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GENETIC MECHANISMS AND CLINICAL AND DIAGNOSTIC FEATURES OF CONGENITAL ANOMALIES OF SEXUAL DEVELOPMENT

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Abstract
Infertility is often caused by congenital anomalies of sexual development and is associated with an unfavorable reproductive prognosis. In recent years, the development of assisted reproductive technologies has significantly improved the reproductive prognosis of infertile patients. Improvement of reproductive prognosis in congenital anomalies of sexual development largely depends on timely diagnosis of anomalies and rational management of patients

Keywords: Congenital anomalies of genital development, bicornuate uterus, genetics, diagnosis, aplasia of uterus and vagina.

Introduction

The problem of human reproduction is closely intertwined with biological, medical, social, and philosophical aspects. The expansion and deepening of research in this area is associated with an unfavorable demographic situation [1,3,4,6]. In Europe, doctors are widely practicing by not waiting for women to reach 15-20 years of age, but rather beginning examinations earlier, at 12-13 years of age, if signs of sexual maturation are absent by this time [1,3,4,6]. According to these researchers, only early diagnosis of factors that naturally impair the development of reproductive organs guarantees the appropriate selection of a treatment strategy, which will subsequently contribute not only to a reduction in gynecological morbidity, but also to an increase in the quality of life for such patients [1,3,4,6].

To obtain a complete anatomical picture of a particular malformation of the uterus and vagina, a comprehensive approach using several non-invasive and/or invasive diagnostic methods is necessary. Initially, ultrasound is used as a screening tool to obtain a visual picture – 2D ultrasound is used for all malformations of the female genital organs. This method is simple, non-invasive, and accessible, and provides essential information

about the anatomical features of the malformation. However, the results of this method depend on the physician's experience and technical equipment [2, 6, 7].

Ultrasound with three-dimensional reconstruction (3D ultrasound) has good reproducibility, a high level of accuracy, provides additional and more reliable images, and allows for evaluation of the

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cervix and vagina. However, it is less accessible and requires more specialized training than 2D ultrasound [4, 7].

MRI is the gold standard in diagnosing female genital anomalies, as it provides objective and reliable three-dimensional information about the anatomy of the genital organs and peritoneum, with the exception of the fallopian tubes. MRI can be used in all cases of diagnosing malformations of the uterus and vagina, including obstructive malformations, but also for malformations of other organs and systems. This method is more expensive and less accessible, and requires a qualified specialist to interpret the results [3, 8, 9].

Echohysterosalpingography (ECHO-HSG) is a minimally invasive method that provides information about the condition of the cervix and uterine cavity, but its effectiveness also depends heavily on the qualifications of the examiner. Trauma from improper placement of an intrauterine catheter and dilation of the uterine cavity during this procedure can alter its internal contours, thereby leading to false-negative results [46, 48].

X-ray hysterosalpingography (X-ray hysterosalpingography) provides information only about the uterine cavity and fallopian tubes. X-ray hysterosalpingography is an invasive and painful examination. This diagnostic method does not allow for assessing the external contour of the uterus, differentiating between an intrauterine septum and a bicornuate uterus, does not provide information about the presence of a rudimentary closed horn, and cannot be used for vaginal and/or cervical obstruction [4,7].

Hysteroscopy is a minimally invasive procedure that provides reliable information about the condition of the vaginal walls, cervical canal, and uterine cavity, although it does not assess the external contours or thickness of the uterine wall. To assess the external contour of the uterus, the structure of the peritoneum, and concomitant genital diseases, an invasive method, laparoscopy, is used both for visual diagnostics and for immediate treatment. Laparoscopy does not allow for assessment of uterine wall thickness and relies entirely on the surgeon's experience and subjective assessment, as well as the two-dimensional image obtained through hysteroscopy [1, 2, 4].

