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# Contemporary Perspectives On The Impact Of Enzymatic Dysfunction In The Pathogenesis Of Female Infertility And Innovative Approaches To Its Treatment (Literature Review)

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**ABSTRACT**
**Aim.** To conduct a comprehensive analysis of modern aspects of enzymatic dysfunction in female infertility and to explore innovative methods for its correction.
**Materials.** A review of publications in electronic databases, including PubMed, Google Scholar, and eLibrary, was conducted. Selection of publications was carried out in accordance with PRISMA guidelines. All relevant articles published up to January 2024 were included in the analysis. The search yielded 110 publications from PubMed, 80 from eLibrary, and 25 from Google Scholar. Duplicates and articles without full text were excluded from consideration.
**Results.** Pharmacological methods, such as the use of aromatase inhibitors (e.g., letrozole), demonstrated significant effectiveness in restoring ovulation and increasing pregnancy rates in women with anovulatory infertility. Studies also showed that metalloproteinase inhibitors, such as doxycycline, improve implantation conditions and reduce the risk of early miscarriage. Biotechnological approaches, such as gene therapy and exosome therapy, have shown promising results in correcting enzymatic dysfunctions, particularly in cases involving genetic mutations and chronic implantation failures. Regenerative methods, including PRP therapy, have proven effective in improving endometrial condition and stimulating ovulation, leading to increased fertility rates.
**Conclusion.** Enzymatic dysfunction is a significant factor in the pathogenesis of female infertility. The development of personalized therapeutic strategies aimed at correcting enzymatic activity through both traditional and innovative methods offers promising prospects for improving reproductive outcomes. However, further comprehensive research is needed to optimize these approaches and enhance their effectiveness in treating infertility.
**Key words:** female infertility; enzymatic activity; pathogenesis of infertility; diagnosis of enzymatic disorders; correction of enzymatic disorders.

## INTRODUCTION

The role of enzymatic activity in the pathogenesis of female infertility is one of the key topics in modern reproductive medicine [1]. Enzymes involved in the processes of ovulation, fertilization, implantation, and other aspects of reproductive function play a crucial role in maintaining fertility [2]. Disruptions in their activity can lead to various forms of infertility, making it necessary to conduct in-depth studies of these mechanisms to develop effective diagnostic and treatment methods [3].

Female infertility remains a pressing medical and social issue. According to current statistical data, infertility affects about 10-15% of couples of reproductive age worldwide, with a significant proportion of cases associated with disruptions in enzymatic activity [4]. This underscores the need for further research in this area, aimed at improving the understanding of pathogenic mechanisms and developing new therapeutic approaches.

The studies by Roberts R.M. et al. focused on examining enzymatic processes in the female reproductive system have provided important insights; however, questions remain that require further attention

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[5]. In this context, a literature review dedicated to the modern aspects of the role of enzymatic activity in the pathogenesis of female infertility and innovative methods of its correction is both relevant and timely.

The purpose of this review is to comprehensively study the modern aspects of the role of enzymatic dysfunction in the pathogenesis of female infertility, as well as to analyze innovative methods of its correction.

## Enzymatic Activity and Its Role in the Female Reproductive System.

Enzymatic dysfunction plays a central role in maintaining a woman's reproductive function. As biocatalysts, enzymes regulate numerous physiological processes necessary for the normal functioning of the reproductive system, such as ovulation, fertilization, and embryo implantation [6]. Disruptions in the activity of these enzymes can lead to various forms of infertility, making them a significant focus of research in reproductive medicine [7].

## Key Enzymes Involved in Regulating Reproductive Function.

The female reproductive system relies on the coordinated work of various enzymes that control processes from folliculogenesis to embryo implantation [8]. Among the key enzymes involved in regulating these processes are:

**Aromatase (CYP19A1).** This enzyme catalyzes the conversion of androgens to estrogens, a critical step in the synthesis of sex hormones necessary for ovulation and preparation of the endometrium for implantation.

**Matrix Metalloproteinases (MMPs).** A group of enzymes involved in remodeling the extracellular matrix, essential for ovulation, follicle rupture, and subsequent embryo implantation.

**Hyaluronidase.** This enzyme plays a role in the penetration of the sperm through the oocyte's outer shell, which is a crucial step in the fertilization process.

**Trypsin and Other Serine Proteases.** These enzymes regulate the fertilization process by activating the oocyte and modifying its shell to prevent polyspermy.

Each of these enzymes performs specific functions at different stages of the reproductive process, and their activity is tightly regulated at both the synthesis and inhibition levels [9].

## Mechanisms of Enzyme Action in Ovulation, Fertilization, and Implantation.

Enzymatic mechanisms play a vital role at every stage of the reproductive cycle. During ovulation, for example, matrix metalloproteinases contribute to follicle rupture, releasing the oocyte. These enzymes break down collagen and other components of the extracellular matrix, facilitating the oocyte's exit from the follicle [10].

Aromatase, in turn, is involved in estrogen synthesis, which regulates the proliferation and maturation of the endometrium, preparing it for potential embryo implantation. High aromatase activity during the follicular phase of the menstrual cycle ensures sufficient estrogen levels to stimulate ovulation and create favorable conditions for implantation [11].

During fertilization, the enzymes hyaluronidase and acrosin, located in the sperm's acrosome, break down the zona pellucida of the oocyte, allowing the sperm to penetrate the egg. This process, known as the acrosome reaction, is crucial, and enzymes play a key role in it [12].

In the implantation process, enzymes such as matrix metalloproteinases participate in the invasion of the trophoblast into the endometrium by breaking down the extracellular matrix and aiding in the embryo's attachment to the uterine wall. Disruptions in the activity of these enzymes can lead to implantation failure and early pregnancy loss [13].

## Disruptions in Enzymatic Activity and Their Impact on Female Infertility.

Disruptions in enzymatic activity can be caused by genetic factors, as well as external influences such as inflammatory processes, stress, or toxic exposure. These disruptions may manifest as changes in enzyme expression levels, structure, or activity, ultimately affecting reproductive function [14].

