defect, and aortopulmonary septal defect, the so-called aortopulmonary window.

Type 2 Mullerian duet aplasia, unilateral renal aplasia and cervicothoracic somite dysplasia (MURCS) syndrome includes:

a) Müllerian ducts aplasia;
b) malformations of the urinary system manifesting as a unilateral kidney;
c) anomaly of cervico-thoracic somites.

Very rarely, VACTERL association occurs with Mayer-Rokitansky-Küster-Hauser syndrome, *i.e.* the co-occurrence of defects of the vertebrae, kidneys, heart and limbs as well as anal and esophageal atresia as well as tracheoesophageal fistula [18].

Treatment

Treatment of MRKH syndrome can be divided into invasive and non-invasive treatment. In the first place, we introduce dilator therapy to expand the vaginal recess. Frank's method is a first-line treatment due to fewer complications and relatively high efficacy. It is important to start therapy only at the moment of full awareness and emotional readiness for intercourse by the patient. Invasive treatment involves the production of a vagina to allow for

painless sexual contact. The Vecchietti technique is often performed as a first-line invasive therapy using the constant pressure of the so-called olive to produce the vagina and can be performed from a laparoscopic approach. The Davydov-Moore method uses peritoneal recesses to produce the vagina. It provides great comfort to the patient due to the proper hormonal response and adequate hydration of the neovagina. The McIndoe technique allows you to achieve the result using anthological skin grafting from the buttocks or abdominal cavity. Methods of producing neovagina from the ileum section and oral mucosa [19] are also described. Despite the use of autologous tissues and a low rate of complications, patients after surgery are recommended to continue treatment with dilators due to the possibility of secondary vaginal stenosis.

Another problem that young women suffering from MRKH syndrome have to face is infertility. In 2012, the first successful uterine transplant was carried out, enabling the offspring of patients with the described syndrome to be born [19].

ANDROGEN INSENSITIVITY SYNDROME

The syndrome is the most common cause of gender development disorders in people with the 46 XY karyotype.

The virilization period occurs between the 8th and 14th week of pregnancy. The disorder occurring in the described syndrome occurs as a result of mutation of the androgen receptor gene located on the Xq11-12 chromosome, mostly based on the mother's germline [20].

Symptoms

The syndrome can be divided into the following types:

1. CAIS total androgen insensitivity syndrome — manifested by the female phenotype. There is a development of the external female genital organs — the vagina and labia, while the internal genital organs, *i.e.* the uterus, fallopian tubes and the upper part of the vagina, are not formed. This is due to the conversion of testosterone produced by the current testes to estradiol and receptor insensitivity to androgens. Normal breast development occurs, while low levels of androgens in the blood result in underdevelopment of the nipples. Phenotypic girls are higher than healthy girls due to the gene controlling the growth of GCY present on the Y chromosome, as well as poor pubic and axillary hair and gynoid obesity [20].

The diagnosis of CAIS can be made in the prenatal period after demonstrating the 46 XY karyotype and the presence of male external genitalia or in puberty due to primary amenorrhea. Elevated levels of AMH and testosterone in the newborn's serum raise suspicions. The syndrome is often accidentally diagnosed at the time of inguinal hernia surgery in girls because gonads are present within the inguinal canal in 48% of CAIS cases. In about 35% of cases, the testes are located within the abdominal cavity, while they are rarely detected in the major labia [21];

2. PAIS benign androgen insensitivity syndrome — characterized by residual androgen receptor function, which leads only to partial masculinization of the external genitalia. Patients are brought up as men, therefore the treatment consists in testosterone and dihydrotestosterone substitution. This means that the external genitalia can also vary from enlarged labia to smaller penis size;

3. MAIS partial androgen insensitivity syndrome — this is the mildest and least recognized type. There is masculinization of the genitals, and the presence of micropenis and gynecomastia is the observed abnormality. However, the syndrome often remains asymptomatic, and infertility is the main problem faced by male patients [19]. It is the problem of infertility that is often the first cause of starting diagnostics for gender development disorders.

Treatment

Treatment is not only based on constant psychological care due to the increased risk of depressive disorders and gender identification problems. Due to the increased risk of carcinogenesis after puberty, it is necessary to perform a gonadectomy after puberty process. This has a positive effect on the process of creating phenotypically female characteristics, as well as bone mineralization, osteogenesis and proper functioning of the cardiovascular system [22]. Girls use the aforementioned dilators to widen the vagina due to the short, blindly terminated vagina. Hormone replacement therapy is used in patients after gonadectomy and in children who underwent the procedure before the end of puberty. Currently, in people suffering from CAIS, it is recommended to use estradiol in transdermal form and continue until menopause in healthy women [21]. In order to increase the symptoms of virilization of external organs in patients with PAIS, treatment with high doses of testosterone or dihydrotestosterone is used in the intramuscular or local supply. The maximum effect of

therapy is usually achieved after about six months, after which hormone therapy is used in maintenance doses [20]. Hyperlipidemia should be monitored during hormone therapy.

People suffering from gender development disorders are at an increased risk of developing germ cell tumors. It has been proven that the development of neoplastic lesions depends, among others, on age — the risk of carcinogenesis increases significantly after puberty, which is why laparoscopic gonadectomy is recommended for phenotypic women. If the testicles are left, the risk increases to 50%. Ultrasound is the method of choice for monitoring gonads, while MRI scan [20] is recommended for assessing abdominal gonads.

Defects of external and internal genitalia in girls require in-depth diagnostics. In everyday practice, it is important to perform 2D and 3D ultrasound in the doctor's office, but it should be remembered that the gold standard for the diagnosis of congenital defects of the female genital organs is magnetic resonance imaging due to the possibility existence of concomitant defects. Auxiliary methods include diagnostic laparoscopy, hysterosalpingography or hysteroscopy. Appropriate diagnosis and treatment tailored to the patient's problem not only eliminates pain, but also significantly increases the comfort of life.

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Conflict of interest

The authors declare no conflict of interest.

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