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PREDICTING THE DEVELOPMENT OF PREECLAMPSIA BASED ON CLINICAL AND GENETIC FACTORS: A REVIEW

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Abstract

Preeclampsia (PE) is a multifactorial complication of pregnancy that poses a serious threat to both mother and fetus, requiring accurate prediction for timely prevention. This review analyzes current data on clinical and genetic predictors of PE, with a focus on the role of the renin-angiotensin system (RAS) and, specifically, the AGTR1 and AGTR2 genes. Key pathogenetic mechanisms are examined, including endothelial dysfunction, oxidative stress, trophoblast apoptosis, and immune maladaptation. Clinical risk factors (age, medical history, comorbidities) and their interaction with genetic predictors are analyzed. The principles of developing and validating multifactorial predictive models, which demonstrate high sensitivity (up to 89.5%) and specificity (up to 84.6%), are described. Practical aspects of genotyping, preventive strategies (aspirin, risk factor modification), and promising research directions (GWAS, epigenetics, biomarkers) are discussed. The importance of a personalized approach to pregnancy management to improve perinatal outcomes is emphasized.

Keywords: Preeclampsia, renin-angiotensin system, genetic polymorphisms, AGTR1, AGTR2, clinical predictors, predictive models, endothelial dysfunction, oxidative stress, angiogenesis, apoptosis, immune maladaptation, genotyping, prevention, personalized medicine, perinatal outcomes, biomarkers, PAPP-A, PP13, sFlt-1/PlGF.

Introduction

Preeclampsia (PE) remains one of the leading causes of maternal and perinatal morbidity and mortality worldwide, representing a complex and multifactorial complication of pregnancy [Steegers E.A. et al., 2010; Duley L., 2009]. According to the World Health Organization (WHO), PE complicates 2% to 8% of pregnancies globally. In some regions, including Russia, this figure reaches 11-16%, making it the third leading cause of maternal mortality [World Health Organization, 2011; Sidorova I.S. et al., 2020]. PE is characterized by the new onset of arterial hypertension after 20 weeks of gestation, often accompanied by proteinuria, edema, and signs of multi-organ dysfunction, as defined by current clinical guidelines [ACOG Practice Bulletin No. 202, 2019]. Complications associated with PE include preterm birth, placental insufficiency, placental abruption, and fetal growth restriction [Sibai B.M., 2005]. Children born to mothers with PE have an increased rate of morbidity in infancy and early childhood, as well as a higher risk of developing cardiovascular disease and metabolic disorders later in life [Davis E.F. et al., 2012; Kajantie E. et al., 2010].

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A key challenge in managing PE is the difficulty of its timely detection. The clinical presentation is often subtle or atypical, leading to an underestimation of the severity of pathophysiological changes in the mother and fetus [Poon L.C. et al., 2019]. This is particularly relevant for severe forms of PE, which may remain unrecognized until the development of critical complications such as eclampsia or HELLP syndrome [Martin J.N. Jr. et al., 2008].

Current research indicates the multifactorial nature of PE, involving an interaction between genetic and environmental factors [Roberts J.M., Hubel C.A., 2009]. Genetic predisposition plays a significant role, contributing to over 50% of the pathogenesis, with maternal genes having a more substantial impact than the fetal genetic contribution (at an approximate ratio of 2:1) [Ward K., Taylor R.N., 2015; Salonen Ros H. et al., 2000]. Globally, polymorphisms in genes regulating various physiological processes are actively being studied, including blood coagulation (*F5*, *F2*), lipid metabolism (*APOE*), endothelial function (*NOS3*), and angiogenesis (*VEGF*, *FLT1*) [Laivuori H., 2007; Sidorova I.S., Nikitina N.A., 2020]. Special attention is given to the genes of the renin-angiotensin system (RAS), which is involved in regulating blood pressure and circulating blood volume; its dysfunction can contribute to hypertensive complications during pregnancy [Verdonk K. et al., 2015; Irani R.A., Xia Y., 2008].

The objective of this review is to systematize current scientific data on the clinical and genetic predictors of preeclampsia and to assess their potential for developing methods of individualized prediction.