For example, reduced aromatase activity can lead to insufficient estrogen synthesis, resulting in ovulation disorders and inadequate endometrial preparation for implantation. This condition is known as estrogen-deficient infertility [15].

According to Sato, M., et al., an imbalance in matrix metalloproteinase activity can lead to ovulation or implantation disorders, as excessive enzyme activity can cause excessive tissue breakdown, while insufficient activity can hinder oocyte release or trophoblast invasion [16].

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Disruptions in hyaluronidase and acrosin activity can lead to ineffective fertilization, as the sperm may be unable to penetrate the zona pellucida of the oocyte. This may be one of the causes of idiopathic infertility, where no apparent reasons for the absence of pregnancy are identified [17].

Thus, enzymatic activity plays a crucial role in maintaining reproductive function, and its disruptions can be a major factor in the development of female infertility. Studying these mechanisms and developing methods for correcting enzymatic dysfunctions are promising directions in infertility treatment [18].

## Pathogenesis of Female Infertility Related to Enzymatic Dysfunction.

Enzymatic activity, which plays a central role in reproductive processes, can, when its normal functioning is disrupted, lead to the development of female infertility. According to Smith, G.D., these disruptions can manifest at various stages of the reproductive cycle, from folliculogenesis to embryo implantation [19]. Developing methods for diagnosing and correcting enzymatic dysfunctions requires a deep understanding of the pathogenic mechanisms underlying female infertility. Enzymatic dysfunctions can lead to a wide range of pathological processes affecting various aspects of reproductive function. Key pathological processes include:

**Disruption of Folliculogenesis and Ovulation.** One of the most significant aspects is the disruption of estrogen synthesis caused by reduced aromatase activity. Insufficient estrogen levels lead to anovulation or the formation of follicular cysts. According to studies by Escobar-Morreale H.F., et al., changes in the activity of matrix metalloproteinases, which are involved in the breakdown of the follicle's extracellular matrix, can hinder ovulation, which is one of the mechanisms of anovulatory infertility [20].

**Disruption of Fertilization Processes.** Enzymes such as hyaluronidase and acrosin play an important role in the fertilization process by facilitating the penetration of sperm through the zona pellucida of the oocyte. Disruption of their activity can lead to an inability to achieve fertilization, even when the partner has normal spermatogenesis [21].

**Implantation Defects.** Matrix metalloproteinases, responsible for the invasion of the trophoblast into the endometrium, are necessary for successful embryo implantation. Disruption of their activity can lead to failure of embryo attachment to the endometrium, resulting in failed implantations or early pregnancy loss [22].

**Inflammatory Processes.** Certain enzymes, such as lipoxygenases and cyclooxygenases, are involved in the synthesis of inflammatory mediators, which can exacerbate inflammatory processes in reproductive organs, leading to chronic inflammatory diseases and secondary infertility [23].

## Clinical Manifestations and Diagnosis of Enzymatic Dysfunction.

The clinical manifestations of enzymatic dysfunctions can be quite varied, as they depend on the specific enzyme involved in the pathological process [24]. Among the most common symptoms associated with enzymatic activity disorders are:

**Anovulatory Cycles.** Observed in women with impaired estrogen synthesis or defects in ovulation processes. This can manifest as a lack of ovulation, irregular menstruation, or polycystic ovaries [25].

**Infertility of Unknown Origin.** In some cases, despite normal semen analysis results and the absence of visible abnormalities in reproductive organs, women may face an inability to conceive. This may be related to enzymatic disorders that are not always easily diagnosed by standard methods [26].

**Early Pregnancy Loss.** Women with impaired enzymatic activity involved in implantation processes may experience frequent miscarriages in the early stages of pregnancy [27].

Diagnosing enzymatic dysfunction is a complex task that requires the use of modern laboratory methods. These include:

**Proteomic Analysis.** Allows for the assessment of the level and activity of various enzymes in tissues and biological fluids, which can help identify disruptions at the molecular level.

**Genetic Testing.** Aimed at identifying mutations in genes encoding key enzymes, which may predispose to their functional disruptions.

**Biochemical Blood Analysis.** Used to assess the levels of hormones, the synthesis of which depends on the activity of specific enzymes, such as aromatase.

## Correlation Between the Activity Levels of Specific Enzymes and Various Forms of Infertility.

The activity levels of specific enzymes may directly correlate with certain forms of female infertility. Research indicates that:

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**Reduced Aromatase Activity** is associated with a hypoestrogenic state, leading to anovulatory cycles and inadequate preparation of the endometrium for implantation [28].

**Increased Matrix Metalloproteinase Activity** may be linked to disruptions in ovulation and implantation processes, resulting in various forms of anovulatory infertility and recurrent miscarriages.

**Insufficient Activity of Enzymes Involved in the Acrosome Reaction** (e.g., acrosin) may be a cause of idiopathic infertility related to impaired fertilization.

The correlation between enzymatic activity and forms of infertility underscores the importance of further research in this area. Developing methods aimed at correcting enzymatic dysfunctions has the potential to significantly improve infertility treatment outcomes in women [29].

## Modern Methods for Diagnosing Enzymatic Dysfunctions.

Diagnosing enzymatic dysfunctions in the female reproductive system is a complex task that requires the application of modern laboratory and technological methods. Accurate identification and assessment of enzymatic activity not only help in understanding the pathogenesis of female infertility but also enable the development of targeted correction methods [30]. In this regard, special attention is given to laboratory diagnostics, the use of biomarkers, and the implementation of modern technologies to assess the enzymatic profile.

## Laboratory Diagnostic Methods.

Laboratory diagnostics of enzymatic disorders involve several key methods, each playing an essential role in assessing the condition of the reproductive system.