Uterine and vaginal aplasia is sometimes associated with the presence of one or two uterine rudiments, most often located on the lateral pelvic walls, in which functioning endometrium may be detected. Diagnosis in such patients is primarily based on ultrasound data. Patients with uterine and vaginal aplasia may have associated genital pathologies, such as external genital endometriosis and ovarian tumors. This defect is also associated with developmental anomalies of the urinary tract, skeleton, hearing, and heart [2, 6].

MRI is used to further clarify anatomical structures and detect genital/extragenital pathology. Diagnostic MRI images do not show the uterus and vagina, but rather visualize muscular ridges—uterine rudiments. The ovaries are typically located high in the parietal wall. In some cases, a single normal kidney or pelvic dystopia is detected, less commonly, a duplication of the kidney or duplication of the renal pelvis [1, 2, 3, 5].

Diagnosis of vaginal aplasia with a functioning uterus begins with ultrasound, which allows for the detection of hematometra and/or hematocolpos, as well as the determination of the extent of the aplastic portion of the vagina. In complete vaginal aplasia, hematometra and hematosalpinx are visualized, and often endometrioid ovarian cysts are seen, while in partial vaginal aplasia,

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hematocolpos is seen. MRI allows for more extensive imaging, the possibility of suspecting extragenital pathology, and a reliable diagnosis [1, 2, 3, 5].

A diagnosis of unicornuate uterus is initially made using ultrasound, which reveals an elongated uterine body and a single fallopian tube extending from it. A rudimentary horn may sometimes be suspected [1, 2, 3, 5, 7, 10].

A unicornuate uterus can also be diagnosed using hysterosalpingography (HSG), but this only provides information about the spindle-shaped uterine cavity, tapering at the apex and often displaced toward the pelvis. Overall, the picture resembles a single horn of a bicornuate uterus. The presence of a rudimentary horn not communicating with the main cavity cannot be detected using HSG. MRI reveals two separate uterine horns, clearly separated by myometrial tissue. The smaller uterine horn is considered rudimentary. A communicating rudimentary horn of a unicornuate uterus should be identified as filled with contrast material on HSG or visualized on MRI [1, 2,3,5,9,10,11].

A rudimentary horn in a unicornuate uterus can be functional (containing endometrium) or nonfunctional (containing fibrous tissue). When endometrium is present in the rudimentary horn (cavity), MRI reveals an area of increased echogenicity. A

nonfunctional rudimentary horn reveals fibrous tissue and a low signal on T2-weighted MR images. As discussed previously, a rudimentary horn in a unicornuate uterus may or may not communicate with the main uterus; therefore, a combination of HSG and MRI helps establish a definitive and correct diagnosis [1, 2, 3, 5, 7].

On hysteroscopy, the cavity of a unicornuate uterus is round, unlike the normal triangular shape. A single fallopian tube orifice is visible. If a closed rudimentary horn is present, a characteristic cicatricial retraction is observed at the origin of the horn. During laparoscopy, a rudimentary horn is determined, which is smaller in size than the main uterus and extends slightly above the internal os, located on the lateral side [1, 2,3,5,8,11].

A bicornuate uterus has two symmetrical uterine cavities that merge caudally and have a small connection between the two cavities, usually at the isthmus. Another variant of a bicornuate uterus is divided to the internal os. In both variants, there is a single cervix and a connection between the cavities. A bicornuate uterus can be diagnosed using both ultrasound and MRI. These methods allow for an assessment of both the internal and external contours of the uterus. This cannot be said of HSG, hysteroscopy, and laparoscopy, as in the first two cases, visualization is limited to information on the uterine cavity, while in the third case, it is limited to the external contour of the uterus, which can impact treatment tactics and outcomes. Accordingly, endoscopic methods should be used in combination [1, 2, 3, 5]. Uterine and vaginal duplication on ultrasound and MRI images reveals two separate uterine bodies, not communicating with each other and located widely apart, two cervixes, and two vaginas separated by a longitudinal septum. A single uterine cavity, divided by a partial or complete intrauterine septum, is differentiated using MRI based on the external contour of the uterine body. If the external contour of the uterine cavity is represented by a single structure, the diagnosis is in favor of an intrauterine septum; if there is a small cleft, the diagnosis is in favor of a sciatic uterus; if the cleft extends deeper or to the internal os, the diagnosis is in favor of a bicornuate uterus.

