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PROTEOMIC MARKERS IN THE DIAGNOSIS AND PROGNOSIS OF FEMALE INFERTILITY: CURRENT APPROACHES AND PERSPECTIVES

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Abstract:

Aim. To conduct a comprehensive analysis of the role of proteomic markers in the diagnosis and prognosis of female infertility.

Materials. The review includes publications from electronic databases such as PubMed, Google Scholar, and eLibrary, selected according to PRISMA guidelines. The analysis included 82 publications from PubMed, 56 publications from eLibrary, and 22 publications from Google Scholar.

Results. Proteomic markers, such as anti-Müllerian hormone (AMH), osteopontin, and inflammatory markers, demonstrated high sensitivity and specificity in the diagnosis of female infertility. The application of these markers has improved the prediction of treatment outcomes, including in vitro fertilization (IVF), and contributed to a more accurate assessment of ovarian reserve. Current approaches include the integration of proteomic data with other omics technologies to create personalized treatment strategies.

Conclusion. Proteomic markers have significant potential in the diagnosis and prognosis of female infertility. Their implementation in clinical practice requires further research and standardization of methods, which will improve women's reproductive health and enhance the effectiveness of infertility treatment.

Keywords: *proteomic markers; female infertility; diagnosis; prognosis; reproductive health; personalized medicine.*

Introduction

Female infertility represents a serious medical and social problem affecting millions of women worldwide [1]. Modern methods of diagnosing and treating infertility often rely on hormonal profile analysis, ultrasound examinations, and other clinical data [2]. However, despite progress in this field, a significant number of cases of female infertility remain unexplained, highlighting the need for new biomarkers and diagnostic methods [3]. In recent years, proteomic markers have attracted the attention of researchers as a promising tool for improving the diagnosis and prognosis of female infertility [4].

Proteomic markers, which are proteins and peptides detected in biological fluids and tissues, reflect the functional state of cells and tissues at the molecular level. Their application in reproductive medicine can contribute to the more accurate identification of pathological changes leading to infertility and to predicting the effectiveness of various therapeutic interventions. The study of proteomic markers allows for a deeper understanding of the pathogenesis of infertility, the identification of new diagnostic targets, and the development of personalized treatment approaches [5].

The aim of this review is to evaluate the role of proteomic markers in the diagnosis and prognosis of female infertility, as well as to analyze current approaches to their application in clinical practice. The review also aims to assess the prospects for the development of proteomic technologies and their integration with other omics approaches to improve the accuracy of diagnosis and the effectiveness of infertility treatment.

Proteomics as a Research Method

Proteomics is the science that studies the complete set of proteins (proteome) in an organism, organ, tissue, or cell, as well as their changes under various conditions. Proteomics involves not only the identification and quantification of proteins but also the analysis of their functions, interactions, and modifications. Unlike genomics, which studies a stable set of genes, proteomics allows the exploration of dynamic changes occurring at the protein level in response to various internal and external factors [6].

In medical research, proteomics plays an important role because proteins are key performers of biological functions and often change under various pathological conditions [7]. Proteomic markers can be used for the diagnosis, prognosis, and monitoring of diseases, including female infertility. Due to their ability to reflect the functional state of cells and tissues, proteomic markers provide unique opportunities for more accurate diagnosis and the development of personalized therapeutic approaches [8].

Methods of Analyzing Proteomic Markers

Various technologies are used to analyze proteomic markers, each with its own advantages and limitations. Here are some key methods used in proteomic research:

Mass Spectrometry (MS). This is the main method for proteome analysis, which allows the identification and quantification of proteins in complex mixtures. Mass spectrometry involves the ionization of proteins, their fragmentation, and the measurement of fragment masses. MS can be used for both global analysis of the entire proteome and targeted analysis of individual proteins.

Proteomic Chips. These devices allow the simultaneous analysis of a large number of proteins using the principle of specific binding of antigens to antibodies applied to the chip's surface. Proteomic chips are effective for the rapid screening of protein markers in clinical samples and can be used for the diagnosis of various diseases, including infertility.

Two-Dimensional Gel Electrophoresis (2D-GE). This method involves the separation of proteins by their isoelectric point and molecular mass. After separation, proteins can be identified and quantified using mass spectrometry. 2D-GE is often used to study changes in protein expression in various diseases.