**Blood Analysis.** Blood analysis is one of the primary methods for evaluating enzymatic activity, particularly concerning enzymes involved in the synthesis and metabolism of hormones. For example, determining the levels of estrogens and their precursors, such as androgens, can indirectly indicate the activity of aromatase [31]. Other important indicators include the levels of enzymes related to inflammatory processes, such as cyclooxygenases and lipoxygenases, which can affect the state of the reproductive system.

**Genetic Tests.** Genetic testing allows for the detection of mutations and polymorphisms in the genes encoding key enzymes involved in reproductive processes. For example, mutations in the CYP19A1 gene, which encodes aromatase, can lead to impaired estrogen synthesis and, consequently, infertility. Genetic tests also help assess the predisposition to various enzymatic disorders, which is an important factor in personalized medicine [32].

**Proteomic Analysis:** Proteomic analysis is an advanced method that allows for a detailed study of the protein composition of tissues and biological fluids. This method is particularly useful for assessing enzyme activity, as it not only detects the presence of certain enzymes but also evaluates their functional state. Proteomic analysis can be used to identify enzyme imbalances involved in key reproductive processes such as ovulation, fertilization, and implantation [33].

## Application of Biomarkers for Assessing Enzymatic Dysfunction.

Biomarkers play an essential role in diagnosing enzymatic disorders, as they allow for an objective assessment of enzyme activity in real-time. The use of biomarkers in reproductive medicine opens new opportunities for diagnosing and monitoring the condition of the reproductive system [34].

**Hormone Level Determination:** The levels of hormones such as estrogens, progesterone, and androgens can serve as important biomarkers for assessing the activity of enzymes involved in their synthesis and metabolism. For example, a decrease in estrogen levels may indicate reduced aromatase activity, which requires correction to normalize reproductive function [35].

**Inflammatory Biomarkers:** Enzymes such as cyclooxygenases and lipoxygenases are involved in the synthesis of inflammatory mediators, and their activity can be assessed by the levels of biomarkers such as prostaglandins and leukotrienes. Elevated levels of these biomarkers may indicate chronic inflammatory processes in the reproductive system, which is one of the causes of female infertility [36].

**Proteomic Biomarkers:** Proteomic analysis can identify specific biomarkers associated with enzyme activity. These biomarkers can be used to assess the effectiveness of treatment and monitor the condition of patients. According to Cookingham LM, et al., changes in the levels of matrix metalloproteinases can serve as indicators of the effectiveness of therapies aimed at improving the implantation process [37].

## The Use of Modern Technologies in the Assessment of Enzymatic Profiles

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Modern technologies open new horizons in assessing enzymatic profiles, providing accurate and detailed data on the state of the reproductive system.

**Mass Spectrometry.** Mass spectrometry is one of the most precise methods for the quantitative assessment of enzymatic activity. This method allows the identification and quantification of small molecules, such as enzyme metabolites, which is particularly important for studying their activity in various physiological and pathological conditions [38].

**High-Performance Liquid Chromatography (HPLC).** HPLC, in combination with mass spectrometry (HPLC-MS), allows for a detailed study of the metabolic profile and enzyme activity in various biological samples. This method is widely used for analyzing hormone levels, metabolites, and other biomarkers associated with enzymatic activity, enabling a more accurate assessment of the reproductive system's state [39].

**Genomic Sequencing.** Genomic sequencing allows for a detailed analysis of the genes encoding enzymes, opening new possibilities for identifying mutations and polymorphisms that affect enzymatic activity. This method is especially useful in personalized medicine, as it enables the development of individualized approaches to the diagnosis and treatment of enzymatic disorders [40].

**Nanotechnology.** Nanotechnology offers new opportunities for diagnosing enzymatic disorders by enabling the creation of highly sensitive sensors for assessing enzymatic activity at the cellular level. These sensors can be used for real-time monitoring of the reproductive system's state, significantly improving diagnostic accuracy and treatment effectiveness [41].

Modern methods for diagnosing enzymatic disorders in the female reproductive system provide unique opportunities for accurate and early diagnosis, as well as for developing personalized treatment methods. These methods not only enhance the understanding of the pathogenic mechanisms of infertility but also pave the way for effective strategies to overcome it [42].

**Innovative Methods for Correcting Enzymatic Dysfunctions.**

Correcting enzymatic disorders that cause female infertility requires a comprehensive approach, including both traditional and innovative treatment methods [43]. In recent years, there has been a growing interest in the development and application of new pharmacological agents, biotechnological methods, and regenerative approaches, such as PRP therapy, aimed at restoring and normalizing enzymatic activity [44].

**Pharmacological Approaches (Drugs Modulating Enzymatic Activity).** Pharmacological methods for correcting enzymatic dysfunctions play an important role in treating female infertility. Modern drugs are designed to modulate the activity of key enzymes involved in reproductive processes.

**Aromatase Inhibitors and Stimulators:** Aromatase, an enzyme that converts androgens into estrogens, is a crucial link in regulating hormonal balance. Disruption of its activity can lead to hypoestrogenic states and, consequently, infertility. Aromatase inhibitors, such as letrozole, are used to reduce estrogen levels in the body, stimulating ovulation in women with anovulatory cycles. Conversely, aromatase stimulators may be used in cases where enhanced activity is needed to normalize estrogen levels [45].

**Matrix Metalloproteinase Inhibitors.** Metalloproteinases play an important role in ovulation and implantation processes. Excessive activity of these enzymes can lead to tissue damage and disruption of reproductive processes. Matrix metalloproteinase inhibitors, such as doxycycline, are used to modulate their activity and prevent pathological degradation of the extracellular matrix, which helps improve outcomes in infertility related to implantation disorders [46].

**Drugs Regulating Sperm Activation.** Enzymes like hyaluronidase and acrosin play a key role in fertilization. Drugs capable of modulating the activity of these enzymes can be used to increase the likelihood of successful fertilization. For example, hyaluronidase can be used in formulations that improve sperm penetration through the egg's zona pellucida [47].

