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MODERN APPROACHES TO THE DIAGNOSIS OF MALE INFERTILITY

INTRODUCTION

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Abstract: Male infertility is one of the most pressing issues in modern reproductive medicine. According to the World Health Organization (WHO), approximately 10–15% of couples of reproductive age experience infertility, and in nearly half of these cases, the male factor plays a significant role. In recent decades, the decline in male reproductive health indicators, deterioration of semen quality, and the increasing prevalence of infertility have further intensified the medical and social importance of this problem.

Male infertility is not limited only to impaired reproductive function; in some cases, it may also serve as an early sign of endocrine, genetic, metabolic, and oncological diseases. Therefore, a comprehensive diagnostic approach is of great importance in the evaluation of male infertility. The development of modern diagnostic methods has significantly expanded the possibilities of identifying etiological factors, assessing reproductive prognosis, and developing individualized treatment strategies.

Today, in the diagnosis of male infertility, alongside traditional clinical and laboratory tests, molecular-genetic studies, hormonal profile assessment, ultrasound diagnostics, functional sperm tests, and artificial intelligence–based analytical systems are widely used. These methods contribute to the early detection of pathological changes in the reproductive system and increase treatment effectiveness.

In this regard, studying modern approaches to the diagnosis of male infertility, evaluating their clinical significance, and analyzing their role in medical practice is considered one of the important scientific tasks.

Research objective: to analyze modern diagnostic methods used in the diagnosis of male infertility based on scientific literature.

Research tasks:

- to study the etiology and pathogenesis of male infertility;
- to evaluate the capabilities of modern diagnostic methods;
- to analyze the clinical significance of laboratory and instrumental examinations;
- to review promising diagnostic technologies and future directions.

Definition and Classification of Male Infertility

Infertility is a pathological condition characterized by the absence of pregnancy after one year of regular unprotected sexual intercourse. Male infertility is characterized by a reduction or loss of fertilization ability due to anatomical, functional, genetic, or endocrine disorders of the male

reproductive system. According to modern data, the male factor is identified in 20–30% of all infertility cases alone, while in 30–40% of cases both male and female factors are involved.

In clinical practice, male infertility is divided into primary and secondary forms. Primary infertility is observed when a man has never achieved a pregnancy. Secondary infertility is characterized by impaired reproductive function in men who previously had fertility.

From a pathogenetic point of view, male infertility is classified into obstructive and non-obstructive types. In obstructive infertility, spermatogenesis is preserved, but the transport of sperm through the reproductive ducts is impaired. This condition may develop due to vas deferens agenesis, narrowing of the reproductive ducts, or post-inflammatory changes.

Non-obstructive infertility is associated with impaired spermatogenesis and is considered the most common form of male infertility. In this condition, sperm production in the testes is partially or completely disrupted. Genetic syndromes, hormonal disorders, varicocele, and toxic factors are among the main causes of non-obstructive infertility.

According to the World Health Organization classification, male infertility is also divided into pretesticular, testicular, and posttesticular forms. In the pretesticular form, hormonal deficiency affecting spermatogenesis occurs due to hypothalamic-pituitary dysfunction. In the testicular form, the pathological process occurs directly in the testicular tissue. In the posttesticular form, sperm transport or ejaculation is impaired.

This classification is of great importance in clinical practice for identifying etiological factors and selecting optimal diagnostic and treatment strategies.

Etiology and Pathogenesis . **Male infertility is a polyetiological disease, and its development involves genetic, hormonal, anatomical, infectious, and environmental factors. In most cases, infertility arises as a result of the combined influence of several factors.**

Genetic factors are among the most important causes of male infertility. Chromosomal abnormalities, especially Klinefelter syndrome, are frequently observed in cases associated with azoospermia and severe oligozoospermia. Microdeletions in the AZF region of the Y chromosome are one of the most common genetic causes of impaired spermatogenesis. Mutations in the CFTR gene are associated with congenital bilateral absence of the vas deferens, leading to obstructive infertility.

Hormonal disorders also significantly affect reproductive function. Disruption of the hypothalamic-pituitary-gonadal axis leads to impaired secretion of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone. As a result, spermatogenesis is reduced or completely stopped. Hypogonadotropic hypogonadism, hyperprolactinemia, and thyroid gland disorders are important endocrine causes of male infertility.

Among anatomical factors, varicocele is the most common pathology. Varicocele is characterized by dilation of the testicular veins, leading to increased testicular temperature, hypoxia, and oxidative stress. These changes negatively affect sperm count, motility, and morphology. In addition, cryptorchidism, testicular trauma, and congenital abnormalities of the reproductive tract may also contribute to reduced fertility.

