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MALE INFERTILITY: ETIOLOGY AND PATHOGENESIS

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Abstract:

Male infertility is a complex and multifactorial condition that affects approximately half of couples with reproductive problems. The etiology of the disease includes genetic abnormalities, endocrine disorders, inflammatory and infectious processes, anatomical and obstructive disorders, immunological factors, as well as lifestyle and environmental influences. The pathogenesis of male infertility is associated with impaired spermatogenesis, hormonal imbalance, oxidative stress, sperm DNA fragmentation, and immunological damage. Despite advances in molecular genetics and reproductive medicine, a significant proportion of cases remain idiopathic, highlighting the need for further research. This review summarizes current data on the causes and mechanisms of male infertility, emphasizing current concepts, diagnostic challenges, and prospects for clinical and experimental research.

Keywords: Male infertility, etiology of infertility, pathogenesis of infertility, spermatogenesis, genetic factors of infertility, oxidative stress, hormonal regulation, epigenetics of infertility.

INTRODUCTION. Male infertility is a leading problem in reproductive medicine, affecting a significant number of couples of reproductive age. According to the World Health Organization, approximately 10–15% of couples experience infertility, and in half of these cases, the primary or contributing factor is related to male reproductive dysfunction [1].

In recent years, there has been a trend toward a decline in sperm quality parameters, including sperm concentration, morphology, and motility, as confirmed by large population studies and meta-analyses [5]. The main causes of decreased fertility are considered to be genetic and endocrine disorders, inflammatory and infectious diseases, as well as exogenous and behavioral factors, including smoking, obesity, occupational hazards, and environmental exposures [9–7].

Contemporary research highlights the importance of molecular and epigenetic mechanisms that influence spermatogenesis and sperm quality, including DNA methylation abnormalities, microRNA expression, and histone modifications [15, 22]. Particular attention is paid to the role of oxidative stress, immunological processes, and sperm DNA damage in the development of idiopathic male infertility [13, 23].

Despite advances in diagnosis and treatment, a significant proportion of male infertility cases remain unexplained. This underscores the need for a systematic study of the etiology and pathogenesis of male reproductive dysfunction using modern molecular, genetic, and clinical methods.

The aim of this review is to summarize and analyze current data on the causes and mechanisms of development of male infertility, including genetic, endocrine, immunological, inflammatory, anatomical and exogenous factors, and to consider new perspectives of diagnosis and treatment.

Concept and classification of male infertility.

Male infertility is defined as the inability of a man to conceive after regular, unprotected sexual intercourse for at least 12 months. This condition is heterogeneous in origin and clinical manifestations, necessitating a multi-level classification. Modern approaches to classifying male infertility are based on pathogenic mechanisms, the location of the disorder, and the degree of impairment of spermatogenesis.

Clinically, a distinction is made between primary and secondary male infertility. Primary infertility is diagnosed in men whose partners have never conceived, while secondary infertility develops after previously achieved fertility and is more often associated with acquired factors, including inflammatory diseases, surgical interventions, and metabolic disorders [1].

Depending on the underlying mechanism of development, the following forms of male infertility are distinguished: secretory infertility caused by impaired spermatogenesis in the testicles; obstructive infertility associated with impaired patency of the vas deferens with preserved sperm production; immunological infertility associated with the formation of antisperm antibodies; combined forms in which several pathogenetic mechanisms are simultaneously present. An additional classification based on spermogram parameters is used, including oligozoospermia, asthenozoospermia, teratozoospermia, azoospermia, and their combinations. This approach is important for determining the prognosis and choosing treatment

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tactics, including assisted reproductive technologies (ART) [1].

Etiology of male infertility.

The etiology of male infertility is multifactorial and includes genetic, endocrine, inflammatory, anatomical, immunological, and exogenous factors. In some cases, a specific etiological factor cannot be identified, allowing the disease to be classified as idiopathic.

Genetic factors. Genetic disorders play a key role in the development of severe forms of male infertility, particularly azoospermia and severe oligozoospermia. According to modern research, genetic causes are found in 15–25% of men with spermatogenesis disorders [13].

The most studied chromosomal abnormalities are those associated with Klinefelter syndrome (47,XXY). Patients with this syndrome experience progressive testicular failure, hypogonadism, and a marked reduction or complete absence of spermatogenesis. The incidence of Klinefelter syndrome among men with azoospermia reaches 10–12% [14].

Microdeletions of the AZF locus of the Y chromosome, including the AZFa, AZFb, and AZFc regions, are of significant clinical significance. Deletions of these regions lead to disruption of germ cell differentiation and arrest of spermatogenesis at various stages. AZFa and AZFb deletions are generally associated with an unfavorable prognosis, whereas with AZFc, sperm can be obtained through testicular biopsy and ART can be used [18].

Since 2020, the field of identifying monogenic forms of male infertility has been rapidly developing. The use of next-generation sequencing has enabled the identification of mutations in genes responsible for meiosis, sperm flagellum formation, and mitochondrial function. These data significantly expand our understanding of idiopathic infertility and form the basis for personalized diagnostics [6].