Immunoaffinity Methods. These include various techniques based on the specific binding of proteins to antibodies, such as ELISA (enzyme-linked immunosorbent assay). These methods allow the detection and quantification of specific proteins in biological samples.

Advantages and Limitations of Proteomic Analysis.

Proteomic analysis has several advantages that make it an important tool in reproductive medicine:

High Sensitivity and Specificity. Modern proteomic methods, especially mass spectrometry, offer high sensitivity and specificity, allowing the detection of small changes in protein levels.

Dynamic Study of Proteins. Proteomics allows the analysis of changes in protein expression in response to various physiological and pathological processes, which is especially important for studying dynamic processes such as ovulation and implantation.

Integration with Other "Omics" Approaches. Proteomics can be integrated with genomics, transcriptomics, and metabolomics to create a more complete understanding of the pathogenesis of female infertility.

However, despite all its advantages, proteomic analysis also has several limitations:

Complexity of Data and Their Interpretation. Proteomic studies generate large volumes of data that require complex analysis and interpretation, which can be challenging without appropriate software and expert experience.

Dependence on Sample Quality. The results of proteomic analysis strongly depend on the quality and quantity of the initial material, which requires strict control over the collection and storage of samples.

High Cost of Research. Proteomic studies require expensive equipment and reagents, limiting their widespread use in routine clinical practice.

Despite these limitations, proteomics continues to develop, offering new opportunities for the diagnosis and treatment of female infertility.

Proteomic Markers and Their Role in the Pathogenesis of Female Infertility

Proteomic markers are proteins and peptides whose expression can change depending on the state of the reproductive system [9]. In the context of female infertility, key markers include proteins associated with folliculogenesis, ovulation, implantation, as well as inflammatory and immune responses [10]. Some of the most significant proteomic markers associated with various forms of infertility include:

Activation and Inhibition of Metalloproteinases (MMPs). These enzymes play a key role in remodeling the extracellular matrix, which is crucial for ovulation and implantation processes. Imbalance in MMP activity can lead to pathologies such as endometriosis and implantation failure.

Antioxidant Proteins. For example, superoxide dismutase (SOD) and catalase, which protect cells from oxidative stress. Reduced activity of these proteins can lead to oocyte damage and impaired quality, resulting in infertility.

Protein Kinases. Proteins such as protein kinase C (PKC) regulate numerous cellular processes, including cell proliferation and apoptosis. Dysregulation of their activity can affect follicular maturation and embryo development.

Immune Proteins. Cytokines and other inflammatory mediators, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), can influence inflammatory processes in the reproductive system, often associated with infertility caused by inflammatory diseases.

Molecular Mechanisms of Proteomic Markers in Infertility

Changes in the proteome can significantly affect a woman's reproductive function, contributing to the pathogenesis of various forms of infertility. Key molecular mechanisms include:

Disruptions in Folliculogenesis. Proteomic markers such as anti-Müllerian hormone (AMH) and inhibin B are associated with the quantity and quality of follicles. Changes in the expression of these markers may indicate reduced ovarian reserve and impaired follicular maturation.

Ovulation Disorders. Proteins involved in regulating ovulation, such as gonadotropins and their receptors, may undergo changes, leading to anovulation or impaired release of the oocyte.

Implantation Defects. Proteomic markers related to endometrial receptivity, such as integrins and osteopontin, play an important role in embryo attachment to the uterine wall. Disruptions in their expression can cause unsuccessful implantation attempts [11]. These mechanisms underscore how changes in proteomic markers can lead to the disruption of key processes necessary for successful conception and pregnancy maintenance.

Interaction of Proteomic Markers with Other Molecular Pathways

Proteomic markers rarely act in isolation; their functions and effects often depend on interactions with other molecular pathways, including genomic, transcriptomic, and metabolic processes [12]. These interactions can be complex and multifaceted:

Genetic Pathways. Proteomic markers may change as a result of genetic mutations or epigenetic modifications that affect the expression of certain genes. For example, mutations in genes encoding antioxidant defense enzymes may lead to decreased levels of corresponding proteins and increased oxidative stress.