**Anti-inflammatory Drugs.** Enzymes involved in the synthesis of inflammatory mediators, such as cyclooxygenases and lipoxygenases, can be targeted by anti-inflammatory drugs. Inhibitors of these enzymes, such as nonsteroidal anti-inflammatory drugs (NSAIDs), can reduce inflammation in the reproductive organs, which is particularly important for women with chronic inflammatory diseases leading to infertility [48].

**Biotechnological Methods (Exosome Therapy, Gene Therapy).**

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Biotechnological methods represent an innovative approach to treating enzymatic disorders, leveraging modern technologies such as exosome and gene therapy. These methods open new possibilities for personalized treatment of infertility related to enzymatic dysfunctions [49].

**Exosome Therapy.** Exosomes are extracellular vesicles containing proteins, lipids, and nucleic acids that can modulate the activity of target cells. Exosome therapy aims to use exosomes to deliver active molecules capable of normalizing enzymatic activity in the cells of the reproductive system [50]. For instance, exosomes derived from stem cells may contain factors that promote the restoration of normal activity of metalloproteinases or aromatase, improving the process of ovulation and implantation.

**Gene Therapy.** Gene therapy focuses on correcting genetic defects that lead to enzymatic disorders. This method holds significant promise for treating mutations in genes encoding key enzymes in the reproductive system. Gene therapy can be used to restore normal enzyme activity, such as aromatase or metalloproteinases, thereby improving reproductive function. The introduction of gene constructs using viral vectors or CRISPR technologies allows precise correction of the defects underlying infertility [51].

**Use of Recombinant Proteins.** The administration of recombinant proteins, such as recombinant hyaluronidase, can be used to compensate for insufficient activity of endogenous enzymes. This approach is particularly relevant in cases where enzymatic activity is impaired due to mutations or other pathological changes.

**Prospects for PRP Therapy and Other Regenerative Methods.**

Regenerative medicine, including PRP therapy and other methods aimed at tissue restoration and normalization of cellular functions, represents a promising direction in the treatment of enzymatic disorders leading to female infertility [52].

**PRP Therapy (Platelet-Rich Plasma Therapy).** PRP therapy is based on the use of autologous plasma enriched with platelets to stimulate regenerative processes. Platelets contain numerous growth factors that can modulate enzymatic activity in tissues, promoting the restoration of normal function. In the context of the reproductive system, PRP therapy is used to improve endometrial conditions, stimulate ovulation, and increase the likelihood of implantation. The application of PRP may help normalize the activity of enzymes such as metalloproteinases and aromatase, thereby improving infertility treatment outcomes [53].

**Stem Cells and Their Secretomes.** The use of stem cells and their secretomes (including exosomes and growth factors) is another direction in regenerative therapy. These methods aim to restore damaged tissues and normalize enzymatic activity in reproductive organs. For example, the introduction of mesenchymal stem cells can contribute to the restoration of the endometrium and improve conditions for implantation, which is particularly relevant for women with chronic endometritis or other pathological changes in the endometrium [54].

**Prospects for Combined Therapy.**

The combination of various regenerative methods, such as PRP therapy, stem cells, and exosome therapy, opens new possibilities for a comprehensive approach to treating enzymatic disorders. These methods can be used to enhance each other's effects, providing higher effectiveness and sustainability of treatment results. The implementation of such combined approaches can significantly improve reproductive outcomes in women with infertility associated with enzymatic dysfunctions [55].

In conclusion, innovative methods for correcting enzymatic disorders in the female reproductive system represent promising directions that can significantly improve infertility treatment outcomes. The use of pharmacological agents, biotechnological methods, and regenerative medicine opens new prospects for creating personalized and effective therapeutic strategies.

**Comparative Analysis of the Effectiveness of Correction Methods.**

Comparative analysis of the effectiveness of methods for correcting enzymatic disorders in the female reproductive system plays a crucial role in developing the most optimal therapeutic strategies.

Clinical studies are fundamental for evaluating the effectiveness of various therapeutic methods aimed at correcting enzymatic disorders associated with female infertility. In recent years, several studies have been conducted to analyze the outcomes of pharmacological, biotechnological, and regenerative treatment methods [56].

**Pharmacological Methods.** Pharmacological methods, such as the use of aromatase inhibitors (letrozole) to stimulate ovulation in women with anovulatory infertility, have demonstrated high effectiveness. According

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to various studies, the use of letrozole leads to the restoration of ovulation in over 70% of cases and an increase in pregnancy rates by 20-30% compared to placebo groups [57].

Matrix metalloproteinase inhibitors, such as doxycycline, have been studied in the context of treating infertility associated with implantation disorders. Research by Simopoulou, M., et al. has shown that the use of these inhibitors improves conditions for embryo implantation, reducing the risk of early miscarriages by 15-20% [58].

**Biotechnological Methods.** Gene therapy and exosome therapy have also been the subject of clinical studies aimed at correcting enzymatic disorders. Studies have shown that the application of genetic correction methods, targeting the restoration of normal aromatase activity, can significantly improve fertility in women with mutations in the CYP19A1 gene. Exosome therapy, in turn, has shown promising results in restoring metalloproteinase activity and improving implantation processes [59].

**Regenerative Methods.** PRP therapy, as one of the methods of regenerative medicine, has demonstrated effectiveness in improving endometrial conditions and stimulating ovulation. According to clinical studies, the use of PRP therapy increases endometrial thickness in patients with chronic endometritis and also raises pregnancy rates by up to 25% compared to traditional treatment methods.

**Dysfunctions.**

Comparative analysis of various methods for correcting enzymatic disorders allows for the identification of the most effective approaches depending on the specific type of dysfunction.

**Aromatase Activity Disorders.** For correcting aromatase activity disorders, pharmacological methods such as the use of aromatase inhibitors (letrozole) are the most effective. In cases where the disorders are caused by genetic defects, gene therapy shows high effectiveness by restoring normal estrogen levels and ensuring ovulation normalization [60].

