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GENETIC AND MOLECULAR BIOMARKERS IN PREDICTING PREGNANCY COMPLICATIONS USING ARTIFICIAL INTELLIGENCE

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ABSTRACT

Pregnancy complications, in particular preeclampsia and other forms of placental dysfunction, remain one of the leading causes of maternal and perinatal morbidity and require improvement in early diagnosis methods. Traditional clinical criteria often reveal pathology at the stage of clinical manifestation, which limits the possibilities of prevention and timely intervention. In recent years, special attention has been paid to the use of biomarkers of placental and endothelial dysfunction, as well as artificial intelligence and machine learning methods for early prediction of adverse pregnancy outcomes. The review analyzes current data on the role of angiogenic, inflammatory, and molecular markers, as well as integrative digital models in personalized perinatal diagnostics. It is shown that the combination of biomarker approaches and intelligent analytical tools is a promising direction, but requires further clinical validation, standardization and consideration of ethical aspects of implementation.

KEYWORDS: perinatal diagnostics, preeclampsia, biomarkers, angiogenic factors, artificial intelligence, machine learning, personalized medicine.

INTRODUCTION

Pregnancy complications remain one of the key causes of maternal and perinatal morbidity and mortality worldwide, despite significant progress in obstetrics and perinatal medicine [1-3]. According to the World Health Organization, preeclampsia and related hypertensive disorders complicate up to 5-8% of pregnancies globally, and in the Russian Federation their contribution to the structure of severe maternal complications and premature birth remains consistently high. A significant clinical problem lies in the fact that traditional diagnostic criteria based on the assessment of blood pressure and proteinuria often reveal pathology already at the stage of clinical manifestation, when the possibilities of prevention are limited [7-9].

In recent years, more and more attention has been paid to innovative approaches to perinatal diagnostics aimed at early prediction of pregnancy complications even before the onset of pronounced clinical symptoms. In this context, circulating biomarkers of placental dysfunction, including soluble tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF), are of particular interest, reflecting key links in impaired angiogenesis-dependent pregnancy adaptation [10]. Changing their ratio is considered as one of the most promising tools for stratifying the risk of preeclampsia, fetal growth retardation and premature birth.

Simultaneously with the development of biomarker diagnostics, artificial intelligence and machine learning methods are being actively introduced into perinatal practice, allowing the analysis of large amounts of clinical, laboratory and instrumental data [12]. The use of artificial intelligence algorithms opens up new opportunities for personalized prediction of adverse pregnancy outcomes and optimization of surveillance tactics for high-risk pregnant women. However, despite the growing interest in these technologies, the number of prospective clinical trials assessing their real prognostic value remains limited, especially in the context of national health systems [14-16].

An additional complication is the high heterogeneity of pregnancy complications, including preeclampsia, placental insufficiency, and inflammatory-associated disorders, which requires an integrated approach to interpreting biomarker and digital data. To date, there is a lack of a sufficient number of generalizing reviews in the Russian and international literature that systematically analyze the combined use of biomarkers and artificial intelligence specifically in the context of perinatal diagnostics [1-3, 11-14].

In this regard, the integration of molecular markers and intelligent analytical tools into a single predictive model focused on early detection of pregnancy complications is becoming an urgent task of modern obstetric science.

The purpose of this review is to analyze modern innovative approaches to perinatal diagnostics with an emphasis on the role of biomarkers and artificial intelligence methods in predicting pregnancy complications, as well as to assess their potential clinical significance and directions for further research.
Materials and methods. A literature review and analysis of scientific publications devoted to innovative approaches to perinatal diagnostics, with an emphasis on biomarkers and artificial intelligence methods in predicting pregnancy complications, has been conducted. The search for sources was carried out in the databases eLibrary, PubMed, Google Scholar and Google Academy using the keywords "perinatal diagnostics", "preeclampsia", "biomarkers", "artificial intelligence", "machine learning". Additional criteria were restrictions on the publication period (the last 5 years), language (Russian and English), and type of research. The review included systematic reviews, meta-analyses, randomized and cohort studies, as well as original full-text articles that are publicly available and contain statistically sound results. A total of 54 publications corresponding to the objectives of this review were selected and analyzed according to the specified criteria.