Endocrine causes. Endocrine disorders account for 5–10% of male infertility cases and are associated with dysfunction of the hypothalamic-pituitary-gonadal axis. Gonadotropins—follicle-stimulating hormone (FSH) and luteinizing hormone (LH), as well as testosterone—play a central role in regulating spermatogenesis. Hypogonadotropic hypogonadism is characterized by reduced gonadotropin secretion and can be congenital or acquired. FSH deficiency leads to impaired Sertoli cell function, while LH deficiency reduces testosterone production by Leydig cells, which negatively impacts all stages of spermatogenesis [10].

Hypergonadotropic hypogonadism develops with primary testicular damage and is accompanied by elevated gonadotropin levels against a background of decreased testosterone production. This condition is often observed in genetic syndromes, toxic exposures, and following inflammatory diseases. Thyroid dysfunction, hyperprolactinemia, and metabolic disorders, including obesity and insulin resistance, are also significant, indirectly affecting hormonal balance and reproductive function in men [16].

Infectious and inflammatory factors. Inflammatory diseases of the male reproductive system are a significant cause of secondary infertility. Orchitis, epididymitis, prostatitis, and urethritis can lead to testicular damage, obstruction of the vas deferens, and deterioration of sperm quality. Sexually transmitted infections, including chlamydia, gonorrhea, and mycoplasma, are particularly significant. Chronic inflammation is accompanied by increased levels of proinflammatory cytokines and activation of oxidative stress, which negatively impacts sperm and their DNA [8].

Anatomical and obstructive causes. Varicocele is one of the most common anatomical causes of male infertility, diagnosed in 15–20% of men in the general population and up to 40% of patients with primary infertility. The pathogenic mechanisms of varicocele include impaired venous outflow, increased scrotal temperature, hypoxia, and increased oxidative stress. Obstructive infertility can also be associated with congenital absence of the vas deferens, post-inflammatory strictures, and the consequences of surgical interventions. In this case, spermatogenesis may be preserved, but sperm transport is impaired [20].

Immunological factors of male infertility. Immunological male infertility is considered a specific form of reproductive dysfunction, in which fertility impairment is caused by the development of autoimmune reactions against one's own sperm. Normally, spermatogenic cells are isolated from the immune system by the functioning of the blood-testicular barrier. Damage to this barrier leads to contact between sperm antigens and immune cells, activating autoimmune mechanisms [11].

The key pathogenetic factor in this form of infertility is the formation of antisperm antibodies (ASA), which can be detected in seminal plasma, serum, and on the surface of sperm. ASA impair sperm motility, promote agglutination, and interfere with the acrosomal reaction and sperm-oocyte interaction [3].

The development of immunological infertility is facilitated by inflammatory diseases of the scrotum, testicular trauma, surgical interventions, varicoceles, and infections associated with the destruction of the blood-testicular barrier. Modern research emphasizes that immunological mechanisms often coexist with other forms of infertility, aggravating their progression

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and reducing the effectiveness of standard treatments [21].

Exogenous and behavioral factors. In recent years, attention has been growing to the role of environmental and lifestyle factors in the development of male infertility. Exogenous factors can have both a direct toxic effect on the spermatogenic epithelium and an indirect effect through hormonal and metabolic disturbances. Among the most significant factors are smoking, alcohol consumption, and drug use. Nicotine and its metabolites cause increased oxidative stress, decreased sperm concentration and motility, and increased DNA fragmentation. Chronic alcohol consumption is associated with impaired testosterone secretion and altered spermatogenesis [2].

Occupational hazards, including exposure to heavy metals, pesticides, organic solvents, and ionizing radiation, also have an adverse effect. These factors can lead to epigenetic changes, DNA damage, and disruption of meiotic division of germ cells [4].

Obesity and metabolic syndrome are considered independent risk factors for male infertility. Excess adipose tissue contributes to increased aromatization of testosterone into estrogens, the development of hypogonadism, and chronic inflammation, which negatively impacts sperm parameters [7].

Pathogenesis of male infertility.

The pathogenesis of male infertility is a complex, multi-layered process involving hormonal, cellular, molecular, and immunological mechanisms. Regardless of the primary cause, most forms of infertility are mediated by impaired spermatogenesis and sperm function.

Spermatogenesis disorders. Spermatogenesis is a highly organized process that includes mitotic division of spermatogonia, meiosis, and postmeiotic differentiation of spermatozoa. Damage to any of these stages can lead to quantitative and qualitative abnormalities in sperm. Genetic defects, hormonal imbalances, and toxic exposures cause germ cell apoptosis, meiotic arrest, and the formation of morphologically abnormal spermatozoa. The severity of spermatogenesis disorders varies from moderate oligozoospermia to complete azoospermia [12].