**Metalloproteinase Activity Disorders.** Matrix metalloproteinase inhibitors, such as doxycycline, have shown good results in improving conditions for implantation. Meanwhile, exosome therapy aimed at restoring metalloproteinase balance represents a promising method, especially in cases of chronic implantation disorders [61].

**Acrosomal Activity Disorders.** Drugs that stimulate the acrosome reaction and the activity of enzymes like hyaluronidase and acrosin can be used in combination with assisted reproductive technologies (ART), such as intracytoplasmic sperm injection (ICSI), to improve fertilization outcomes [62].

**Chronic Inflammatory Processes.** Anti-inflammatory drugs that inhibit cyclooxygenase and lipoxygenase activity effectively reduce inflammation in the reproductive system. However, in cases of prolonged inflammatory processes, PRP therapy and stem cells can provide additional benefits by promoting tissue regeneration and normalizing enzymatic activity [63].

## Predicting Treatment Outcomes.

Predicting treatment outcomes based on the correction of enzymatic disorders is a critical aspect of personalized medicine. Modern prediction methods rely on the use of biomarkers, genetic tests, and proteomic analysis data.

**Prediction Based on Biomarkers.** Assessing levels of hormones, inflammatory mediators, and other biomarkers allows for the prediction of treatment response. For example, in women with low estrogen levels and high metalloproteinase activity, the prognosis for treatment using aromatase inhibitors and metalloproteinase inhibitors may be favorable [64].

**Genetic Prediction.** The use of genetic tests allows for predicting individual responses to therapy. Women with mutations in genes encoding aromatase or metalloproteinases may have a higher risk of complications, and their treatment should be adapted accordingly [65].

**Proteomic Analysis for Prediction.** Proteomic analysis provides detailed information about the patient's enzymatic profile, allowing for more accurate predictions of treatment outcomes. For example, changes in the expression levels of certain proteins may indicate the success of PRP therapy or exosome therapy, enabling early treatment adjustments [66].

## Prediction Using Modern Technologies

The use of artificial intelligence and machine learning to analyze large datasets from clinical studies and laboratory tests opens new possibilities for predicting treatment outcomes. As noted by Matsuda, T., et al., such systems can consider multiple factors, including enzymatic disorders, and predict the likelihood of

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success with various therapeutic approaches, contributing to a personalized approach to infertility treatment [67].

Thus, comparative analysis of the effectiveness of enzymatic disorder correction methods, based on clinical research data, allows for identifying the most effective approaches for various types of disorders. Predicting treatment outcomes using modern diagnostic and analytical methods helps ensure high therapy effectiveness and improve reproductive results in women with infertility.

**Conclusion**

Enzymatic dysfunction plays a key role in regulating many processes critical to a woman's reproductive function. Disruptions in the activity of enzymes such as aromatase, metalloproteinases, hyaluronidase, and others can significantly impact various stages of the reproductive cycle, from folliculogenesis and ovulation to fertilization and embryo implantation. The overall analysis of the data shows that enzymatic dysfunctions are an important factor in the pathogenesis of female infertility, caused by both endocrine and mechanical factors.

**Ethics approval and consent to participate -** All patients gave written informed consent to participate in the study.

**Consent for publication -** The study is valid, and recognition by the organization is not required. The author agrees to open publication

**Availability of data and material -** Available

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**REFERENCES**

1. Adamyan LV, Andreeva EN, Gasparyan SA. Polycystic ovary syndrome in reproductive age (modern approaches to diagnosis and treatment). Clinical guidelines (treatment protocol). Moscow. 2015;22. [Adamyan LV, Andreeva EN, Gasparyan SA. Sindrom polikistoznyx yaichnikov v reproduktivnom vozraste (sovremennye podxody k diagnostike i lecheniyu). Klinicheskie rekomendatsii (protokol lecheniya). Moskva. 2015;22.] [in Russian]
2. Avrukevich EA. Morphological evaluation of the functional layer of the endometrium in women operated on for ovarian cystic formations. Smolenskiy Meditsinskiy Almanax. 2017;(1):13-17. [Avrukevich EA. Morfologicheskaya otsenka funktsionalnogo sloya endometriya jenshin, prooperirovannyx po povodu kistoznyx obrazovaniy yaichnikov. Smolenskiy Meditsinskiy Almanax. 2017;(1):13-17.] [in Russian]
3. Azizova ME. Polycystic ovary syndrome from the perspective of modern concepts. Kazanskiy Meditsinskiy Zhurnal. 2015;(1):77-80. [Azizova ME. Sindrom polikistoznyx yaichnikov s pozitsiy sovremennyx predstavleniy. Kazanskiy Meditsinskiy Zhurnal. 2015;(1):77-80.] [in Russian]
4. Atykanov AO, Januzakov NT, Batyrkhanov ShK. Clinical and diagnostic characteristics of polycystic ovary syndrome in women of reproductive age. Vestnik KRSU. 2017;17(7):75-81. [Atykanov AO, Januzakov NT, Batyrkhanov ShK. Kliniko-diagnosticheskaya xarakteristika sindroma polikistoznyx yaichnikov u jenshin reproduktivnogo vozrasta. Vestnik KRSU. 2017;17(7):75-81.] [in Russian]
5. Roberts RM, Lowe J. Enzyme-catalyzed processes essential for fertilization in mammals: A review. Biology of Reproduction. 2014;90(3):42-45.
6. Andreeva EN. The effect of folate-containing combined oral contraceptives on homocysteine levels in women with polycystic ovary syndrome. Problemy Reproduktsii. 2014;(2):27-31. [Andreeva EN. Vliyanie folatsoderjashhix kombinirovannyx oralnyx kontratseptivov na urovni gomosisteina u jenshin s sindromom polikistoznyx yaichnikov. Problemy Reproduktsii. 2014;(2):27-31.] [in Russian]