Modern concepts of the pathogenesis of pregnancy complications as the basis of perinatal diagnosis
In recent years, a number of studies have demonstrated a close relationship between impaired placental function, endothelial activation, and the development of pregnancy complications, primarily preeclampsia. Convincing data presented in the works of M.A. Chegaeva, M.K. Shishkina, and E.V. Ponomarenko confirm the leading role of early trophoblast invasion disorders and incomplete remodeling of spiral arteries in the formation of placental insufficiency. According to the authors, it is chronic placental ischemia that triggers a cascade of pathological reactions, including hypoxic stress, systemic inflammation, and endothelial dysfunction.
A number of studies have shown that under conditions of placental hypoxia, excessive secretion of antiangiogenic factors occurs, primarily soluble tyrosine kinase-1 (sFlt-1), which leads to functional inactivation of VEGF and PlGF. This confirms the hypothesis of the key role of angiogenic imbalance in the pathogenesis of preeclampsia, as well as other pregnancy complications, including fetal growth retardation and premature birth. Tomkiewicz and Darmochwał-Kolarz, based on the analysis of clinical and laboratory data, showed that changes in the levels of angiogenic biomarkers can be detected long before the manifestation of clinical symptoms.
Systemic inflammation is considered as another significant component of pathogenesis that enhances endothelial dysfunction and vascular disorders. The studies of Khalimova F.T. and Shukurov F.A. revealed associations between immuno-inflammatory reactions, including antiphospholipid mechanisms, and an increased risk of complicated pregnancy. The authors emphasize that immune disorders can enhance angiogenic imbalance and contribute to the progression of placental insufficiency.
Along with protein markers, increasing attention is being paid to the regulatory role of microRNAs and galectins involved in the control of angiogenesis and trophoblastic invasion. Karadzov Orlic and Joksic have shown that dysregulation of these molecules is associated with impaired placental development and can be considered as an additional tool for early diagnosis. The data obtained indicate that the pathogenesis of pregnancy complications is multifactorial and cannot be explained by an isolated violation of a single signaling pathway.
Thus, the results of modern research confirm that the combination of placental dysfunction, endothelial activation, and systemic inflammation forms the pathophysiological basis for the use of biomarkers and digital prediction models [18]. The integration of angiogenic, immunoinflammatory, and molecular parameters makes it possible to more accurately assess the individual risk of pregnancy complications and opens up prospects for personalized perinatal diagnosis.

Biomarkers in perinatal diagnostics: from classical indicators to molecular signatures
Despite significant advances in perinatal medicine, hypertensive pregnancy disorders, including preeclampsia, are still registered in 5-10% of pregnant women and remain a significant factor in maternal and perinatal morbidity. The clinical course of preeclampsia is characterized by pronounced variability, from subclinical forms to severe, potentially life-threatening conditions, which significantly complicates the early detection of high-risk patients [20]. Diagnostic criteria used in routine practice, based mainly on the assessment of blood pressure and the presence of proteinuria, usually record the already unfolding pathological process and have limited prognostic information. In this regard, biomarkers reflecting early disorders of placental function and maternal vascular adaptation are of particular interest [21-23].
The most studied and clinically significant group of biomarkers are angiogenic and antiangiogenic factors, primarily soluble tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF). The imbalance between these molecules is considered as a key link in the pathogenesis of placental dysfunction and endothelial damage. An increase in the concentration of sFlt-1 against the background of a decrease in PlGF levels often precedes the clinical manifestations of preeclampsia and is associated with the development of systemic vascular disorders. The sFlt-1/PlGF ratio has proven to be a reliable short-term forecasting tool with a high negative prognostic value, which makes it possible to effectively exclude the development of the disease in the near future and optimize the management of pregnant women [24].
In addition to angiogenic factors, increasing attention is being paid to inflammatory and immune markers, including highly sensitive C-reactive protein, interleukins, and peripheral blood cell composition. These parameters reflect the systemic inflammatory response accompanying pathological implantation and impaired remodeling of spiral arteries [16-18]. Despite their lower specificity compared to angiogenic markers, their use in

combined models increases overall prognostic accuracy and allows for a deeper assessment of the degree of involvement of immune-inflammatory mechanisms.