Injecting a contrast agent into each individual cervix during ECE allows for the identification of two separate uterine horns, resembling a unicornuate uterus in morphology [1, 2, 3, 5, 8].

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Another unusual anomaly that may have a similar appearance on hysterosalpingography is a complete intrauterine septum. MRI allows us to distinguish between a complete septum, which has a normal fundal contour, and a duplex uterus with
widely separated uterine horns and two cervixes. Furthermore, ultrasound cannot detect this developmental defect and differentiate between a complete and incomplete intrauterine septum [1, 2, 3, 5].

A saddle-shaped bicornuate uterus is identified by ultrasound, hysterosalpingography, and MRI based on the presence of a soft, wide protrusion in the fundus. Due to the presence of an indentation in the upper portion of the uterus, this anomaly is often considered a mild form of bicornuate uterus. Expert opinions regarding a saddle-shaped uterus vary: some believe that a saddle-shaped uterus is assessed based on its external contour, while others believe that it is based on its internal contour [1, 2, 3, 5, 9, 12].

T-shaped uterine cavity can be diagnosed using ultrasound, MRI, ECE, and hysteroscopy. Laparoscopic imaging in this case does not provide any information regarding the presence of a malformation. The introduction of new imaging techniques in recent years has increased the detection rate of uterine and/or vaginal malformations, particularly rare ones [1, 2, 3, 5]. Thus, it is necessary to use a comprehensive approach for visual diagnosis of each developmental defect, to assess the correlation between the results of different research methods and their diagnostic accuracy, which will allow for the subsequent selection of the correct method and extent of treatment.

Congenital anomalies or malformations are anatomical and morphological changes in an organ that occur early in utero. The causes of congenital malformations are quite varied. They can be caused by mutations, as well as their combined effects [4,5]. Many researchers believe that intrauterine malformations are caused by both hereditary (endogenous) and environmental (exogenous) factors [1, 2, 3, 5].

Other authors have demonstrated in their studies how the influence of adverse external factors on the fetus (hypoxia, hyper- and hypothermia, ionizing radiation, chemical compounds, pathogenic microbes, and alcohol) can cause the development of genital malformations [1, 2, 3, 5, 7, 9]. According to various authors, congenital malformations in 13-25% are caused by genetic reasons (monogenic defects - autosomal and sex-linked), multifactorial disorders (caused by a combination of genetic and environmental factors) and chromosomal mutations in the form of translocation, deletion, duplication and inversion, in 10% of congenital disorders are caused by external factors, and in 65% of cases the cause of the disorder cannot be established [1, 2,3,5].

Genetic studies of patients with uterine and vaginal malformations allow us to assess the type of hereditary disorder and predict the likelihood of future generations with developmental defects [1, 2, 3, 5].

Despite the extensive research devoted to the etiology and pathogenesis of female genital malformations, unresolved issues remain. Currently, geneticists are focusing their efforts on identifying the genes responsible for these defects. Of greatest scientific interest is uterine and vaginal aplasia syndrome. It is characterized by the congenital absence of the uterus, cervix, and vagina in phenotypically normal girls with a 46, XX karyotype. Agenesis of the female genital organs can also occur in combination with other rare syndromes, such as McKusick-Kaufman

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syndrome (MKKS gene, locus 20p12), Bardet-Biedl syndrome (MKKS gene, locus 20p12 and several other genes on different chromosomes), Wolf-Hirschhom syndrome (deletions of chromosome 4p16.3), and Goldenhar syndrome, which may indicate common etiological factors [1,6].

Heterogeneity of uterine and vaginal aplasia suggests the presence of molecular defects in the development of internal organs that are closely linked during embryogenesis. Indeed, uterine and vaginal aplasia manifests as a result of damage occurring at 5-6 weeks of gestation, affecting the intermediate mesoderm and leading to fusion of the Müllerian ducts. The renal system also develops from the mesoderm, which explains the renal agenesis or ectopia often associated with aplasia of the uterus and vagina [2,3].