Transcriptomic Connections. Proteomic markers often correlate with changes in mRNA expression, allowing them to be used for more accurate diagnosis. For instance, changes in the expression of genes regulating inflammatory processes may be reflected in the levels of corresponding cytokines.

Metabolic Pathways. Proteomic markers may be linked to metabolic disorders, such as hormone imbalances or disrupted cellular energy metabolism. For example, proteins involved in glucose metabolism can influence folliculogenesis and oocyte quality [13].

Thus, the interaction of proteomic markers with other molecular pathways plays a key role in the pathogenesis of female infertility, opening new opportunities for a comprehensive approach to the diagnosis and treatment of this condition.

Diagnostic Significance of Proteomic Markers

Proteomic Markers in the Early Diagnosis of Infertility: Early diagnosis of female infertility plays a key role in the timely identification of pathology and the prescription of appropriate treatment. Proteomic markers, due to their ability to reflect changes in biological processes at the molecular level, can be used to identify the risk of infertility long before clinical symptoms appear [14]. Some of the proteomic markers that can be used for early diagnosis include:

Anti-Müllerian Hormone (AMH): The level of AMH correlates with the number of antral follicles in the ovaries and is used to assess ovarian reserve. A decrease in AMH levels may indicate early depletion of ovarian reserve, which is a predictor of infertility [15].

Interleukin-6 (IL-6): This cytokine is associated with inflammatory processes in the reproductive system, and its elevated levels may indicate inflammatory conditions, such as endometriosis, which can lead to infertility [16].

Osteopontin: A protein involved in the attachment of the embryo to the endometrium. Changes in its level may signal implantation problems, which can be an early indicator of infertility [17].

These markers allow physicians to identify patients at increased risk of developing infertility and to initiate preventive treatment or more intensive monitoring of reproductive health.

Comparative Analysis of Diagnostic Accuracy of Proteomic Markers: The effectiveness of different proteomic markers in diagnosing infertility varies depending on their specificity and sensitivity. Comparative analysis of the diagnostic accuracy of these markers helps to determine the most informative ones and assess how well they work in combination:

AMH and FSH (Follicle-Stimulating Hormone): AMH is considered a more accurate marker of ovarian reserve than FSH because its level does not depend on the day of the menstrual cycle and is less prone to fluctuations.

CA-125 and HE4: These markers are traditionally used for diagnosing ovarian cancer but can also be useful in assessing the risk of infertility associated with endometriosis. In combination, these markers provide higher accuracy than when used separately.

Proteomic Panels: Using multi-component panels of markers that include various proteins and peptides significantly improves diagnostic accuracy. Such panels can account for different aspects of the pathogenesis of infertility, from inflammation to hormonal balance [18].

Comparative analysis shows that using a combination of several markers often yields better results than using a single marker, making such approaches preferable in clinical practice [19].

Application of Proteomic Markers in Clinical Practice: Proteomic markers are gradually finding their application in clinical practice, although their use is not yet widespread [20]. Currently, the main areas of implementation of proteomic markers are:

Ovarian Reserve Diagnosis: The use of AMH to assess ovarian reserve is becoming a standard in reproductive medicine, especially when planning in vitro fertilization (IVF).

Assessment of Inflammatory Processes: Proteomic markers, such as IL-6, are used to diagnose inflammatory conditions that can lead to infertility [21]. This allows for timely prescription of antibacterial or anti-inflammatory therapy.

Personalized Medicine: Proteomic data are used to create personalized treatment plans for infertility. For example, the levels of certain markers can be used to determine the optimal ovarian stimulation regimen or predict the success of IVF [22].

The introduction of proteomic markers into routine diagnostics faces several challenges, such as the need to standardize analytical methods and the high cost of equipment. However, technological advancements and increased accessibility of these methods promise to enhance their role in the future. In the long term, broader use of proteomic markers could significantly improve the diagnosis and treatment of infertility, making treatment approaches more accurate and personalized [23].

Prognostic Significance of Proteomic Markers

Proteomic markers play a crucial role in predicting the success of various infertility treatments, such as in vitro fertilization (IVF) and pharmacotherapy [24]. Their use allows for a more accurate assessment of the likelihood of a successful outcome and helps in selecting the optimal treatment plan for each patient:

AMH and IVF Success. The level of anti-Müllerian hormone (AMH) is widely used to predict ovarian response to stimulation in IVF protocols. A high level of AMH is typically associated with better IVF outcomes, including a greater number of retrieved oocytes and higher chances of a successful pregnancy [25].