Hormonal mechanisms of pathogenesis. Hormonal regulation of spermatogenesis is accomplished through the coordinated interaction of the hypothalamus, pituitary gland, and testes. Impaired secretion of gonadotropins or testosterone leads to disorganization of the spermatogenic epithelium and a decrease in the production of mature sperm. Local testosterone concentrations in the testes, which should significantly exceed their systemic levels, play a particularly important role. A decrease in intratesticular testosterone, even with normal serum levels, can be accompanied by significant suppression of spermatogenesis [24].

Oxidative stress and sperm DNA damage. Oxidative stress is considered one of the central pathogenetic mechanisms of male infertility. Excessive formation of reactive oxygen species leads to damage to the lipid membranes of sperm, disrupting their motility and DNA integrity [23].

Sperm DNA fragmentation is associated with a decreased likelihood of natural conception and an increased risk of miscarriage and ART failure. Sources of oxidative stress can include inflammation, varicocele, smoking, and metabolic disorders [5].

Immunopathogenetic mechanisms. Immunological reactions in the male reproductive system can exacerbate sperm damage through the activation of cytokines, complement, and cellular immunity. Antisperm antibodies not only impair sperm function but also contribute to increased oxidative stress, creating a vicious cycle of adverse events [13].

The role of epigenetic mechanisms. In recent years, epigenetic changes have been considered an important factor mediating the influence of environment and lifestyle on spermatogenesis. DNA methylation, histone modifications, and regulation of microRNA expression in spermatozoa can alter their functional activity without altering the nucleotide sequence of the genome [15].

Accumulating evidence suggests that smoking, obesity, exposure to endocrine factors and chronic stress are associated with epigenetic disturbances that can be transmitted to offspring and affect the reproductive health of the next generation [22].

Biomarkers of male infertility.

One promising area is the search for reliable biomarkers that allow for an objective assessment of a man's reproductive potential. In addition to standard spermogram parameters, sperm DNA fragmentation indices, oxidative stress levels, microRNA profiles, and spermatogenesis protein expression are being actively studied. The use of such markers can significantly improve diagnostic accuracy, improve prediction of treatment effectiveness, and optimize the use of assisted reproductive technologies [14].

Personalized approach and ART.

Modern male infertility treatment approaches focus on a personalized approach, taking into account individual etiological and pathogenetic factors. Genetic testing, assessment of hormonal status, and molecular abnormalities allow for a more precise treatment strategy and the selection of the optimal ART method. The integration of andrological diagnostics and reproductive technologies is particularly important,

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aimed not only at achieving pregnancy but also at reducing the risk of transmitting genetic and epigenetic disorders to offspring [17].

CONCLUSION.

Male infertility is one of the most pressing issues in reproductive medicine, significantly impacting the psychological, social, and reproductive health of couples. Current data confirm that male infertility is a multifactorial condition caused by the interaction of genetic, endocrine, immunological, inflammatory, anatomical, and exogenous factors.

Genetic disorders, including chromosomal abnormalities, Y-chromosome microdeletions, and mutations in individual genes, play a key role in severe forms of infertility, such as azoospermia and severe oligozoospermia. These data highlight the need for genetic screening in men with spermatogenesis disorders and the integration of testing results into clinical practice to determine optimal treatment strategies and plan assisted reproductive technologies.

Endocrine factors, including hypogonadism, gonadotropic dysfunction, thyroid dysfunction, and metabolic disorders, directly impact semen quality and sperm function. At the same time, exogenous factors, including smoking, alcohol, obesity, occupational hazards, and exposure to endocrine factors, can exacerbate pathogenic processes, creating conditions conducive to the development of oxidative stress and sperm DNA damage.

Inflammatory and immunological processes also play a significant role. Chronic infections of the male reproductive organs, varicoceles, and damage to the blood-testicular barrier contribute to the formation of antisperm antibodies, activation of the cytokine response, and increased oxidative stress, which exacerbates spermatogenesis disorders and reduces the likelihood of natural conception.

The study of the molecular and epigenetic mechanisms of male infertility occupies a special place in modern concepts. DNA methylation abnormalities, altered microRNA expression, and histone modifications affect sperm quality and can have long-term consequences, including the inheritance of reproductive disorders. These discoveries open new prospects for the development of biomarkers that allow for more accurate assessment of male fertility and predictive value of treatment.

Despite advances in diagnosis and treatment, a significant proportion of male infertility cases remain idiopathic. This highlights the need for further research using modern methods of molecular biology, genetics, epigenetics, and reproductive medicine. A personalized approach based on a comprehensive assessment of etiology and pathogenesis will optimize therapeutic strategies, increase the effectiveness of assisted reproductive technologies, and minimize risks to offspring.

In conclusion, male infertility should be considered a systemic disease requiring a multidisciplinary approach, including andrology, endocrinology, genetics, and immunology. A comprehensive study of the etiological and pathogenetic factors, as well as the introduction of innovative diagnostic and therapeutic methods, will ensure significant progress in improving male reproductive function and increasing the chances of successful conception for couples facing infertility.

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