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LABORATORY ISSUES IN THE DIAGNOSIS OF MALE INFERTILITY

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Abstract:

Laboratory diagnostics of male infertility are primarily developing in the morphological direction. However, spermogram results may be prone to subjective errors and variability. While biochemical tests are stable, they are not adapted for working with spermatozoa. Male infertility arises under the influence of various factors, including social, ecological, and demographic, which complicates diagnosis. Therefore, new approaches are necessary for identifying disorders of spermatogenesis, such as reduced sperm count, decreased motility, or increased pathological forms. Research, particularly focused on developing and validating biomarker-based methods, is ongoing. The identification of biomarkers, analysis of genetic and epigenetic changes, microbiota, and the use of automated systems for analysis can improve diagnostic accuracy. Innovative approaches will enable more precise infertility diagnosis and allow for more individualized treatment methods.

Keywords: Male infertility, laboratory diagnostics, spermogram, biochemical tests, biomarkers, genetic analysis, microbiota, automated systems, validation, spermatozoa.

INTRODUCTION

The methods for laboratory diagnosis of male infertility are primarily developing in the morphological direction. Currently, the main indicators determining the fertilizing ability of sperm are the concentration of spermatozoa, their motility, and the number of spermatozoa with normal morphology. The spermogram, which cannot provide complete information about potential disturbances in the spermatogenesis process, is the most widely used test method. Male infertility is caused by various factors, including social, ecological, and demographic factors, which complicate diagnosis. Therefore, new approaches are needed to identify the causes of spermatogenesis disorders, such as a decrease in sperm count, reduced motility, or an increase in pathological forms. In Uzbekistan, the biochemical methods for diagnosing male infertility are limited because the methodology is underdeveloped and there are no pre-analytic standards [1].

OBJECTIVE

To analyze the laboratory diagnostic issues in the diagnosis of male infertility and propose new approaches and methodologies.

Materials and Methods

In the course of our research and writing of this article, we used various scientific literature and electronic resources, including scientific articles, books, journals, reviews, and official documents. The data was sourced from databases such as PubMed, Web of Science, Google Scholar, as well as from periodicals in the field of neuroimmunology. Modern and verified data were used to ensure the accuracy and reliability of the information presented in our work.

DISCUSSION

Spermogram has been accepted as the main method for laboratory diagnostics of male fertility, and the methods for determining spermatozoa count have been in clinical practice since 1929. At the same time, the understanding of the relationship between spermatozoa concentration and male reproductive capacity is still not fully resolved, and it is not possible to clearly define the lower limits of the indicators in the spermogram at present. This issue has not been fully addressed yet [2]. Furthermore, despite the World Health Organization (WHO) efforts to improve the analysis [3], there are still subjective errors in laboratories when evaluating spermatozoa motility and morphology, and there is significant variability in the results [4]. For instance, the error rate in determining spermatozoa morphology and motility in laboratories in the Russian Federation reaches up to 78%.

Biochemical tests certainly have stable characteristics in analysis, but manufacturers often suggest applying these test systems to blood plasma or serum, as the test systems designed for working with spermatozoa have not been sufficiently validated. In recent years, serious revisions have been made to traditional terminology and conceptual approaches in laboratory medicine, primarily as a result of efforts to introduce global standards into medical laboratory practices. In Russia, the concepts of method validation and verification are still new for many laboratories, and these processes must be carried out in laboratory

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work. The validation process includes assessing the analytical performance of the method, ensuring that it meets quality objectives and is accepted for practical use. The difference between validation and verification lies in that validation checks the acceptability of analytical results before applying a method in practice, whereas verification is aimed at proving the initial effectiveness of the method by the manufacturer. Therefore, before introducing any method into medical practice, it is essential to prove its correct functioning in the laboratory [5].

Moreover, although all necessary measures for evaluating the effectiveness of test systems before their release to the market have been adopted, each laboratory will have the ability to verify the methods that suit their conditions. One of the key measures in assessing the analytical effectiveness of these methods is identifying errors and, at the same time, determining acceptable thresholds for the results to be considered clinically acceptable.

Thus, before introducing laboratory analysis methods, it is of significant importance to implement validation and verification processes to ensure their analytical effectiveness, minimize errors, and ensure acceptance in clinical diagnostic practice. In this regard, necessary actions will be taken to ensure the accuracy of the results obtained for analysis and to align them with international standards.

The concept of a biomarker is defined as an indicator that is quantitatively and objectively measured as a response to a specific physiological state, pathological process, or ongoing treatment. The National Institutes of Health (NIH) in the USA defines three main types of biomarkers:

Type 0: A marker that indicates the presence of a disease and correlates with its clinical symptoms;

Type I: A marker related to the therapeutic effect and mechanism of action of a drug;

Type II (predicting clinical outcome, "surrogate endpoint," according to English literature): A marker that allows predicting the positive or negative outcome of a disease and the effectiveness of treatment.