Infectious factors cause inflammatory processes in the male reproductive system, leading to impaired spermatogenesis. Epididymitis, orchitis, prostatitis, and sexually transmitted infections may result in reduced sperm quality and obstruction of the reproductive ducts. Chronic inflammation increases oxidative stress, which in turn leads to sperm DNA damage.

Lifestyle and environmental factors also have a significant impact on male reproductive health. Smoking, alcohol consumption, drug use, obesity, physical inactivity, and chronic stress negatively affect spermatogenesis. Moreover, pesticides, heavy metals, industrial toxins, and ionizing radiation can impair sperm function.

From a pathogenetic perspective, oxidative stress plays a key role in the development of male infertility. Excess production of reactive oxygen species leads to lipid peroxidation of sperm membranes, DNA fragmentation, and increased cellular apoptosis. As a result, sperm fertilizing ability decreases and reproductive outcomes worsen.

Thus, male infertility is a condition associated with multiple etiological factors and complex pathogenetic mechanisms, and identifying its causes remains one of the main tasks of modern diagnostics.

Modern Diagnostic Methods. **Effective diagnosis of male infertility requires a comprehensive approach. The modern diagnostic algorithm includes anamnesis collection, physical examination, laboratory testing, and instrumental investigations. The main goal of diagnosis is to identify the cause of infertility, evaluate reproductive prognosis, and develop an individualized treatment strategy.**

Clinical Diagnosis

The diagnostic process begins with detailed history taking. Information is collected about infertility duration, previous pregnancies, sexual activity, past surgeries, childhood diseases, cryptorchidism, trauma, infections, and medications. Occupational exposure, toxic substances, radiation exposure, and family history are also assessed.

During physical examination, body habitus, secondary sexual characteristics, presence of gynecomastia, body mass index, and signs of androgen deficiency are evaluated. Testicular size, consistency, and position are assessed. Varicocele, hydrocele, epididymal pathology, and congenital anomalies of the reproductive ducts may also be detected.

Clinical examination often determines the direction of further laboratory and instrumental tests and plays an important role in etiological diagnosis.

Semen analysis is the primary and mandatory test in the diagnosis of male infertility. According to the World Health Organization (2021) guidelines, semen samples should be collected after 2–7 days of abstinence.

The following parameters are evaluated:

- Ejaculate volume
- Sperm concentration
- Total sperm count
- Motility parameters
- Morphological features
- Vitality
- Leukocyte count
- pH level of ejaculate

Based on semen analysis results, azoospermia, oligozoospermia, asthenozoospermia, teratozoospermia, or their combinations may be diagnosed. Since semen parameters may vary over time, at least two examinations are recommended.

In recent years, Computer Assisted Semen Analysis (CASA) systems have been widely introduced. These technologies allow more precise evaluation of sperm motility and morphology.

Hormonal tests play an important role in evaluating reproductive system function and identifying endocrine causes of infertility. In particular, assessment of hormonal profiles is recommended in patients with significant abnormalities in semen analysis.

The main tests include:

- Follicle-stimulating hormone (FSH)
- Luteinizing hormone (LH)
- Total and free testosterone
- Prolactin
- Estradiol
- Thyroid hormones

An increase in FSH levels may indicate damage to the spermatogenic epithelium. A decrease in testosterone is associated with hypogonadism and impaired reproductive function. Hyperprolactinemia suppresses gonadotropin secretion, negatively affecting spermatogenesis.

Hormonal diagnosis is important for identifying endocrine causes of male infertility and selecting an appropriate individualized treatment strategy.

Genetic Diagnosis. **In recent decades, genetic diagnosis has become an integral part of male infertility evaluation. Studies have shown that a significant proportion of patients with severe oligozoospermia and azoospermia have underlying genetic abnormalities.**

Karyotyping is the main method for detecting chromosomal abnormalities. The most common chromosomal disorder associated with male infertility is Klinefelter syndrome. In this condition, the presence of an additional X chromosome leads to impaired testicular function and reduced spermatogenesis.

Microdeletions in the AZFa, AZFb, and AZFc regions of the Y chromosome are among the most important genetic causes of severe spermatogenic failure. These mutations disrupt sperm production and are often associated with azoospermia.

Testing for CFTR gene mutations is also important. These mutations are associated with congenital bilateral absence of the vas deferens and represent a major cause of obstructive infertility.

The introduction of genetic testing allows assessment of reproductive prognosis, planning of assisted reproductive technologies, and evaluation of the risk of transmitting genetic disorders to offspring.

Instrumental Diagnostics

Instrumental methods play an important role in assessing the anatomical and functional state of the male reproductive system. They complement clinical and laboratory findings and help determine the exact cause of infertility.