For a long time, the syndrome was considered a sporadic anomaly, but the increasing number of familial cases supports the hypothesis of a genetic etiology [1, 2, 3, 5].

In familial cases, the syndrome is transmitted as an autosomal dominant trait with incomplete penetrance and variable expression. This suggests the involvement of either mutations in the main developmental gene or a more limited chromosomal imbalance. According to the author, only 68 cases of familial SMRKH have been registered [1, 8].

According to L.V. Adamyan et al. (2008), genetic factors play an important role not only in the embryogenesis of uterine and vaginal malformations but also in the etiopathogenetic mechanisms of endometriosis formation [2, 4]. Analyzing the data and various clinical cases on the combination of MRKH syndrome with external and internal endometriosis, a group of authors noted the relationship between these diseases and

suggested that they are multifactorial diseases, the causes of which may be genetic polymorphisms, heredity, hormonal influences on estrogen and progesterone receptors [11].

The key role of the WNT, HOXA, and PAX genes, which play a significant role in the embryonic development of the genitals, is widely debated in the literature [1, 2].

The WNT family includes a group of genes involved in embryonic development. Furthermore, WNT genes play a well-established role in the development of the mammalian urogenital system [1, 2, 3, 5].

Among several genes in this group, Wnt4 is the major sex-determining gene and is required for the invagination of coelomic epithelial cells, while Wnt9b is expressed by the epithelium of the Wolffian ducts and promotes the elongation of the Müllerian ducts [1, 2, 3, 5].

In humans, Wnt4 was the first gene associated with uterine developmental defects and concomitant hyperandrogenism. A Wnt4 mutation inhibits the repression of ovarian steroid enzymes and causes abnormal expression of 17a-hydroxylase, causing hyperandrogenism in these patients. In their studies, Biason-Lauber et al. identified mutations in the Wnt4 gene in only four patients with uterine and vaginal aplasia and hyperandrogenism [1, 2, 3, 5, 8, 9].

In a study by Philibert R. et al. (2008), functional DNA analysis was performed in 28 adolescent girls with primary amenorrhea and uterine and vaginal aplasia. It was shown that the mutation induces significantly increased expression of enzymes involved in androgen biosynthesis (3beta-hydroxysteroid dehydrogenase and 17alpha-hydroxylase). Therefore, it was proposed that müllerian agenesis syndrome with features of androgenization due to heterozygous Wnt4 mutations is a distinct clinical entity that can be distinguished from classical müllerian agenesis [1, 9].

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Interestingly, Ravel S. et al. (2009) did not observe mutations in the Wnt7a gene, which typically cause various limb malformations with additional genitourinary malformations, in a study with müllerian agenesis [4,7].

In 2014, Wang and colleagues reported the first Wnt9b mutation associated with müllerian agenesis in a Chinese population; however, another study did not confirm this association [10, 36].

A possible role of Wnt9b mutations in müllerian agenesis was identified in a recent study, in which the authors found five heterozygous missense mutations and a heterozygous nonsense mutation in patients with müllerian agenesis type 1 [2,4].

Homeobox-containing genes belong to a large family that includes the HOX clusters. Several Hoxa genes (Hoxa 9-13 and Hoxb 9-13) play a crucial role in the development of the female reproductive tract and are therefore considered putative candidates for the development of müllerian agenesis [3].

In humans, mutations in the Hoxa 13 gene or deletions of the HOXA gene cluster primarily affect the genitourinary tract and skeleton. Mutations in the coding region of Hoxa 13 cause hand-foot-and-mouth syndrome (HFGS), which is characterized by defects in Müllerian duct fusion in women (ranging from the longitudinal septum of the vagina to duplication of the uterus and cervix) and malformations of the urinary tract in women [1, 2, 3, 5].