In recent years, high-resistance technologies aimed at identifying proteomic, transcriptomic, and metabolomic signatures of pregnancy complications have been actively developing. The detection of circulating microRNAs, ring RNAs, and placental proteins such as PP13, annexin A2, and GDF-15 expands the understanding of the molecular heterogeneity of preeclampsia [27]. These data create prerequisites for the transition from the use of single markers to the formation of complex biomarker panels.

Of particular importance in this context is the integration of biomarker data with artificial intelligence and machine learning methods. Digital prognostic models allow us to take into account complex nonlinear relationships between clinical characteristics, laboratory parameters and the dynamics of the gestational process. According to a number of studies, such approaches are superior to traditional algorithms in predicting unfavorable maternal and perinatal outcomes.

However, the clinical use of biomarkers is limited by the so-called "windows of applicability" associated with gestational age, population characteristics, and the presence of concomitant pathology. The information content of individual indicators can vary significantly at different stages of pregnancy, which requires a differentiated approach to their interpretation [29]. The economic feasibility and organizational capabilities of the healthcare system remain additional factors influencing the introduction of innovative diagnostic technologies.

As shown in Table 1, the use of biomarker strategies in combination with clinical assessment makes it possible to optimize the primary triage of pregnant women with suspected preeclampsia, more accurately determine the risk level and reduce the frequency of unjustified hospitalizations.

Table 1: Modern biomarkers and digital approaches in the perinatal diagnosis of pregnancy complications [30-35]

Marker/ Technology Group	Key indicators	Pathophysiological significance	Clinical use and limitations
Angiogenic and antiangiogenic factors	sFlt-1, PlGF, sFlt-1/PlGF	They reflect an imbalance of angiogenesis associated with impaired trophoblast invasion, placental ischemia, and the development of endothelial dysfunction underlying preeclampsia and OCD	They are used for short-term prediction of preeclampsia, risk stratification, and management tactics; the information content depends on the gestational age
Inflammatory markers	ratio hs-CRP, IL-6, IL-1b, TNF-α	The systemic inflammatory response of the mother is characterized, associated with pathological placentation and vascular damage	They are used as additional markers in multibiomarker models; they have limited specificity
Immune cell indexes	Ratio of neutrophils to lymphocytes, platelet indices	They reflect the activation of innate immunity and endothelial-thrombotic changes in pregnancy complications	They are available for routine practice, but require interpretation in combination with clinical and biochemical data
Proteomic markers	PP13, GDF-15, annexin A2	They are associated with immune regulation, apoptosis, and adaptation of the placenta to hypoxia	Promising for early screening, but so far limited to research applications
Transcriptomic markers	miRNA, circRNA, lncRNA	They reflect the regulation of the expression of genes involved in angiogenesis, inflammation, and vascular remodeling	A potential basis for personalized diagnostics; there is no standardization of methods
Metabolic profiles	Amino acids, lipid mediators, energy metabolites	They reflect disorders of energy metabolism and oxidative stress in placental insufficiency	They are used in scientific research; they require a complex analytical infrastructure
Digital models and AI	Machine learning algorithms, neural networks	They allow us to identify non-linear relationships between biomarkers, clinical data, and pregnancy outcomes	They increase the accuracy of forecasting, but require validation and clinical interpretability

Multibiomarker panels	Biomarker combinations + clinical data	An integrative approach to assessing the risk of pregnancy complications	The most promising direction, limited by cost and availability

Note. sFlt-1 — soluble FMS-like tyrosine kinase-1; PlGF — placental growth factor; hs-CRP — highly sensitive C-reactive protein; IL — interleukin; TNF-α — tumor necrosis factor-α; miRNA — microRNAs; circRNA — ring RNAs; lncRNAs — long non-coding RNA; GDF-15 — growth differentiation factor-15; PP13 — placental protein-13; AI — artificial intelligence; ZRP — fetal growth retardation.