Scrotal ultrasound is the most commonly used method. It allows assessment of testicular size, structure, and blood flow. It can also detect varicocele, hydrocele, testicular tumors, and other pathological conditions.

Doppler ultrasound is used to evaluate testicular blood circulation. It is particularly valuable in diagnosing varicocele due to its high sensitivity and specificity.

Transrectal ultrasound (TRUS) provides evaluation of the seminal vesicles, prostate gland, and reproductive ducts. This method is important in identifying causes of obstructive azoospermia.

Magnetic resonance imaging (MRI) is usually used in complex clinical cases. It provides high-resolution images of soft tissues and helps detect anatomical abnormalities.

In some patients, testicular biopsy may also be performed. This method allows direct assessment of spermatogenesis and retrieval of sperm for assisted reproductive technologies. It is especially important in cases of non-obstructive azoospermia.

Thus, modern instrumental diagnostic methods play a key role in identifying anatomical and functional causes of male infertility and are an essential part of the comprehensive diagnostic algorithm.

Advanced Molecular and Functional Diagnostic Methods

Although traditional diagnostic methods are important in evaluating male infertility, in some cases reproductive failure may occur even when semen analysis results are normal. Therefore, in recent years, advanced laboratory technologies assessing the molecular and functional status of spermatozoa have been widely introduced. These methods allow a deeper evaluation of male reproductive health and the detection of hidden pathological changes.

Sperm DNA Fragmentation. **Integrity of sperm DNA is a crucial factor for normal fertilization and embryo development. DNA fragmentation is characterized by damage to the genetic material of spermatozoa and may be associated with infertility, recurrent pregnancy loss, and reduced success of assisted reproductive technologies.**

Methods used to assess DNA fragmentation include the TUNEL assay, Sperm Chromatin Structure Assay (SCSA), Comet assay, and Sperm Chromatin Dispersion (SCD) test. Studies have shown that increased DNA fragmentation is associated with reduced fertilization rates and poor embryo quality.

Oxidative stress plays an important role in the pathogenesis of male infertility. Excess production of reactive oxygen species (ROS) leads to damage of sperm membranes, DNA fragmentation, and impaired cellular function.

Assessment of ROS levels and antioxidant defense systems is considered one of the promising directions in modern laboratory diagnostics. High levels of oxidative stress are particularly observed in cases of varicocele, infections, smoking, and exposure to environmental toxins.

In addition to sperm count and motility, evaluation of functional capacity is also important. The acrosome reaction test assesses the ability of sperm to penetrate the egg's outer layer. In addition, hyaluronic acid binding tests and assays evaluating interaction with the zona pellucida are also used.

These technologies are important for identifying causes of reproductive failure and predicting outcomes of assisted reproductive technologies.

In recent years, the development of artificial intelligence (AI) has significantly influenced reproductive medicine and andrology. AI-based algorithms are increasingly used to analyze large volumes of clinical and laboratory data, improving diagnostic accuracy.

Computer Assisted Semen Analysis (CASA) systems automatically evaluate sperm concentration, motility, and morphology. These systems reduce human error and improve reproducibility of results.

Machine learning algorithms enable prediction of male infertility risk by integrating semen parameters, hormonal profiles, and genetic data. Some studies have shown that AI-based systems can match or even exceed expert-level accuracy in sperm morphology assessment.

AI is also increasingly used in assisted reproductive technologies. It plays an important role in embryo evaluation, sperm selection, and prediction of fertilization success.

In the future, AI systems integrating genomic, proteomic, and clinical data are expected to play an even greater role in diagnosing male infertility.

Modern approaches to male infertility assessment are based on guidelines developed by the World Health Organization (WHO), American Urological Association (AUA), American Society for Reproductive Medicine (ASRM), and European Association of Urology (EAU).

The diagnostic algorithm typically begins with history taking and physical examination, followed by semen analysis. If abnormalities are detected, additional hormonal, genetic, and instrumental tests are recommended.

In patients with azoospermia, differentiation between obstructive and non-obstructive forms is essential. Hormone levels (especially FSH), testicular size, genetic testing, and ultrasound imaging are important in this differentiation.

According to EAU and AUA guidelines, karyotyping and Y-chromosome microdeletion testing are recommended in cases of severe oligozoospermia or azoospermia. In suspected obstructive infertility, CFTR gene mutation testing is recommended.

Sperm DNA fragmentation testing is advised in cases of repeated assisted reproductive technology failure, unexplained infertility, or recurrent pregnancy loss.

Modern international guidelines emphasize the importance of an individualized and comprehensive diagnostic approach. Based on diagnostic findings, a personalized treatment and follow-up strategy should be developed for each patient.

