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Modern Capabilities of Radiological and Endoscopic Diagnosis of Müllerian Anomalies

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Annotation: Congenital sexual anomalies often lead to serious disorders of the reproductive system and are associated with a poor prognosis for childbirth. However, in recent years, due to the active development of assisted reproductive technologies, it has become possible to significantly improve reproductive outcomes in infertile patients. The main factor in successful treatment in such cases remains timely and accurate diagnosis of congenital anomalies, as well as well-structured tactics for managing such patients.

The article reviews clinical, instrumental and laboratory diagnostic methods, including ultrasound, MRI, endoscopic methods, as well as molecular genetic studies, which allow not only to identify the anomaly, but also to determine its etiology.

Keywords: congenital anomalies of the development of the genital organs, bicornuate uterus, genetics, diagnostics, uterine and vaginal aplasia.

Introduction.

Müllerian duct anomalies are the most important congenital malformations of the female reproductive system, characterized by morphological and functional abnormalities of the uterus, cervix, and vagina. These pathologies are recognized as the main cause of infertility, recurrent miscarriages, premature births, and other reproductive complications.

In recent years, the rapid development of diagnostic technologies in medicine has created new opportunities for the diagnosis of Müllerian anomalies. In addition to traditional ultrasound and X-ray methods, advanced radiological methods such as three-dimensional ultrasound (3D UTT),

magnetic resonance imaging (MRI), as well as endoscopic methods such as hysteroscopy and laparoscopy significantly increase the accuracy of diagnosis.

In a modern approach, the integrated use of radiological and endoscopic examinations plays an important role in determining the type, degree, and clinical significance of Müllerian anomalies. Therefore, improving diagnostic capabilities, increasing the quality of visualization, and developing individual treatment strategies in this area are among the urgent scientific issues of modern obstetrics and gynecology.

Relevance of the Problem. The problem of human reproductive health encompasses biological, medical, social, and philosophical aspects. The expansion and deepening of scientific research in this area is largely driven by the relevance of demographic issues [1,3,4,6]. In developed countries, special attention is paid to the early diagnosis and prevention of gynecological diseases, which facilitates their prevention and timely treatment.

In Europe, the practice of early screening of women's reproductive health is widespread. If girls aged 12-13 years show no signs of puberty, specialists recommend diagnostic procedures [1,3,4,6]. According to experts, the timely detection of developmental anomalies of the genital organs allows for the correct selection of a treatment strategy, which subsequently contributes not only to a reduction in the prevalence of gynecological diseases but also to an improvement in the quality of life of patients [1,3,4,6].

Comprehensive diagnosis of congenital anomalies of the female reproductive system requires the use of both traditional and modern research methods. To obtain an objective picture of pathological changes, a combination of non-invasive and invasive techniques is used, each playing a specific role in clarifying the clinical diagnosis.

One of the basic tools for primary diagnostics is ultrasound (2D ultrasound), which is widely used as a screening method to detect structural anomalies of the genital organs. This method is highly accessible and safe, and allows for a preliminary understanding of the structural features of the area being examined. However, its diagnostic accuracy is limited and largely depends on the level of training of the specialist performing the examination, as well as the technical characteristics of the equipment [2, 6, 7].

Three-dimensional ultrasound reconstruction (3D ultrasound) demonstrates high diagnostic accuracy and reproducibility of the data obtained. Its use provides advanced visualization capabilities, allowing for a more detailed assessment of the anatomical structure of the lower genital tract, including the cervix and vagina. However, its use is limited by its higher cost and the need for specialized training of the diagnostic physician, making it less accessible than 2D ultrasound [4,7].

Magnetic resonance imaging (MRI) is considered the most reliable method for diagnosing congenital anomalies of the female genital organs. This method provides three-dimensional visualization of the anatomy of the pelvic organs, with the exception of the fallopian tubes, and can detect various malformations, including obstructive anomalies. Despite its high diagnostic accuracy, MRI is an expensive method that requires a qualified specialist to interpret the resulting images, limiting its widespread use [3,8,9]. Echohysterosalpingography (ECHO-HSG) is a minimally invasive diagnostic method for assessing the cervix and uterine cavity. This method is relatively safe, but its accuracy largely depends on the qualifications of the specialist performing the examination. It is important to note that incorrect insertion of a rubber catheter into the uterus can lead to tissue injury, and dilation of the uterine cavity with air and the formation of a balloon in the catheter can misinterpret the internal contours, which in some cases leads to false-positive or false-negative results [46, 48].