Osteopontin and Embryo Implantation. Osteopontin, a protein associated with endometrial receptivity, can predict the success of embryo implantation after IVF. A high level of osteopontin in the endometrium is linked to an increased likelihood of successful implantation [26].

Proteomic Inflammatory Markers and Pharmacotherapy. Elevated levels of inflammatory markers, such as interleukin-6 (IL-6), may indicate the need for anti-inflammatory therapy to improve infertility treatment outcomes, particularly in cases associated with endometriosis or chronic inflammation [27]. These findings demonstrate how proteomic markers can be used to predict individual responses to treatment and enhance the effectiveness of therapeutic interventions.

Development of Prognostic Models Based on Proteomic Data

Developing prognostic models based on proteomic data is a promising area in reproductive medicine [28]. These models can integrate data from multiple proteomic markers and consider other clinical parameters, allowing for more accurate predictions of treatment outcomes:

Multi-Component Proteomic Panels: Including several proteomic markers in one panel enables the creation of more accurate models for predicting treatment outcomes [29]. For example, a combination of AMH, osteopontin, and inflammatory markers can be used to predict IVF success and embryo survival.

Machine Learning for Analyzing Large Proteomic Data: Using machine learning methods to analyze large volumes of proteomic data opens new possibilities for developing prognostic models. These models can be tailored to individual patient characteristics, improving prediction accuracy.

Clinical Decisions Based on Proteomics. Developing software and tools for clinicians that integrate proteomic data and assist in making optimal treatment strategy decisions. These prognostic models can significantly improve the personalization of treatment, making it more accurate and effective [30].

Proteomic Markers and Long-Term Prognosis of Reproductive Health.

Proteomic markers not only assist in the short-term but can also be used to predict long-term reproductive health outcomes, such as pregnancy success and embryo survival:

Proteomic Markers and Embryo Survival. Some markers, such as proteins associated with apoptosis or cell adhesion, can predict how successfully an embryo will develop after implantation [31]. This can aid in selecting the most viable embryos for transfer.

Predicting Miscarriage Risk. Markers such as osteopontin and certain cytokines can be used to assess the risk of miscarriage. For instance, an imbalance in these markers' levels may indicate a higher risk, necessitating additional monitoring and potential intervention [32].

Long-Term Fertility Prognosis. Proteomic markers can also be used to predict long-term fertility, helping to determine if additional interventions, such as repeat IVF cycles or hormonal support, will be needed in the future [33]. Thus, proteomic markers play a crucial role in developing long-term strategies for maintaining and restoring reproductive health, providing better insight into potential risks and treatment outcomes [34].

Modern Approaches to the Use of Proteomic Markers

Personalized medicine aims to tailor treatment to the individual characteristics of the patient, which is especially important in the context of infertility treatment [35]. Proteomic markers play a key role

in this strategy, as they allow the identification of specific biological processes occurring in a woman's body and the adaptation of treatment to these processes:

Individualization of IVF Protocols. Proteomic markers, such as AMH and proteins associated with endometrial receptivity, can be used to create individualized ovarian stimulation protocols and determine the optimal timing for embryo transfer [36].

Selection of Pharmacotherapy. The use of proteomic data allows for determining which medications will be most effective for a particular patient, considering her biological characteristics, such as inflammation levels or hormonal imbalances [37].

Real-Time Treatment Monitoring. Proteomic markers can be used to monitor the effectiveness of treatment and make timely adjustments to therapeutic approaches. For example, changes in the levels of certain proteins may indicate the need to modify drug dosages or treatment strategies [38]. This approach not only increases the effectiveness of treatment but also minimizes side effects, improving the patient's overall condition and reproductive outcomes.

Integration of Proteomic Data with Other Omics Technologies

Modern biomedicine is increasingly moving towards the integration of data from various "omics" disciplines to create a more complete and accurate picture of patient health [39]. The integration of proteomic data with other omics technologies, such as genomics, transcriptomics, and metabolomics, opens new possibilities for a comprehensive approach to the diagnosis and treatment of infertility:

Genomics and Proteomics. Genomic data can provide information about the predisposition to certain diseases, while proteomic markers reflect the current health status. Combining these data can help predict the development of infertility and choose the most effective methods of prevention and treatment [40].