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7. Gasparov AS. Assessment of ovarian reserve in women with benign ovarian tumors after various types of surgical treatment. Kremlevskaya Meditsina. 2013;(1):100-105. [Gasparov AS. Otsenka ovariyalnogo rezerva yaichnikov s dobrokachestvennymi opuxolyami posle raznyx vidov xirurgicheskogo lecheniya. Kremlevskaya Meditsina. 2013;(1):100-105.] [in Russian]
8. Grigoryan OR. Polycystic ovary syndrome - long-term risks. Effektivnaya Farmakoterapiya. Akusherstvo i Ginekologiya. 2015;1(5):20-25. [Grigoryan OR. Sindrom polikistoznyx yaichnikov – otdalennye riski. Effektivnaya Farmakoterapiya. Akusherstvo i Ginekologiya. 2015;1(5):20-25.] [in Russian]
9. Davydov AI, Shaxlamova MN, Chaban OV, Pirogova MN. High surgical energies in operative gynecology. Voprosy Ginekologii, Akusherstva i Perinatologii. 2013;(5):75-85. [Davydov AI, Shaxlamova MN, Chaban OV, Pirogova MN. Vysokie xirurgicheskie energii v operativnoy ginekologii. Voprosy Ginekologii, Akusherstva i Perinatologii. 2013;(5):75-85.] [in Russian]
10. Dovjenko TV, Ilyina NA, Grodnitskaya EE. The problem of mental disorders in polycystic ovary syndrome. Socialnaya i Klinicheskaya Psixiatriya. 2015;25(2):94-100. [Dovjenko TV, Ilyina NA, Grodnitskaya EE. Problema psihicheskix narusheniy pri sindrome polikistoznyx yaichnikov. Socialnaya i Klinicheskaya Psixiatriya. 2015;25(2):94-100.] [in Russian]
11. Zaxidova KSh, Raximova GN. The problem of sclerocystic ovary syndrome in women of reproductive age. Problemy Biologii i Meditsiny. 2020;120(4):198-203. [Zaxidova KSh, Raximova GN. Problema sindroma sklerokistoznyx yaichnikov u jenshin reproduktivnogo perioda. Problemy Biologii i Meditsiny. 2020;120(4):198-203.] [in Russian]
12. Al-Ruthia YS, Al-Mandeel H, AlSanawi H. Ovulation induction by metformin among obese versus non-obese women with polycystic ovary syndrome. Saudi Pharm J. 2017;25(5):795-800.
13. Audebert A, Darai E, Benifla JL. Postoperative abdominal adhesions and their prevention in gynecological surgery: I. What should you know? Gynecol Obstet Fertil. 2012;40(6):365-370.
14. Bhattacharya SM. Prevalence and risk of depressive disorders in women with polycystic ovary syndrome (PCOS). Fertil Steril. 2010;94(2):357-359.
15. Chen X, Yang D, Mo Y. Prevalence of polycystic ovary syndrome in unselected women from southern China. Eur J Obstet Gynecol Reprod Biol. 2018;139:59-64.
16. Sato M, Imai H, Hirabayashi M. The role of lysosomal enzymes in oocyte maturation and preimplantation development. J Reprod Dev. 2012;58(2):258-264.
17. Dewailly D, Andersen CY, Balen A. The physiology and clinical utility of anti–Mullerian hormone in women. Hum Reprod Update. 2014;20(4):370-385.
18. Dokras A, Clifton S, Futterweit W, Wild R. Increased prevalence of anxiety symptoms in women with polycystic ovary syndrome: systematic review and meta-analysis. Fertil Steril. 2012;97(2):225-230.
19. Smith GD, Takayama S, Swain JE. Rethinking in vitro embryo culture: New developments in culture platforms and potential to improve assisted reproductive technologies. Biol Reprod. 2012;86(5):1-10.
20. Escobar–Morreale HF, Luque–Ramirez M, Gonzalez F. Circulating inflammatory markers in polycystic ovary syndrome: a systematic review and meta-analysis. Fertil Steril. 2011;95(3):1048-1058.
21. Fauser BC, Tarlatzis BC. Frontiers in Gynecological Endocrinology: Volume 3: Ovarian Function and Reproduction – From Needs to Possibilities. Springer. 2015;207.
22. Lizneva D, Diamond MP, Azziz R, Suturina L, Kirubakaran R, Mykhalchenko K, Chernukha G. Phenotypes and body mass in women with polycystic ovary syndrome identified in referral versus unselected populations: systematic review and meta-analysis. Fertil Steril. 2016;106(6):1510-1520.
23. Mitra S, Nayak PK, Agrawai S. Laparoscopic ovarian drilling: an alternative but not the ultimate in the management of polycystic ovary syndrome. J Nat Sci Biol Med. 2015;6(1):40-48.
24. Zagrebelnaya IV. Modern aspects of the pathogenesis and treatment of endocrine infertility. Mejdunarodniy Meditsinskiy Zhurnal. 2010. [Zagrebelnaya IV. Sovremennye aspekty patogeneza i lecheniya endokrinogo besplodiya. Mejdunarodniy Meditsinskiy Zhurnal. 2010.] [in Russian]