X-ray hysterosalpingography (X-ray hysterosalpingography) is used to visualize the uterine cavity and fallopian tubes. Despite its diagnostic value, this method is considered invasive and is associated with discomfort or pain for the patient. The main disadvantage of X-ray

hysterosalpingography is its inability to provide information on the external contour of the uterus, as well as the inability to differentiate an intrauterine septum from a bicornuate uterus. In addition, this method does not allow the detection of an additional closed horn and cannot be used in cases of cervical or vaginal obstruction [4,7].

Hysteroscopy is a minimally invasive diagnostic procedure that allows for a visual assessment of the uterine mucosa, including the cervical canal and vagina. This method provides a high degree of information when examining the internal structure of the uterus, but does not provide information on the external contours of the organ or the thickness of its walls.

Laparoscopy is used for comprehensive visualization of the reproductive organs. Through minimal incisions, it allows for the visualization of pathological processes on the screen and simultaneous surgical correction. However, laparoscopy does not always provide an accurate assessment of the uterine wall thickness.

Therefore, to obtain complete information about the condition of the uterus and its structures, it is advisable to use a combination of various diagnostic methods, including hysteroscopy, laparoscopy, and ultrasound. [1, 2, 4].

In some cases of Mayer-Rokitansky-Küstner-Hauser syndrome (MRKH), one or two additional uterine lesions located in the lateral parts of the pelvis are detected. These rudimentary structures may contain a functional endometrium, causing clinical manifestations such as cyclic pain or hematometra formation. Initial diagnosis typically begins with ultrasound, which can detect the absence of the uterus and vagina, as well as determine the level of vaginal aplasia and the presence of rudimentary uterine structures. However, for a more detailed assessment of the anatomical features and the detection of associated anomalies, magnetic resonance imaging (MRI) is recommended. MRI provides high-quality images, allowing visualization of rudimentary uterine structures, their structure, and the presence of a functional endometrium, as well as assessment of the ovaries, which are often located high in the parietal wall. Furthermore, MRI effectively identifies associated developmental anomalies of the urinary tract, such as a unilateral kidney, pelvic dystopia of the kidney, or duplication of the renal pelvis. Thus, the combined use of ultrasound and MRI ensures accurate diagnosis and allows for the development of optimal management strategies for patients with müllerian agenesis. If the horn consists of fibrous tissue, its structure is characterized by low intensity on T2-weighted images. An important aspect of diagnosis is assessing the relationship of the rudimentary horn to the main uterine cavity, which requires the combined use of HSG and MRI [1, 2, 3, 5, 7].

During hysteroscopic examination, the cavity of a unicornuate uterus is visualized as round, in contrast to the triangular shape typical of a normal uterus. A single fallopian tube opening is a diagnostic marker for this anomaly. In cases of a rudimentary horn that does not communicate with the main cavity, cicatricial retraction is detected at the site of its origin. Laparoscopic examination allows for additional confirmation of the presence of a rudimentary horn, which is typically smaller in size than the main uterus and located laterally, slightly above the internal os [1, 2, 3, 5, 8, 11].

A bicornuate uterus is characterized by the presence of two symmetrical cavities that are partially connected inferiorly, primarily in the area of the uterine isthmus. In some cases, the cavities are separated as far as the internal os. Regardless of the form of this anomaly, a bicornuate uterus typically has a single cervix and maintains communication between the uterine cavities. The most informative diagnostic methods for this anomaly are ultrasound (US) and magnetic resonance imaging (MRI), which allow for clear visualization of both the internal and external contours of the uterus. Unlike hysterosalpingography (HSG), hysteroscopy, and laparoscopy, ultrasound provides a noninvasive and more complete assessment of the organ's anatomical features, especially when using three-dimensional reconstruction. While HSG and hysteroscopy provide a representation only of the internal contours and boundaries of the uterus, laparoscopy only reveals the external boundaries. Therefore, endoscopic methods are

recommended to be used in combination to improve diagnostic accuracy and select the optimal treatment strategy [1, 2, 3, 5].