As a result, the information presented in table 1 reflects the evolution of approaches to assessing the risk of pregnancy complications, from individual indicators to their integrated use. Against this background, the introduction of artificial intelligence and machine learning methods is of particular importance, ensuring the integration of biomarker and clinical data in order to improve the accuracy of the forecast.

Artificial intelligence and machine learning in predicting pregnancy complications

Preeclampsia remains one of the most clinically and prognostically complex pathologies of pregnancy, which is largely due to its heterogeneous course and variable risk of adverse outcomes for mother and fetus. Despite the widespread introduction of biomarkers, including the sFlt-1/PlGF ratio, accurate individual risk assessment is still difficult, especially at the initial treatment stage [39]. In this regard, more and more attention is being paid to artificial intelligence and machine learning methods capable of analyzing large amounts of heterogeneous data and identifying hidden patterns inaccessible to traditional statistical approaches.

Machine learning algorithms are used in obstetrics primarily as tools for integrating clinical, laboratory, and instrumental parameters into a single predictive model [41]. Unlike classical algorithms, such models take into account non-linear interactions between blood pressure indicators, biochemical markers, ultrasound data and gestation period. This is especially important in preeclampsia, where clinical symptoms often lag behind molecular and vascular changes.

The contribution of Burns et al. The goal is to demonstrate the real clinical benefits of biomarkers in everyday practice, which creates the basis for their subsequent inclusion in machine learning algorithms. The authors showed that sFlt-1/PlGF data obtained from hospitalized patients with hypertensive pregnancy disorders allow for more informed decisions about management tactics. Khosla et al. We complemented this approach with an analysis of the clinical symptoms and economic consequences of suspected preeclampsia, emphasizing the importance of accurate forecasting to reduce the burden on the healthcare system.

The work of Palma Dos Reis et al. She expanded the scope of angiogenic markers, showing their prognostic value not only for diagnosis, but also for estimating the time before delivery and the likely method of delivery. These results are especially important for building models predicting short-term pregnancy outcomes. Wah et al. We have contributed to the standardization of data by demonstrating the comparable diagnostic effectiveness of various commercial tests, which is crucial for the training and reproducibility of AI models.

A special place is occupied by the work of Hoyler et al., in which a machine learning model was validated to predict adverse outcomes associated with preeclampsia based on real clinical data. The authors have shown that algorithms based on a limited number of routinely available parameters are capable of achieving high predictive accuracy without loss of clinical interpretability. This is an important step towards the practical implementation of AI support for clinical decisions.

Machine learning models are used not only to predict preeclampsia as such, but also to assess the risk of premature birth, the development of HELLP syndrome and other adverse perinatal outcomes. The use of ensemble methods and gradient boosting makes it possible to form flexible models that adapt to various clinical scenarios [42-44]. At the same time, the integration of biomarkers significantly increases the predictive value compared to models based solely on clinical data.

An important advantage of the introduction of artificial intelligence is the possibility of more accurate risk stratification and personalization of monitoring pregnant women. This potentially reduces the frequency of unjustified hospitalizations and invasive interventions, while increasing the safety of high-risk patients. However, the use of AI comes with a number of limitations, including the risk of algorithmic bias, dependence on the quality of the source data, and the need for clinical interpretation of the results.

An additional challenge remains the introduction of such models into real clinical practice, where transparency of algorithms and trust from doctors are required [45]. Without adequate validation and adaptation to specific populations, even highly accurate models may be of limited use. Thus, artificial intelligence should be considered not as a substitute for clinical thinking, but as a decision support tool.

Taken together, modern research shows that the integration of biomarkers, clinical parameters, and machine learning methods forms a promising direction for the development of perinatal diagnostics [46]. Further prospective studies are needed to assess the clinical efficacy, safety, and cost-effectiveness of such approaches in routine obstetric practice.