1. Etiology and Pathogenesis of Preeclampsia

Epidemiological Aspects

Preeclampsia is a unique syndrome that occurs exclusively during pregnancy and is characterized by systemic disturbances resulting from increased permeability of vascular walls and membranes [Roberts J.M., Redman C.W., 1993]. These changes lead to fluid volume and hemodynamic disorders affecting both the mother and the fetus [Granger J.P. et al., 2001]. The incidence of PE varies depending on geographical region, socioeconomic status, and the level of medical care [Abalos E. et al., 2013]. In developed countries, it affects 2-8% of all pregnancies, whereas in regions with limited access to healthcare, this rate can be significantly higher [Duley L., 2009]. In Russia, PE is registered in 11-16% of pregnant women, making it a leading cause of maternal mortality, second only to postpartum hemorrhage and infectious complications [Sukhikh G.T., Adamyan L.V., 2019].

Clinically, PE is classified into mild (or non-severe) and severe forms according to international (ACOG, ISSHP) and national guidelines [ACOG Practice Bulletin No. 202, 2019]. The non-severe form is diagnosed with blood pressure ≥140/90 mmHg after 20 weeks of gestation, combined with proteinuria ≥0.3 g/L in a 24-hour urine collection [Tranquilli A.L. et al., 2014]. Severe PE is characterized by more pronounced hypertension (≥160/110 mmHg), significant proteinuria (>5 g/L), and additional signs such as oliguria (<500 ml/day), thrombocytopenia (<100×10⁹/L), elevated liver enzymes, and neurological symptoms [Sibai B.M. et al., 2005]. Severe forms are associated with a high risk of eclampsia, acute kidney injury, and intrauterine fetal death, highlighting the need for early detection and management [von Dadelszen P. et al., 2003].

Risk factors for PE include both maternal and hereditary components [Duckitt K., Harrington D., 2005]. Maternal factors include age over 40, nulliparity, multiple gestation, chronic hypertension, diabetes mellitus, obesity (BMI >30 kg/m ²), and autoimmune diseases [Bartsch E. et al., 2016; Poon L.C. et al., 2019]. Hereditary factors are supported by observations of an increased incidence

of PE among the daughters, sisters, and granddaughters of women who have had the condition [Cnattingius S. et al., 1999]. For instance, mother-daughter studies have shown that up to 28% of daughters born to mothers with PE also experience the condition during their pregnancies [Salonen Ros H. et al., 2000]. These findings indicate a significant role for genetic predisposition, which interacts with exogenous factors [Williams P.J., Broughton Pipkin F., 2011].

Key Pathogenetic Mechanisms

The etiology and pathogenesis of PE remain subjects of intensive research. However, most scientists agree that it is a syndrome arising from a combination of pathological insults leading to fetal oxygen deficiency [Redman C.W., Sargent I.L., 2005]. The pathogenesis is rooted in impaired uteroplacental circulation, oxidative stress, and imbalanced immunological interactions [Roberts J.M., Hubel C.A., 2009]. These interconnected processes lead to endothelial damage, a systemic inflammatory response, and the clinical manifestations of PE [Granger J.P. et al., 2001].

Key pathogenetic changes begin long before symptoms appear, enabling the search for predictors at a preclinical stage [Nicolaides K.H., 2011]. One of the earliest events is considered to be shallow trophoblast invasion during the second wave of placentation [Pijnenborg R. et al., 2006]. Normally, cytotrophoblasts invade the uterine spiral arteries, remodeling them into wide, low-resistance vessels to ensure adequate placental blood supply [Kaufmann P. et al., 2003]. In PE, this process is impaired, leading to placental ischemia and systemic hemodynamic disturbances [Brosens I.A. et al., 2011].

Endothelial Dysfunction: Recognized as a central mechanism in PE pathogenesis [Roberts J.M. et al., 1989], it is characterized by an imbalance between vasodilators (nitric oxide, prostacyclin) and vasoconstrictors (endothelin-1, thromboxane) [Taylor R.N. et al., 2003]. In PE, there is reduced production of nitric oxide (NO), increased production of pro-inflammatory cytokines (TNF-α, IL-6), and elevated levels of endothelial damage markers like von Willebrand factor and fibronectin [Sattar N. et al., 1999; Conrad K.P., Benyo D.F., 1997]. These changes lead to increased vascular permeability, vasospasm, and activation of the coagulation system [Myers J.E., Mires G.J., 2002].