On ultrasound and MRI, the double uterus and vagina appear as two separate, non-contacting uterine bodies, located separately at a distance. It's also important to be able to diagnose two cervixes. In some cases, patients are diagnosed with a double vagina with a longitudinal septum between the two canals. To differentiate between intrauterine septa, magnetic resonance imaging (MRI) allows for an assessment of the external contour of the uterus: if the external contour is uniform, the diagnosis is more often in favor of an intrauterine septum. If MRI reveals a slight concavity in the fundus, this is a saddle-shaped uterus. If the depression reaches the level of the internal os or extends deeper, a bicornuate uterus is diagnosed.

Contrast enhancement during echosalpingography (ESG), when a substance is injected into each cervix, allows for the visualization of isolated horns, morphologically resembling a unicornuate uterus. However, if the superior contour of the uterus remains continuous, the most likely diagnosis is an intrauterine septum. A slight indentation at the fundus is interpreted as a saddle-shaped uterus, while a pronounced cleft extending to the level of the internal os indicates a bicornuate uterus with two cavities and two cervixes.

Ultrasound does not always allow for a clear distinction between a complete and partial intrauterine septum. Ultrasound, hysterosalpingography, and MRI are used to diagnose a saddle-shaped uterus, which reveals the smooth dilation and flattening of the fundus characteristic of this form. A saddle-shaped uterus is considered a mild variant of a bicornuate uterus; however, there is disagreement among specialists regarding its interpretation and clinical significance. [1,2,3,5,9,12].

Diagnosis of malformations is possible using ultrasound, MRI, echosalpingography (ESG), and hysteroscopy. Laparoscopy, in contrast to these methods, does not provide information on the presence of structural anomalies. The introduction of modern imaging techniques has contributed to an increase in the detection rate of congenital malformations of the uterus and vagina, especially rare forms [1,2,3,5].

Introducing contrast into a separate bilateral cervix during echosalpingography allows the detection of two separate uterine horns, structurally resembling a unicornuate uterus. One pathology that is difficult to differentiate, but has a similar visual picture during hysterosalpingography (HSG), is a complete intrauterine septum. The use of magnetic resonance imaging (MRI) allows for the highly accurate identification of this condition due to the ability to assess the external contour of the uterine fundus, which remains unchanged in the presence of a septum.

Therefore, comprehensive diagnostics of congenital anomalies of the reproductive system is crucial. Comparing the results of various imaging methods, as well as assessing their informativeness and accuracy, allows for an objective understanding of the nature of the anomaly and the selection of optimal patient management strategies [1, 2, 3, 5].

Congenital anomalies and malformations of the genitourinary system are characterized by anatomical and structural changes in the organ itself or its absence in the early stages of fetal development. The etiology of such anomalies can vary and may be related to heredity or gene mutations [1, 2, 3, 5].

Scientists believe that developmental anomalies arise as a result of endogenous and exogenous factors [1, 2, 3, 5, 7, 9].

Many scientists believe that malformations of the genitourinary system are more associated with exogenous factors such as hyperthermia and hypothermia, radiation, chemicals, etc. According to other scientists, 12-24% of genitourinary anomalies are due to gene mutations, chromosomal abnormalities such as translocations or deletions [1, 2, 3, 5], and in 66% of cases, the cause of

genitourinary anomalies remains unclear.

Mayer–Rokitansky–Küstner–Hauser syndrome (MRKH) is of considerable scientific interest because it is characterized by the congenital absence of the uterus, cervix, and upper two-thirds of the vagina in phenotypically normal girls with the 46,XX female karyotype. Agenia or severe hypoplasia of the female reproductive organs can also be observed in a number of rare genetic syndromes, such as McKusick–Kaufman syndrome (mutations in the MKKS gene, localized in the 20p12 region), Bardet–Biedl syndrome (involving MKKS and other genes), Wolf–Hirschhorn syndrome (deletions in the 4p16.3 region), and Goldenhar syndrome. These observations indicate a possible commonality of pathogenetic mechanisms underlying these disorders.[1,6]

The multigeneity of the absence of the vagina and uterus allows for the detection of molecular abnormalities affecting early embryogenesis, during the fusion of the Müllerian ducts. This syndrome is also associated with renal anomalies, as the kidneys also form from the mesoderm [2,3].