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September 2024

25. Yurasov IV. Modern aspects of management in inflammatory diseases of pelvic organs in women. Dissertation. Dalnevostochnyy Gosudarstvennyy Meditsinskiy Universitet. 2014. [Yurasov IV. Sovremennye aspekty taktiki pri vospalitelnyx zabolevaniyax organov malogo taza u jenshin. Dissertatsiya. Dalnevostochnyy Gosudarstvennyy Meditsinskiy Universitet. 2014.] [in Russian]
26. Kolesnikova L, et al. Oxidative stress as a nonspecific pathogenic link of reproductive disorders (review). Sibirskiy Nauchnyy Meditsinskiy Zhurnal. 2012;32(1):58-66. [Kolesnikova L, et al. Oksidativnyy stress kak nespecificheskoe patogeneticheskoe zveno reproduktivnyx narusheniy (obzor). Sibirskiy Nauchnyy Meditsinskiy Zhurnal. 2012;32(1):58-66.] [in Russian]
27. Xabarov SV, Sterlikova NA. Melatonin and its role in the circadian regulation of reproductive function (literature review). Vestnik Novyx Meditsinskix Texnologiy. 2022;29(3):17-31. [Xabarov SV, Sterlikova NA. Melatonin i ego rol v tsirkadnoy regulyatsii reproduktivnoy funktsii (obzor literatury). Vestnik Novyx Meditsinskix Texnologiy. 2022;29(3):17-31.] [in Russian]
28. Syrkasheva AG, Ilina EO, Dolgushina NV. Infertility in women of older reproductive age: causes, management tactics, prospects for preimplantation genetic screening (review). Ginekologiya. 2016;18(3):40-43. [Syrkasheva AG, Ilina EO, Dolgushina NV. Besplodie u jenshin starshego reproduktivnogo vozrasta: prichiny, taktika vedeniya, perspektivy ispolzovaniya preimplantatsionnogo geneticheskogo skrininga (obzor). Ginekologiya. 2016;18(3):40-43.] [in Russian]
29. Asadova GA. Analysis of current problems in overcoming infertility in women using assisted reproductive technologies in the Republic of Uzbekistan. Meditsinskiye Novosti. 2021;(9):21-23. [Asadova GA. Analiz aktualnyx problem po preodoleniyu besplodiya u jenshin s ispolzovaniem metodov vspomogatelnyx reproduktivnyx texnologiy v Respublike Uzbekistan. Meditsinskiye Novosti. 2021;(9):21-23.] [in Russian]
30. Shukurov FI, Jabbarova YuK. Assessment of ovarian reserve in women with infertility caused by structural ovarian pathologies after endosurgical operations. Vestnik Tashkentskoy Meditsinskoy Akademii. 2016;(2):106-108. [Shukurov FI, Jabbarova YuK. Otsenka ovariyalnogo rezerva u jenshin s besplodiem, obuslovlennym struktornymi patologiyami yaichnikov, perenesshix endoxirurgicheskie operatsii. Vestnik Tashkentskoy Meditsinskoy Akademii. 2016;(2):106-108.] [in Russian]
31. Shukurov FI. Minimally Invasive Surgery In Restoring Reproductive Function Of Female Infertility Caused By Benign Ovarian Structural Changes. Am J Med Med Sci. 2016;6(5):182-185.
32. Shukurov FI, Aypova FM. Features of endosurgical treatment and prediction of recurrence of ovarian follicular cysts. Xirurgiya Uzbekistana. 2016;(4):49-51. [Shukurov FI, Aypova FM. Osobennosti endoxirurgicheskogo lecheniya i prognozirovaniya retsidiva follikulyarnyx kist yaichnikov. Xirurgiya Uzbekistana. 2016;(4):49-51.] [in Russian]
33. Shukurov FI, Aypova FM. The Role of Reproductive Surgery in Diagnostics and Treatment of Combined Pathologies in Women with Infertility Caused by Benign Structural Changes of Ovaries. Am J Med Med Sci. 2019;9(5):210-212.
34. Shukurov FI, Aypova FM. Correction of hormonal disorders in women with infertility caused by benign structural changes of the ovaries after endosurgical treatment. J Teoreticheskoy i Klinicheskoy Meditsiny. 2019;(5):140-141. [Shukurov FI, Aypova FM. Korretsiya gormonalnyx narusheniy u jenshin s besplodiem, obuslovlennym dobrokachestvennymi struktornymi izmeneniyami yaichnikov posle endoxirurgicheskogo lecheniya. Jurnal Teoreticheskoy i Klinicheskoy Meditsiny. 2019;(5):140-141.] [in Russian]
35. Shukurov FI, Jabbarova YuK. The role of immunohistochemical studies in the diagnosis of infertility in women with polycystic ovary syndrome. Abstracts of the XXXI International Congress "New Technologies in the Diagnosis and Treatment of Gynecological Diseases" with a Course of Endoscopy. Moscow. 2018;31-33. [Shukurov FI, Jabbarova YuK. Rol immunogistoximicheskix issledovaniy v diagnostike besplodiya u jenshin s sindromom polikistoznyx yaichnikov. Tezisy XXXI Mejdunarodnogo kongressa "Novye Texnologii v Diagnostike i Lechenii Ginekologicheskix Zabolevaniy" s kursom Endoskopii. Moskva. 2018;31-33.] [in Russian]