Transcriptomics and Proteomics. Transcriptomic data on mRNA can be integrated with proteomic data to study how changes in gene expression are reflected at the protein level, which is particularly useful for understanding the mechanisms of infertility pathogenesis [41].

Metabolomics and Proteomics. Analyzing metabolites along with proteomic markers can help assess energy metabolism and other metabolic processes related to reproductive function, which is important for diagnosing and correcting metabolic disorders in women with infertility. Integrating these data contributes to creating more accurate disease models and allows for the development of personalized treatment strategies that consider multiple biological factors [42].

Proteomic markers continue to be the focus of modern research aimed at improving the diagnosis and prognosis of infertility. Every year, new technologies and methods are emerging that expand the possibilities of proteomics in reproductive medicine:

Development of More Advanced Proteomic Panels. Including dozens or even hundreds of proteins in proteomic panels allows for increased diagnostic accuracy and the prediction of infertility treatment outcomes [43]. These panels take into account various aspects of pathogenesis, such as inflammation, hormonal imbalance, and cellular stress.

Improvement of Mass Spectrometry Technologies. Advances in mass spectrometry technology allow for more precise and rapid identification and quantification of proteins in biological samples, making this method more accessible for clinical practice [44]. These studies and developments open new prospects for using proteomic markers in clinical practice, making infertility diagnosis and treatment more accurate, effective, and accessible.

Discussion

The results of the literature review show that proteomic markers have significant potential in diagnosing and predicting female infertility. Their use can substantially improve diagnostic accuracy, allowing for the identification of various forms of infertility at early stages and predicting treatment responses [45]. Proteomic markers, such as AMH, osteopontin, and inflammatory markers, are already beginning to be implemented in clinical practice, providing a more personalized approach to treatment.

The significance of these markers lies in their ability to reflect the current state of the reproductive system at the molecular level, opening up opportunities for more precise treatment strategy selection and increased treatment effectiveness [46]. The introduction of proteomic markers into routine clinical practice could lead to improved reproductive outcomes and a reduction in the number of unsuccessful IVF cycles and other therapeutic interventions [47].

Despite the obvious advantages, the use of proteomic markers in clinical practice faces several limitations. First, many existing studies are limited in sample size and population diversity, which may limit the generalizability of the results. Second, the high cost of proteomic analysis and the need for sophisticated equipment make its application inaccessible to most clinics.

Additionally, there is limited standardization of proteomic marker analysis methods, making it difficult to compare results between different studies and centers. The lack of clear guidelines and protocols for using proteomic markers in clinical practice is also a significant barrier to their widespread implementation [48].

To overcome existing limitations and more widely implement proteomic markers in clinical practice, additional research is needed, focusing on:

Expanding Clinical Trials. Large multicenter studies involving diverse populations are needed to confirm the diagnostic and prognostic significance of proteomic markers.

Development and Implementation of Standard Protocols. Creating standard protocols for the analysis and interpretation of proteomic data will improve the comparability of results between different studies and clinics. Research focused on integrating proteomics with other omics technologies (genomics, metabolomics) and diagnostic methods can ensure a more comprehensive and accurate approach to treating infertility [49].

Introduction of New Technologies. Developing new technologies that reduce the cost and simplify the proteomic analysis process will make it more accessible for widespread use in clinical practice [50]. These research directions will help overcome existing limitations and open new horizons for using proteomic markers in diagnosing and treating female infertility.

Conclusion

This review confirmed the important role of proteomic markers in diagnosing and predicting female infertility. Markers such as AMH, osteopontin, and inflammatory proteins are effective in assessing ovarian reserve and predicting treatment success, including IVF. These data provide a better understanding of infertility pathogenesis at the molecular level, opening up opportunities for personalized treatment strategies. Proteomic markers have the potential for early diagnosis and monitoring of infertility treatment. Additional research and method standardization are needed for their widespread implementation in clinical practice. In the future, they may become an essential part of comprehensive infertility diagnosis and treatment, contributing to improving women's reproductive health.

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

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