Integrative models: combining biomarkers and artificial intelligence in personalized perinatal medicine

The current stage of development of perinatal medicine is characterized by the transition from an isolated analysis of individual indicators to a comprehensive interpretation of biological and digital data. The integration of

multibiomarker panels with artificial intelligence algorithms opens up new opportunities for more accurate prediction of pregnancy complications and personalization of clinical solutions. These approaches are based on combining information about the inflammatory status, angiogenic balance, immune shifts, and functional parameters of the mother and fetus. Recent studies have shown that machine learning is able to identify hidden nonlinear relationships between biomarkers that are inaccessible to traditional statistical models [47-49].

Works by Wang et al. It has been shown that immune-associated molecular markers combined with several machine learning algorithms can improve the accuracy of early detection of preeclampsia. Similarly, Lv et al. developed predictive models for the early form of preeclampsia, in which the use of ensemble algorithms provided more stable prognostic characteristics compared with classical methods. Of particular interest is the approach of Zhou et al., where fundus images were used to predict preeclampsia, which highlights the potential of non-traditional data sources within integrative models.

Additional expansion of predictive systems is achieved by including continuous monitoring data. According to Hassan et al., wearable sensor devices allow the formation of dynamic pregnancy phenotypes, which is especially important for individual risk stratification. In the context of obstetric care, digital models analyzing cardiotocography demonstrate high clinical significance. For example, McCoy et al. developed a deep learning model for predicting neonatal acidemia based on CTG, showing its potential for real-time use. The development of this concept is presented in the work of Ben M'Barek et al., where the updated DeepCTG® 2.0 model provided more accurate detection of pathological conditions compared to previous versions.

Thus, integrative models make it possible to move from a binary risk assessment to a more flexible forecasting system that takes into account the individual characteristics of the course of pregnancy. This creates the basis for a personalized choice of surveillance tactics, frequency of monitoring, and timeliness of interventions [49]. The clinical applicability of such approaches is determined not only by the accuracy of the models, but also by the possibility of their interpretation in everyday practice. In this context, a special role is played by presenting the results in a form understandable to the doctor, which increases confidence in digital tools.

As shown in Table 2, modern artificial intelligence models successfully integrate biomarker, cardiotocography, imaging, and clinical parameter data, demonstrating consistent diagnostic and predictive effectiveness.

Table 2: The role of biomarkers and artificial intelligence algorithms in personalized pregnancy management [47-53]

A source	Type of data and biomarkers	The AI model	Clinical significance and results
Wang et al., 2025	Immune molecular markers, transcriptomic data	Ensemble ML algorithms (RF, XGBoost)	Improving the accuracy of early detection of preeclampsia; identification of immune signatures of the disease
Lv et al., 2025	Clinical data, angiogenic markers	ML models with cross validation	Effective stratification of the risk of early preeclampsia
Zhou et al., 2023	Fundus images	Deep convolutional neural networks	Noninvasive prediction of preeclampsia
Kifle et al., 2022; Burns et al., 2024	sFlt-1, PlGF, sFlt-1/PlGF ratio	Logistic and ML models	Proven clinical applicability for short-term prognosis of preeclampsia
McCoy et al., 2025	Cardiotocography (FHR, UC)	Deep Learning (DL)	Prognosis of neonatal acidemia in the intranatal period
Ben M'Barek et al., 2025	CTG signals	DeepCTG® 2.0 (CNN)	Improved diagnosis of acidemia compared to the traditional interpretation
Hassan et al., 2022	Wearable sensors, physiological signals	ML and DL algorithms	Dynamic personalized risk stratification
Comprehensive integrative approaches	Biomarkers + CTG + clinical data	Hybrid AI models	The basis of personalized perinatal diagnostics

Note. ML — machine learning; DL — deep learning; RF — random forest; CNN — convolutional neural network; sFlt-1 — soluble FMS-like tyrosine kinase-1; PlGF — placental growth factor; CTG — cardiotocography; FHR — fetal heart rate; UC — uterine contractions.

