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Modern concepts of etiology, pathogenesis and risk factors for preeclampsia

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Preeclampsia is a serious complication of pregnancy and complicates its course in 2-8% of all cases. According to the literature, the disease is associated with an increase in maternal and perinatal morbidity and mortality, and is a predictor of the development of chronic diseases in the distant future, which is an important medical and social issue. Of particular interest is the study of the molecular mechanisms of etiopathogenesis and risk factors for preeclampsia, which, unfortunately, are currently poorly studied and understood, thus dictating the need for further study of this complication of pregnancy. This article discusses the current understanding of the etiology, pathogenesis and risk factors for preeclampsia.

Keywords: preeclampsia; etiology; pathogenesis; risk factors.

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Современные представления об этиологии, патогенезе и факторах риска преэклампсии

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Преэклампсия осложняет течение беременности в 2–8 % всех случаев. Преэклампсия, по данным литературы, ассоциирована с увеличением материнской и перинатальной заболеваемости и смертности, а также является предиктором развития хронических заболеваний в отдаленном будущем, что представляет собой важную медико-социальную проблему. Особый интерес вызывают молекулярные механизмы этиопатогенеза и факторы риска преэклампсии, которые, к сожалению, в настоящее время недостаточно изучены и понятны, что диктует необходимость дальнейшего исследования данного грозного осложнения беременности. В данной статье рассмотрены современные представления об этиологии, патогенезе и факторах риска преэклампсии.

Ключевые слова: преэклампсия; этиология; патогенез; факторы риска.

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ЭКО • ВЕКТОР

According to modern concepts, preeclampsia (PE) is clinically characterized by arterial hypertension (≥140/90 mmHg) and proteinuria (≥0.3 g/day) and is accompanied by edema and impaired function of various organs and systems [1]. These symptoms can occur both during pregnancy (after week 20 of gestation) and in the postpartum period (up to 28 days).

PE complicates the course of pregnancy in 2%–8% of all cases and is one of the major causes of maternal mortality worldwide [2]. Data from the Department of Monitoring, Analysis, and Strategic Development of Healthcare of the Ministry of Health of the Russian Federation in the Statistical Book of 2018 revealed that the incidence of moderate PE in Russia was 27.4 per 1000 births and severe PE was 8.4 [3].

Early-onset of PE (before week 34 of gestation) has the most adverse outcomes for both the mother and the fetus. Women with a history of PE are at high risk for developing chronic arterial hypertension (CAH), type 2 diabetes mellitus (DM), renal failure, coronary heart disease, various forms of arrhythmias, etc. in the long term [4]. Despite the advances in modern medicine, the only effective treatment for PE is delivery regardless of gestational age, which makes a significant contribution to the structure of perinatal morbidity and mortality that are mainly caused by prematurity, chronic hypoxia, and fetal growth retardation [5].

The mechanisms of PE occurrence are extensively studied worldwide, and >30 hypotheses for the development of this pregnancy complication were reported, most of which placentation disorders are the most significant [6]. The two-stage model of PE development that was introduced by Redman in 1991 is currently generally accepted. At stage 1 of PE, abnormal placentation occurs in early pregnancy, which leads to disseminated endothelial dysfunction and "maternal syndrome" at stage 2 [7]. Generally, the mechanisms of early and late PE occurrence are different. Thus, late PE development, which was registered in 88% of all cases, is mainly due to maternal causes (metabolic syndrome, arterial hypertension, chronic kidney disease, etc.) in combination with placental dysfunction. Signs of incomplete remodeling of the coiled arteries are noted in only a small proportion of women with PE that develops after week 34 of gestation [8]. Early-onset was noted in 12% of PE cases and is associated with extensive placental lesions and a higher risk of maternal and fetal complications. A trigger factor for early PE is a placentation impairment at the initial gestational stages [9].

With the physiological course of pregnancy, the syncytiotrophoblast penetrates the endometrium at the time of implantation, which provides histiotrophic nutrition of the embryo until the hematotrophic type of nutrition is established. Then, the retrograde invasion of the endovascular trophoblast into the uterine vessels occurs, which replaces the endothelial lining of the vessels [10]. These rearrangements cause apoptosis of the muscle wall of the spiral arteries, which forms a vascular bed with low intravascular pressure that contributes to adequate placental perfusion maintenance throughout pregnancy. With PE, these processes are disrupted, which ultimately leads to defective trophoblast invasion and impaired formation of uteroplacental blood flow [11].

Early development of the embryo and placenta occurs under conditions of physiologically low oxygen levels (1%–2%), which is probably required to prevent oxidative damage to the fetus and normal functioning of the trophoblast cells [12]. Low oxygen levels stimulate increased expression of hypoxia-induced factors (HIF-1α and HIF-2α) and transforming growth factor β (TGF-β), which also inhibits the transition of the trophoblast to the invasive type. The uteroplacental blood flow intensification starts from week 10 of gestation, which is accompanied by a significantly increased partial pressure of oxygen, decreased expression of HIF-1α/HIF-2α and TGF-β, and trophoblast rearrangement from the proliferative to the invasive type, which ensures the normal uterine vessel transformation. With persistent hypoxia after week 10 of gestation, differentiation processes of the trophoblast are disrupted, which results in its insufficiently deep invasion and atypical transformation of the spiral arteries [13]. One of the mechanisms that disrupt the invasion processes is the persistent hypoxia-mediated overexpression of HIF-1α/HIF-2α and TGF-β. R.E. Albers et al. (2019) revealed that long-term expression of HIF-1α leads to the development of hypertension and renal glomeruloendotheliosis with proteinuria and restriction of fetal growth in mice [14]. HIF-2α/HIF-3α functions as an inhibitor of vascular endothelial growth factor (VEGF) and placental growth factor by activating the signaling pathway of soluble fms-like tyrosine kinase-1 (sFlt-1), which also negatively affects the placental formation [15].