Modern technologies used in the diagnosis of male infertility allow for a deeper understanding of disease mechanisms, improved diagnostic accuracy, and the development of individualized treatment strategies. Along with traditional clinical and laboratory tests, the introduction of molecular genetic methods, advanced imaging techniques, and artificial intelligence–based systems represents one of the major achievements in reproductive medicine.

One of the main advantages of modern diagnostics is the ability to identify hidden and complex causes of male infertility. For example, genetic testing can detect chromosomal abnormalities, Y-chromosome microdeletions, and other hereditary factors. DNA fragmentation tests help identify causes of reproductive failure even in patients with normal semen analysis results.

The development of instrumental diagnostic methods has also significantly improved diagnostic accuracy. High-resolution ultrasound, color Doppler imaging, and magnetic resonance imaging allow early detection of structural abnormalities in the reproductive system. These methods are particularly important in identifying varicocele, obstruction of reproductive ducts, and testicular structural changes.

However, modern diagnostic methods also have certain limitations. First, molecular genetic and advanced laboratory tests are often expensive, which limits their widespread use. In many developing countries, such tests are not accessible to all patients.

In addition, the clinical significance of some diagnostic tests has not yet been fully standardized. For example, there are methodological differences between laboratories in assessing sperm DNA fragmentation or oxidative stress markers, which can complicate interpretation of results.

Another important issue is that even with the most advanced diagnostic methods, the exact cause of infertility cannot always be identified. A significant proportion of male infertility cases remain idiopathic, meaning that no specific etiological factor can be determined using available diagnostic tools.

Thus, although modern diagnostic technologies have significantly expanded the possibilities of identifying male infertility, economic, methodological, and organizational factors must also be considered in their clinical application.

In recent years, scientific progress in reproductive medicine and andrology has significantly expanded the possibilities for diagnosing male infertility. In the future, new technologies aimed at improving accuracy and individualization of diagnostics are expected to be widely implemented in clinical practice.

One of the most promising directions is the development of genomic diagnostics. Advances in whole-genome sequencing technologies are enabling the identification of previously undetectable genetic mutations, leading to a deeper understanding of the genetic basis of male infertility.

The development of proteomics and metabolomics also holds great potential. These technologies allow identification of biomarkers in spermatozoa and seminal plasma, enabling molecular-level disease assessment. In the future, such biomarkers may allow early diagnosis and individualized prognosis of infertility.

Artificial intelligence technologies are also expected to play a key role in the future of reproductive diagnostics. Algorithms integrating large datasets of clinical, laboratory, and genetic information can create individual risk profiles and select the most effective diagnostic strategies for each patient.

In addition, liquid biopsy technologies are gaining increasing attention. Analysis of free nucleic acids and cellular biomarkers obtained from blood or semen may provide non-invasive diagnostic options.

Advanced imaging methods, three-dimensional ultrasound, and high-resolution MRI systems are also expected to further improve the accuracy of reproductive system evaluation.

In the future, the concept of precision medicine will become increasingly important in reproductive medicine. This approach focuses on developing individualized diagnostic and treatment strategies based on each patient's genetic, metabolic, and clinical characteristics.

Thus, scientific progress is shaping a new stage in the diagnosis of male infertility, and the implementation of these technologies in clinical practice will improve diagnostic accuracy and treatment outcomes.

Conclusion. Male infertility is one of the most important issues in reproductive medicine, and the male factor plays a significant role in a considerable proportion of infertile couples worldwide. The multifactorial etiology and complex pathogenesis of the disease require a comprehensive diagnostic approach.

The literature review shows that modern approaches to the diagnosis of male infertility are based on an integrated system of clinical, laboratory, instrumental, and molecular-genetic investigations. Although anamnesis, physical examination, and semen analysis remain the primary diagnostic steps, modern genetic and molecular technologies have significantly expanded diagnostic capabilities.

Ultrasound examination, Doppler imaging, and magnetic resonance imaging play an important role in assessing the anatomy of the reproductive system. Hormonal profiling helps identify endocrine causes of spermatogenesis disorders.

Molecular genetic diagnostics, including karyotyping, Y-chromosome microdeletion testing, and DNA fragmentation analysis, are crucial for identifying hidden causes of male infertility. These methods are particularly valuable in severe spermatogenic disorders and idiopathic infertility.

Artificial intelligence, genomics, proteomics, and other innovative technologies are shaping the future directions of reproductive diagnostics. Their widespread implementation will enable earlier detection, individualized risk assessment, and optimized treatment strategies.

Thus, the use of modern diagnostic approaches improves the accuracy of identifying causes of male infertility, enhances reproductive prognosis, and enables effective individualized patient management. Comprehensive diagnostic algorithms based on international guidelines play a key role in preserving male reproductive health and effectively addressing infertility.

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