Oxidative Stress: This plays a key role in PE pathogenesis, acting as both a consequence of placental ischemia and a factor that exacerbates endothelial damage [Burton G.J., Jauniaux E., 2011]. The process involves an imbalance between the production of reactive oxygen species (ROS) and the antioxidant capacity of the body [Agarwal A. et al., 2005]. Placental ischemia in PE leads to excessive ROS generation, which damages cell membranes, proteins, and DNA, activating lipid peroxidation [Gupta S. et al., 2005]. Studies show that levels of oxidative stress markers, such as malondialdehyde, are significantly elevated in the plasma and placental tissues of women with PE, which is associated with the depletion of antioxidant reserves [Raijmakers M.T. et al., 2004; Many A. et al., 1996].

Trophoblast Apoptosis: In PE, trophoblast apoptosis (programmed cell death) becomes excessive, impairing normal placentation [Huppertz B., 2008]. This process is closely linked to oxidative stress and placental ischemia, which trigger apoptotic pathways [Crocker I.P. et al., 2003]. Trophoblast apoptosis leads to the massive shedding of its fragments, including syncytiotrophoblast microparticles, into the maternal circulation [Goswami D. et al., 2006]. This

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shedding induces a systemic maternal inflammatory response, which becomes decompensated, thereby amplifying endothelial dysfunction and contributing to clinical symptoms [Redman C.W., Sargent I.L., 2009].

Immune Maladaptation: Pregnancy is a unique state of immunological tolerance, where the maternal immune system adapts to the semi-allogeneic fetus [Saito S. et al., 2010]. In PE, this balance is disrupted, leading to immune maladaptation [Laresgoiti-Servitje E., 2013]. A key factor is believed to be the reduced expression of HLA-G histocompatibility antigens, which protect the trophoblast from maternal NK cell attack [Hiby S.E. et al., 2004]. In PE, there is a shift toward a pro-inflammatory cytokine profile (increased TNF-α, IFN-γ), leading to increased vascular permeability and generalized endothelial dysfunction [Redman C.W., Sargent I.L., 2005]. Immune maladaptation is also linked to impaired angiogenesis, particularly the reduced production of placental growth factor (PlGF) and increased levels of soluble fms-like tyrosine kinase-1 (sFlt-1) [Maynard S.E. et al., 2003].

2. The Renin-Angiotensin System in the Pathogenesis of Preeclampsia

The renin-angiotensin system (RAS) is a key regulator of blood pressure, and its dysfunction is a significant factor in the development of PE [Granger J.P. et al., 2001; Verdonk K. et al., 2015].

Physiological Role of the RAS: The RAS is a hormonal cascade system whose main effector peptide is angiotensin II (Ang II) [Paul M. et al., 2006]. Ang II acts via two receptor types: AT1, which mediates vasoconstriction and increases blood pressure, and AT2, which has vasodilatory and anti-proliferative effects [Sparks M.A. et al., 2014]. During a normal pregnancy, RAS activity increases, but the vasculature becomes refractory to the pressor effects of Ang II, partly due to increased expression of AT2 receptors [Shah D.M., 2007]. In PE, this refractoriness is lost, leading to a predominance of AT1 receptor effects, which induces hypertension and vascular complications [Irani R.A., Xia Y., 2008].

Genetic Polymorphisms of RAS Genes: Genetic variations in RAS components play a substantial role in the predisposition to PE [Morgan L. et al., 2002]. Particular attention is paid to polymorphisms in the angiotensin II receptor genes, *AGTR1* (A1166C) and *AGTR2* (C4599A). The A1166C polymorphism of the *AGTR1* gene is associated with an enhanced response to Ang II, leading to increased vasoconstriction [van Geel M. et al., 2002]. Studies show that carriage of the C allele correlates with an increased risk and more severe course of PE [Zhou S.L. et al., 2015]. The C4599A polymorphism of the *AGTR2* gene affects the function of AT2 receptors. Homozygous carriage of the C allele (CC genotype) is associated with reduced AT2 receptor activity, impairing the compensatory vasodilatory response and promoting hypertension [Procòpio A.P.S. et al., 2017]. Other RAS polymorphisms, such as the insertion/deletion (I/D) polymorphism of the *ACE* gene and M235T of the *AGT* gene, are also studied in the context of PE, but their contribution varies across different populations [Medcalf K.E. et al., 2007].