Previously, uterovaginal aplasia (MRKH syndrome) was thought to occur primarily sporadically. However, an increasing number of registered familial cases confirm the genetic nature of this condition [1,2,3,5]. In such familial observations, the syndrome is transmitted via an autosomal dominant inheritance pattern with variable expression and incomplete penetrance. This indicates the possibility of mutations in key genes regulating embryonic development, or limited chromosomal abnormalities. According to the literature, only 68 cases of the familial form of MRKH syndrome have been described [1,8].

According to L.V. Adamyan et al. (2008), genetic factors play a significant role both in the pathogenesis of congenital anomalies of the uterus and vagina, and in the development of endometriosis [2,4]. The observed association between müllerian agenesis syndrome and ectopic endometriosis in a number of clinical cases suggests the presence of a common pathogenetic mechanism. A hypothesis has been put forward about the multifactorial nature of these diseases, based on genetic polymorphisms, hereditary predisposition and the influence of hormonal levels, in particular the effect on estrogen and progesterone receptors [11].

Particular attention in the scientific literature has been given to the role of genes of the WNT, HOXA, and PAX families, involved in the processes of embryogenesis of the reproductive system [1,2]. WNT genes, in particular Wnt4 and Wnt9b, play an important role in the formation of the genitourinary system: Wnt4 is involved in sexual differentiation and also regulates the invasion of luminal epithelial cells; Wnt9b is expressed in the epithelium of the Wolffian ducts and promotes elongation of the Müllerian duct [1,2,3,5].

In humans, Wnt4 was the first identified gene associated with uterine dysgenesis and hyperandrogenism. Mutations in this gene lead to impaired suppression of steroidogenic enzyme activity in the ovaries and to pathological expression of 17α-hydroxylase, which causes the development of hyperandrogenism (Biason-Lauber et al.). In a study by Philibert R. et al. (2008) identified mutations causing increased expression of androgen-synthesizing enzymes in 28 girls with primary amenorrhea and uterine and vaginal dysplasia. These data allow us to consider müllerian agenesis syndrome with hyperandrogenism as a distinct clinical variant of the disease [1,9].

At the same time, a study by Ravel C. et al. (2009) failed to identify mutations in the Wnt7a gene in patients with müllerian agenesis syndrome [4,7]. Later, Wang et al. (2014) first reported mutations in the Wnt9b gene associated with the syndrome in a Chinese population. However, subsequent studies did not confirm a consistent correlation between Wnt9b and this disease [10,36]. However, later studies again pointed to the role of Wnt9b in the etiology of MRKH: five heterozygous missense mutations and one heterozygous nonsense mutation were found in patients with type I syndrome, confirming its pathogenetic significance [2,4].

Homeobox genes, particularly the HOX cluster, play a key role in the development of the female reproductive system. Of particular interest are HOXA9–HOXA13 and HOXB9–HOXB13, which are considered potential candidates for the development of müllerian agenesis syndrome [3]. In humans, mutations in HOXA13 or deletions of the entire HOXA cluster can have a significant impact on the development of the genitourinary system and musculoskeletal system. For example, mutations in the coding region of the HOXA13 gene cause palpebral genital syndrome (HFGS), characterized by impaired fusion of the Müllerian ducts, manifested by vaginal mediastinum, cervical duplication, and urinary tract malformations [1, 2, 3, 5].

Interestingly, deletions of the entire HOXA cluster do not result in more pronounced urogenital anomalies than an isolated mutation in HOXA13. This suggests that dominant mutations in HOXA9, HOXA10, or HOXA11, or dysregulated expression of the HOXA cluster genes, affecting transcription rates and spatiotemporal patterns of their activity, may play a key role. Recent data on mutations in the HOXA13 promoter region further support this hypothesis [1,7].