Surprisingly, deletion of the entire HOXA cluster does not cause more urogenital anomalies than single monoallelic mutations in Hoxa 13. This suggests that either monoallelic dominant mutations in Hoxa 9, Hoxa 10, or Hoxa 11 may be the cause of MRKH syndrome, or other mechanisms may be involved, such as aberrant regulation of HOXA genes affecting either transcription rate or spatiotemporal expression: the recent discovery of a mutation in the Hoxa 13 gene promoter supports this hypothesis [1,7].

Hoxa 9 is expressed in the fallopian tubes, Hoxa 10 in the uterus, Hoxa 11 in the uterus and cervix, and Hoxa 13 in the upper vagina [1,8]. Genes with broad activity in early development (e.g., WT1, PAX2, Hoxa 7, Hoxa 13, and PBX1) have also been proposed as candidates based on the observed phenotypes in mutant mice. However, their role in müllerian agenesis has not been subsequently demonstrated [1, 2, 3, 5].

Of scientific interest, one monozygotic twin develops müllerian agenesis while the other does not, suggesting that the disease is due to differences in phenotype. Thus, the
pathogenetic mechanism of müllerian agenesis may involve epigenetic changes mediated by environmental factors [3].

Rail et al. (2011) investigated differences in transcription products and methylation levels between patients with SMRKH and healthy volunteers using genome-wide analysis. By evaluating two gene clusters, nine potentially causative genes [Hoxa 5, Hoxa 9, WISP2, CDH5, PEG10, MFAP5, LRRC32, RALGPS2] were identified. Six of these genes (CDH5,
MFAP5, WISP2, Hoxa 5, PEG10, and Hox 9) are involved in female genital tract development. Subsequent network analyses identified WISP2, Hox 5, Hox 9, GATA4, and WT1 as key genes in SMRKH [1,3]. WT1 and GATA4 regulate sex determination and differentiation via anti-Müllerian hormone (AMH). WT1 and GATA4 promote AMH expression, leading to Müllerian duct degeneration [2].

Rail et al. (2011) suggested that excessive estrogen exposure and ectopic expression of HOXA may lead to hypoplasia of the female genital organs and cause müllerian agenesis [9].

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De Tomasi et al. (2017) described cases of females with uterine aplasia and renal aplasia in their study, confirming that the GREB1F gene plays an important role in the development of the kidneys and female genital tract [2,4,6].

M.K. Herlin et al. (2019) argue that GREB1F is a new and promising candidate gene in the etiology of müllerian agenesis [5,8]. Interestingly, genital malformations such as bicornuate uterus and Müllerian duct aplasia have occasionally been found in association with renal anomalies in some familial cases displaying mutations in the TCF2 gene. Defects in this gene may thus explain some rare cases of genital malformations, including aplasia, making this gene one of the candidates confirming a genetic link to SMKH, but limited to familial cases with a renal and/or diabetic history [1,5].

Other authors have reported that a significant proportion of disorders of sexual development are etiologically associated with chromosomal abnormalities and affect chromosomes 1-7, 10-18, 22, and X. However, a comparison of the results of various studies revealed only five recurring deletions/duplications in the chromosomal regions lq21.1, 16pll.2, 17ql2, 22qll.21, and Xp22.

Overall, these changes were detected in 28 patients with SMRKH and account for approximately 10% of SMRKH cases [1, 2, 3, 5, 9, 10].

Conclusion

Congenital defects of the genital organs are the result of the interaction of genetic, epigenetic and environmental factors that occur during the complex embryological development of the human reproductive system. They are based on chromosomal abnormalities (e.g. Turner, Klinefelter syndromes), gene mutations, as well as disorders of gonadal differentiation and hormonal regulation.

Modern molecular genetic diagnostic methods - in particular, karyotype analysis, PCR, FISH, genetic sequencing and CGH-array technologies - play an important role in the early detection of these pathologies, the identification of phenotype-genotype relationships and the development of individual treatment strategies.

In the process of clinical diagnosis, the complex use of morphological assessment of the external and internal genital organs, ultrasound, MRI, hormonal tests and genetic studies allows for an accurate differential diagnosis.

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