In fact, a distinction can be made between diagnostic and prognostic biomarkers. Biomarkers of the first type indicate the presence of a disease in the patient, and this marker can be used to identify the type of disease. Sometimes, they can also be used as prognostic biomarkers [6]. There are two main approaches to new biomarkers: hypothesis-driven approach and discovery-driven approach. The discovery-driven approach is typically carried out through screening a range of molecules related to pathology. Such screening often leads to the emergence of new hypotheses.

As the next step, biomarker validation procedures need to be carried out. This process refers to the documented confirmation necessary to ensure that the biomarker fulfills its intended purpose and that its application leads to expected results. There are some challenges in studying biomarkers, especially due to the lack of well-classified standards, the presence of unchanging quantities, or, conversely, difficulties related to high or low concentrations. Therefore, various researchers apply different approaches and divide validation methods into several small categories. However, the most common approach is considered to be "fitness for specific purposes." In this approach, validation of the method should be ensured only for certain situations, and its unsuitability for other alternative needs can be accepted.

In recent decades, a great deal of research has been conducted on potential biomarkers, particularly on the proteins in blood serum, regarding their possibilities in detecting specific diseases. However, only a very small fraction of these biomarkers is actually used in clinical practice. For example, out of over 150,000 published biomarkers, only about a hundred are used in practical healthcare [7]. Of course, the main problem here is often funding, as many new experiments, inter-laboratory collaborations, and resources are required to turn pilot studies into a legal body of work. Many interesting findings from scientific research on male infertility and spermatozoa analysis are rarely used in practice, as they are not sufficiently available in primary laboratories due to technological and financial reasons.

Idiopathic male infertility biomarkers are certainly a high-demand task. The development of idiopathic infertility is not limited to pathogenic processes at the level of the urogenital system but is a pathology of the entire organism. Studying only spermatozoid parameters artificially limits the search for pathophysiological and pathochemical mechanisms. Generally, considering that blood vessels encircle all tissues of the body, blood biomarkers can clearly serve as a source. However, the relationship between the ratio of tested analytes in various biological environments and disease may be very important. Currently, there is no clear understanding of the relationship between certain components in spermatozoa and their counterparts in blood serum, nor is there clear knowledge about the functional characteristics of the blood-testicular barrier.

New approaches and methodologies are of great importance in increasing diagnostic accuracy and

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improving analysis processes in the detection of male infertility. The following suggestions can be made:

1. It is necessary to study the molecular and biochemical mechanisms of infertility more deeply. New biomarker-based tests, such as proteins in blood plasma, genetic and proteomic components in spermatozoa, can increase accuracy in identifying the causes of infertility. It is essential to strengthen validation processes for accurate biomarker identification and optimize test systems.
2. To reduce subjective errors in laboratory work, automated microscopy systems and computer image analysis technologies can be used to assess sperm morphology and motility. These methods improve the accuracy and reproducibility of the analysis.
3. Analyzing the genetic material of spermatozoa and epigenetic changes can provide new insights into the causes of infertility. Using modern genetic analysis methods to detect genetic mutations and chromosomal anomalies increases diagnostic accuracy.
4. The urogenital microbiome of men may also influence infertility. Studying the composition of the microbiome and influencing it can improve sperm quality. The introduction of new biomarkers to detect aging and other microbial changes is necessary.
5. Before introducing new diagnostic methods into practice, it is crucial to ensure their analytical effectiveness and improve validation processes. An individual verification system should be developed based on laboratory conditions to adapt methods to national and international standards.
6. Given that the causes of male infertility are linked to multiple factors, multi-factorial analysis systems combining several tests can be developed. The joint evaluation of blood biomarkers and spermogram results creates an opportunity for more accurate infertility detection.
7. By considering the individual characteristics of each patient, personalized approaches can be applied in infertility diagnosis, improving analysis processes by taking genetic predispositions and individual reactions into account.

The above approaches and methodologies will help improve the accuracy of male infertility diagnosis and enhance the quality of results in practice. These innovative approaches will increase the effectiveness of diagnostics and enable further individualization of treatment methods.

In conclusion, laboratory diagnostics in male infertility detection still encompasses many challenges. Although spermogram remains the primary method, its results are prone to subjective errors and variability. Biochemical tests, although stable, are not tailored for spermatozoid work.

. The processes of validation and verification of methods are still not sufficiently developed. Research focused on new biomarkers could be successful, but there is a lack of financial and technological resources to apply them in clinical practice. Male infertility biomarkers, especially for identifying idiopathic infertility, require new approaches.

New approaches can help improve diagnostic accuracy and enhance the analysis process. Biomarker-based tests, automated systems, genetic and epigenetic analyses, microbiome studies, and improving validation processes could significantly enhance the quality of diagnostics. These approaches will help make infertility detection more accurate and individualized, while also optimizing treatment methods.

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