The expression of individual HOXA genes varies depending on the anatomical site: HOXA9 is predominantly active in the fallopian tubes, HOXA10 and HOXA11 in the uterine body and cervix, and HOXA13 in the distal vagina. In addition, the WT1, PAX2, HOXA7–13, and PBX1 genes are also considered potential candidates for the etiology of müllerian agenesis syndrome. However, experimental studies using mutant mouse models have not yet confirmed their definitive involvement in the development of this pathology [1,2,3,5].

Of particular interest are clinical cases in which müllerian agenesis develops in only one of the identical twins, while the other remains phenotypically healthy. This indicates a possible role of not only genetic, but also epigenetic and environmental factors in the pathogenesis of the disease [3]. In the study by Rail et al. (2011), significant differences in the levels of transcription and DNA methylation were identified between patients with müllerian agenesis and the control group. Genomic analysis allowed us to identify nine key genes: HOXA5, HOXA9, WISP2, CDH5, PEG10, MFAP5, LRRC32 and RALGPS2. Six of them (CDH5, MFAP5, WISP2, HOXA5, PEG10, HOXA9) demonstrate significant activity in the development of structures of the female reproductive system. Network bioinformatics analysis revealed that WISP2, HOXA5, HOXA9, GATA4, and WT1 may be central regulators, suggesting a leading role in the pathogenesis of MRKH syndrome [1,3].

The WT1 and GATA4 genes are involved in the regulation of sexual differentiation by influencing the expression of anti-Müllerian hormone (AMH). Their activity promotes the production of anti-Müllerian hormone (AMH), which initiates the degeneration of the Müllerian ducts and plays a key role in the development of the female reproductive system [2].

According to Rail et al. (2011), excessive estrogen exposure combined with ectopic expression of the HOXA cluster genes may contribute to hypoplasia of the female genital organs and the development of MRKH syndrome [9]. In turn, De Tomasi F. et al. (2017) described clinical cases of uterine and renal aplasia, as well as developmental disorders of both the urinary and reproductive systems, which confirmed the significance of the GREB1L gene (previously designated as GREB1F) in the pathogenesis of these anomalies [2,4,6]. Later, Herlin M.K. et al. (2019) identified GREB1L as a promising candidate gene involved in the etiology of MRKH syndrome [5,8].

Several studies have found an association between developmental anomalies such as bicornuate uterus and Müllerian duct dysplasia and mutations in the TCF2 gene (also known as HNF1B). Defects in this gene may explain rare cases of congenital aplasia, particularly when combined with renal developmental abnormalities or a family history of diabetes, making it an important target for further study of the genetic association with MRKH syndrome [1,5].

Furthermore, some authors point out that a significant number of disorders of sexual development are caused by chromosomal abnormalities affecting regions of chromosomes 1–7,

10–18, 22, and the X chromosome. However, according to the generalized results of a number of genomic studies, only five recurring structural rearrangements (deletions and duplications) were identified with high frequency: 1q21.1, 16p11.2, 17q12, 22q11.21 and Xp22. These anomalies were detected in 28 patients with MRKH syndrome and account for approximately 10% of all registered cases of the disease. [1,2,3,5,9,10].

Conclusion

Müllerian anomalies are congenital malformations resulting from complete or partial nonunion, resorption, or impaired differentiation of the Müllerian ducts during embryonic development of the female reproductive system, which have a serious impact on reproductive health. The correct and early detection of these anomalies relies on the integrated use of modern radiological and endoscopic methods.

In recent years, radiological methods such as three-dimensional ultrasound (3D UTT), magnetic resonance imaging (MRI), hysterosalpingography (HSG) have made it possible to assess uterine and vaginal structural changes with high accuracy. At the same time, endoscopic methods such as hysteroscopy and laparoscopy are of great importance not only for diagnosis, but also for therapeutic interventions.

A combined approach of radiological and endoscopic diagnostics is the most effective way to differentially diagnose Müllerian anomalies, determine their type and extent, and determine the strategy for further reproductive treatment.

Thus, modern radiological and endoscopic diagnostics of Mullerian anomalies is one of the main clinically important areas in the prevention of female infertility, recurrent fetal loss, and obstetric complications.

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