ISSN NO: 2770-2936
September 2024

36. Awonuga AO, Camp OG, Abu-Soud HM. A review of nitric oxide and oxidative stress in typical ovulatory women and in the pathogenesis of ovulatory dysfunction in PCOS. Reprod Biol Endocrinol. 2023;21(1):111.
37. Cookingham LM, Van Voorhis BJ, Ascoli M. Do alterations in follicular fluid proteases contribute to human infertility? J Assist Reprod Genet. 2015;32(5):737-745.
38. Edwards RG, Bavister BD, Steptoe PC. Early stages of fertilization in vitro of human oocytes matured in vitro. Nature. 1969;221(5181):632-635.
39. Shukurov FI. Endocrine disorders in women with infertility caused by benign structural changes of the ovaries. J Teoreticheskoy i Klinicheskoy Meditsiny. 2016;(2):71-73. [Shukurov FI. Endokrinnye rasstrojstva u jenshin s besplodiem, obuslovlennym dobrokachestvennymi struktornymi izmeneniyami yaichnikov. Jurnal Teoreticheskoy i Klinicheskoy Meditsiny. 2016;(2):71-73.] [in Russian]
40. Santos MA, Kuijk EW, Macklon NS. The impact of ovarian stimulation for IVF on the developing embryo. Reproduction. 2010;139(1):23-34.
41. Johnson MH. Enzymes in mammalian embryogenesis: Key players or background noise? J Reprod Fertil. 1998;112(2):361-367.
42. Gracia C, Sammel MD, Freeman EW, Lin H, Nelson DB, Kapoor S. Defining luteal phase deficiency: A model using repeated measures. Fertil Steril. 2005;84(2):376-382.
43. Moffatt O, Auger N, Piquette-Miller M. The role of placental enzyme activity in regulating fetal exposure to drugs. Placenta. 2006;27(8-9):776-786.
44. Mitchell RT, Saunders PT, Sharpe RM. Male infertility: Do genes and environment interact? Semin Reprod Med. 2008;26(2):151-160.
45. Havelock JC, Rainey WE, Carr BR. Ovarian granulosa cell lines as models for study of cell function. Methods Enzymol. 2004;378:169-177.
46. Shukurov FI. Results of intraoperative cytomorphological studies in structural pathology of the ovaries in women with infertility. Byulleten Assotsiatsii Vrachey Uzbekistana. 2016;(3):58-60. [Shukurov FI. Rezultaty intraoperatsionnyx tsitomorfologicheskix issledovaniy pri strukturnoy patologii yaichnikov u jenshin s besplodiem. Byulleten Assotsiatsii Vrachey Uzbekistana. 2016;(3):58-60.] [in Russian]
47. Cha KY, Koo JJ, Ko JJ, Choi DH, Han SY, Yoon TK. Pregnancy after in vitro fertilization of human follicular oocytes collected from non-stimulated cycles, their culture in vitro and their transfer in a donor oocyte program. Fertil Steril. 1991;55(1):109-113.
48. Shukurov FI. The use of Distreptase in the comprehensive rehabilitation therapy of women after laparoscopic removal of ovarian follicular cysts. Infektsiya, Immunitet i Farmakologiya. 2016;(7):122-126. [Shukurov FI. Primenenie preparata Distreptaza v kompleksnoy reabilitatsionnoy terapii u jenshin, posle laparoskopicheskogo udaleniya follikulyarnyx kist yaichnikov. Infektsiya, Immunitet i Farmakologiya. 2016;(7):122-126.] [in Russian]
49. Diedrich K, Fauser BC, Devroey P, Griesinger G. The role of the endometrium and embryo in human implantation. Hum Reprod Update. 2007;13(4):365-377.
50. Nikolaou D, Templeton A, Symonds EM. Early embryo development: The biological base for prediction. Hum Reprod. 2001;16(7):1318-1322.
51. Kim JS, Lee Y, Kim YW. Identification and characterization of protein markers associated with preimplantation embryo development. J Proteome Res. 2008;7(5):2102-2111.
52. Hayashi M, Kuramoto K. Analysis of mitochondrial activity in preimplantation embryos. J Assist Reprod Genet. 2014;31(12):1627-1634.
53. Gellersen B, Brosens JJ, Brosens IA. Decidualization of the human endometrium: Mechanisms, functions, and clinical perspectives. Semin Reprod Med. 2007;25(6):445-453.
54. Shukurov FI, Aypova FM, Yuldasheva NZ. Retrospective analysis of reproductive function in women who underwent endosurgical operations on the ovaries. Novosti Dermatovenereologii i Reproduktivnogo Zdorovya. 2017;(3-4):155-157. [Shukurov FI, Aypova FM, Yuldasheva NZ. Retrospektivnyy analiz reproduktivnoy funktsii u jenshin, perenesshix endoxirurgicheskie

ISSN NO: 2770-2936
September 2024

operatsii na yaichnikax. Novosti Dermatovenereologii i Reproduktivnogo Zdorovya. 2017;(3-4):155-157.] [in Russian]
55. Hsieh YY, Chang CC. Role of reactive oxygen species in the regulation of capacitation and hyperactivation in spermatozoa. Asian J Androl. 2007;9(4):522-529.
56. Richter KS, Rittenberg V, Anderson RE. Laser-assisted hatching: What does it have to offer? J Assist Reprod Genet. 2001;18(2):81-89.
57. Choi YH, Okada K. Role of extracellular matrix enzymes in follicle development and oocyte maturation. Reproduction. 2005;129(4):463-469.
58. Simopoulou M, Giannelou P. The effect of antioxidant supplementation on oxidative stress markers in IVF patients: A systematic review. J Assist Reprod Genet. 2017;34(4):451-461.
59. Amleh A, Dean J. Fertilin and other ADAMs as integrin ligands: Critical factors in oocyte-sperm binding? Biol Rev. 2002;77(3):453-469.
60. Eppig JJ, O'Brien MJ, Wigglesworth K. Mouse oocytes matured in vitro develop parthenogenetically into blastocysts. Dev Biol. 1996;176(2):377-383.
61. Shukurov FI, Jabbarova YuK. Immunohistochemical features of the endometrium in women with infertility caused by benign structural ovarian changes. J Teoreticheskoy i Klinicheskoy Meditsiny. 2018;(2):107-110. [Shukurov FI, Jabbarova YuK. Immunogistoximicheskie osobennosti endometriya u jenshin s besplodiem, obuslovlennym dobrokachestvennymi struktornymi izmeneniyami yaichnikov. Jurnal Teoreticheskoy i Klinicheskoy Meditsiny. 2018;(2):107-110.] [in Russian]
62. Hardy K, Spanos S. Growth factor expression and function in the human and mouse preimplantation embryo. J Endocrinol. 2002;172(2):221-236.
63. Azarnia R, Smith DM. Role of matrix metalloproteinases in mouse embryo hatching. Reproduction. 1999;117(3):721-728.
64. Ebner T, Moser M. Laser-assisted hatching of human embryos: Rationale, benefits, and concerns. J Assist Reprod Genet. 2003;20(1):29-36.
65. Guerin P, El Mouatassim S, Menezo Y. Oxidative stress and protection against reactive oxygen species in the preimplantation embryo and its surroundings. Hum Reprod Update. 2001;7(2):175-189.
66. Hillier SG, Tetsuka M. Role of ovarian stromal tissue in the regulation of steroidogenesis and ovulation in the mammal. Reproduction. 1997;121(5):517-524.
67. Matsuda T, Fukuda Y. The role of metalloproteinases in ovulation and follicular development. Reprod Med Biol. 2000;11(2):61-66.