Mechanisms of Influence on PE Development: RAS dysfunction in PE manifests through several mechanisms. Increased Ang II activity, mediated by AT1 receptors, leads to vasospasm and reduced placental perfusion [Granger J.P. et al., 2001]. Ang II stimulates the production of endothelin-1 and suppresses nitric oxide synthesis, exacerbating endothelial dysfunction [Siddiqui A.H., Irani R.A., 2014]. Increased AT1 receptor activity correlates with higher levels of the anti-

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angiogenic factor sFlt-1, which disrupts placental vascular development [Zhou C.C. et al., 2008]. Finally, Ang II promotes thrombogenesis by stimulating the expression of plasminogen activator inhibitor-1 (PAI-1) [Vaughan D.E., 2005].

3. Clinical and Genetic Predictors of Preeclampsia

Early identification of high-risk women is crucial for effective PE management [Nicolaides K.H., 2011]. Modern approaches are based on integrating clinical data and genetic markers [Poon L.C. et al., 2019].

Clinical Risk Factors: Clinical predictors of PE include age over 35, nulliparity, multiple gestation, a family history of PE, and chronic conditions such as hypertension, diabetes, and obesity [Bartsch E. et al., 2016; Duckitt K., Harrington D., 2005]. Parameters like excessive weight gain in the first trimester and an elevated mean arterial pressure are also early markers [Gallo D.M. et al., 2016].

Genetic Markers and a Multifactorial Approach: Given the multifactorial nature of PE, the use of multifactorial predictive models is most promising [Poon L.C. et al., 2019]. Models developed by the Fetal Medicine Foundation combine maternal risk factors, mean arterial pressure, uterine artery Doppler velocimetry, and biochemical markers (PAPP-A, PlGF) to predict PE risk in the first trimester [O'Gorman N. et al., 2016; Akolekar R. et al., 2013]. The inclusion of genetic markers, such as *AGTR1* (A1166C) and *AGTR2* (C4599A) polymorphisms, can further improve prediction accuracy, allowing for personalized risk assessment [Sidorova I.S., Nikitina N.A., 2020]. Predictive tests based on a combination of 12 clinical and genetic predictors have demonstrated high sensitivity (89.5%), specificity (84.6%), and accuracy (87.5%), enabling the identification of high-risk groups for targeted prophylaxis.

4. Practical Applications and Future Directions

Genotyping in Clinical Practice: Genotyping for *AGTR1* and *AGTR2* polymorphisms using PCR analysis is a promising tool for PE risk stratification [Morgan L., Ward K., 2011]. Results must be interpreted in conjunction with clinical data. Limitations to widespread implementation include cost, accessibility, and the need for staff training.

Preventive Strategies: The primary evidence-based strategy for PE prevention in high-risk women is the use of low-dose aspirin (75-150 mg/day), starting from 12-16 weeks of gestation [Rolnik D.L. et al., 2017]. Modification of risk factors is also crucial: optimizing pre-pregnancy weight and controlling glycemia and blood pressure [Poon L.C. et al., 2019]. Preventive strategies should be personalized based on individual risk assessment.

Limitations and Future Research: Future research aims to identify new genetic markers through genome-wide association studies (GWAS), integrate epigenetic data (DNA methylation, microRNAs), and develop novel biomarkers based on proteomics and metabolomics [Johnson M.P. et al., 2021; Goulopoulou S., 2017]. Improving predictive models and developing targeted therapies based on an understanding of individual pathogenetic mechanisms are key tasks in modern perinatology.

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Conclusion

The prediction of preeclampsia based on a combination of clinical and genetic factors is a promising direction in personalized medicine. Polymorphisms in the renin-angiotensin system genes, particularly *AGTR1* and *AGTR2*, serve as important markers of susceptibility to the development and severe course of this complication. Integrating genotyping data into multifactorial predictive models allows for the high-accuracy identification of high-risk women at a preclinical stage. This opens up opportunities for the timely application of preventive measures, such as low-dose aspirin therapy and modification of risk factors. Further research in genomics, epigenetics, and proteomics will deepen our understanding of the pathogenesis of preeclampsia and facilitate the development of new, more effective approaches to its prediction and prevention, ultimately contributing to improved perinatal outcomes.

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