The presented studies reflect the contribution of various author groups to the development of integrative strategies covering both the antenatal and the intranatal periods. Taken together, these data confirm that the combination of biological markers and artificial intelligence is one of the most promising areas for the development of personalized perinatal medicine [45]. The implementation of such solutions in perinatal centers and healthcare systems can contribute to earlier detection of complications, optimize resources, and improve maternal and fetal outcomes.

Limitations, ethical aspects, and prospects for further research in perinatal diagnostics

The rapid introduction of biomarkers and artificial intelligence algorithms into perinatal diagnostics is accompanied not only by the expansion of diagnostic capabilities, but also by a number of methodological and ethical limitations [52]. One of the key problems remains the lack of standardization of biomarker panels and machine learning algorithms, which makes it difficult to compare results between studies and clinical centers. Even well-studied markers such as angiogenic factors demonstrate variability in diagnostic value depending on gestational age, population characteristics, and clinical context, as indicated by the recommendations of the International Society for the Study of Hypertension in Pregnancy (ISSHP) led by Magee et al.

Similar difficulties are typical for AI models, where limited external validation and the predominance of single-center samples reduce the generalizability of the results obtained. Works by Thadhani et al. It has been shown that even with a high biological validity of angiogenic markers, their clinical interpretation requires strict context and confirmation in independent cohorts. This highlights the need for multicenter research and unified assessment protocols for both biomarkers and digital algorithms.

Special attention is paid to the problem of interpretability of artificial intelligence models, especially in situations of clinically significant decision-making [48]. Despite the high accuracy, the "black box" of deep neural networks limits the trust of clinicians and complicates the allocation of responsibility in case of diagnostic errors. The research by Zhou et al., using deep learning to analyze fundus images in predicting preeclampsia, demonstrates the high potential of the technology, but at the same time emphasizes the need for explicable decision-making mechanisms.

In clinical practice, the responsibility for interpreting AI results remains with the doctor, which requires a clear distinction between the role of the algorithm as an auxiliary tool rather than an autonomous decision-making entity. These issues are closely related to the ethical and legal aspects of the use of AI in obstetrics, including informed consent, personal data protection, and prevention of algorithmic discrimination. The use of wearable sensor systems described by Hassan et al. additionally highlights the issues of confidentiality and long-term storage of sensitive physiological data of the mother and fetus.

In conditions of high vulnerability of pregnant women, ethical standards should be especially strict, and the introduction of new technologies should be phased and controlled. From a legal point of view, there remains uncertainty about the responsibility of developers, medical organizations, and individual specialists when using AI solutions [53]. This requires the development of specialized regulatory frameworks adapted to the specifics of perinatal medicine.

The prospects for further research are related to the transition from isolated biomarkers and individual algorithms to integrative models combining clinical data, molecular indicators and digital technologies. Research that takes into account regional demographic and organizational features of the healthcare system is particularly relevant for Russian practice. The formation of national cohorts and proprietary datasets will improve the accuracy of models and reduce the risk of transferring foreign algorithmic biases.

Thus, further progress in perinatal diagnostics is impossible without a combination of technological innovations with clear ethical and methodological guidelines. Only with transparency, clinical responsibility, and interdisciplinary collaboration can biomarkers and artificial intelligence become reliable tools for improving pregnancy outcomes and perinatal care.

CONCLUSION

Pregnancy complications, including preeclampsia and related forms of placental dysfunction, remain a significant clinical and social problem requiring improved approaches to early diagnosis and prognosis. The analysis showed that biomarkers of placental and endothelial dysfunction, especially angiogenic factors and their ratios, reflect key pathophysiological mechanisms and have high prognostic value. The inclusion of artificial intelligence and machine learning methods allows the integration of biological, clinical and instrumental data, increasing the accuracy of risk stratification and supporting personalized pregnancy management. However, the clinical implementation of these technologies is limited by the problems of standardization, interpretability, and the need for multicenter validation, especially in a national context. Thus, the combination of biomarker approaches and intelligent analytical models represents a promising direction for the development of perinatal diagnostics and can become the basis for improving maternal and perinatal outcomes, subject to further targeted research.

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Contribution of the authors

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