Not only hypoxia has a pathogenic effect, but also systematically repeated episodes of ischemia and reperfusion, which are accompanied by increased reactive oxygen species production, thereby creating a favorable environment for oxidative stress development [16]. Oxidative damage to the placenta induces apoptosis processes, such as the release of various antiangiogenic factors, proinflammatory cytokines, and vasoactive compounds into the mother's bloodstream, which develops major systemic endothelial cell dysfunction, accompanied by inflammation and vasoconstriction [17]. Oxidative stress also potentiates mitochondrial dysfunction. V.R. Vaka et al. (2018) studied mitochondrial dysfunction and its relationship with endothelial dysfunction,

systemic vasospasm, inflammation, and oxidative stress in PE. They concluded that the metabolism in mitochondria is accelerated in PE, which is accompanied by increased levels of calcium ions, impaired phosphorylation processes, and increased formation of reactive oxygen species, which play a significant role in DNA and RNA damage, cell death, and the development of endothelial dysfunction [18]. Free radicals activate the process of lipid peroxidation and the synthesis of products of the cyclooxygenase pathway of the metabolism of arachidonic acid. Thus, T.N. Pogorelova et al. (2019) revealed that in females with PE, the levels of thromboxane B_2 and arachidonic acid in the tissues of the placenta increases by >30% compared to that of the control group, and the concentration of prostacyclin, which is a vasodilator, also decreases by 20% [19]. Arachidonic acid metabolites are involved in the inflammatory process, and also affect the adhesion and aggregation of platelets, which leads to intravascular coagulopathy, thrombosis, placental infarction, and an even greater deterioration in the malfunctioning uteroplacental blood flow [20]. In addition, oxidative stress potentiates the inflammatory response by stimulating the proinflammatory cytokine production, such as tumor necrosis factor α and interleukin (IL) 6, as well as decreased antiinflammatory cytokines (IL-10) synthesis with subsequent cell damage [21]. Simultaneously with the development of oxidative stress, the work of placental antioxidant mechanisms is inhibited, as evidenced by a decreased superoxide dismutase, catalase, and glutathione peroxidase expression in PE [22].

Endothelial dysfunction is central to the "maternal syndrome" pathogenesis of PE and underlies the imbalance of vasoactive mediators, which induces a shift toward increased vasoconstrictor production [23, 24]. Imbalanced circulating angiogenic factors indirectly affect the formation of endothelial dysfunction and PE clinical manifestations, which form a vicious circle. An endogenous antiangiogenic factor (endostatin), sFlt1, is a potent VEGF antagonist that is significantly elevated in PE. VEGF is significant not only in angiogenesis but also in maintaining the normal functioning of the endothelium and controls the formation of endothelial fenestras (a characteristic feature of the endothelium of the renal glomeruli) [25]. Increased expression of sFlt1 (*in vitro*) induces glomerular endotheliosis with the disappearance of fenestras, which histologically resembles renal damage in PE. More severe forms of PE, including hemolysis, elevated liver enzymes, and low platelets syndrome, are also associated with a concomitantly increased level of both sFlt1 and soluble endoglin (which is also an antiangiogenic factor) [26].

Matrix metalloproteinases (MMPs) are of great importance in the formation of endothelial dysfunction in PE. MMP-2, MMP-9, MMP-3, and MMP-13 are directly related to the processes of implantation, trophoblast invasion, and blood vessel remodeling. They are involved in the degradation of endothelin and adrenomedullin, which contributes to the vasodilation of the spiral arteries [27]. A decreased expression of various MMP groups, together with increased endogenous MMP inhibitor synthesis, induces endothelial damage and increases vascular reactivity, which leads to pronounced vasoconstriction [28].

Evidence on the involvement of the renin-angiotensin-aldosterone system in PE pathogenesis has been obtained [29]. F. Herse et al. (2013) found an association between endothelial dysfunction, increased endothelin-1 production, and activation of the expression of autoantibodies to type 1 angiotensin II receptors (AT2R1). Contrary to the physiological course of pregnancy, when low endothelium sensitivity to angiotensin II is noted, the sensitivity to angiotensin II increases in pregnant women with PE, mediated by genetic, immunological, or exogenous factors [30]. One of the potential mechanisms for increasing sensitivity to angiotensin II is the expression of autoantibodies to AT2R1 in PE women, which are produced in response to placental ischemia and systemic inflammation. Autoantibodies to AT2R1 stimulate the production of placental antiangiogenic factors (sFlt1 and sENG), induce the synthesis of the plasminogen activator inhibitor PAI-1 in trophoblast cells, and indirectly affect the activation of coagulation hemostasis [31].

Immune maladjustment of the mother's body also contributes to PE development. The fetus represents a semiallogenic transplant (since 50% of paternal antigens are expressed in the tissues of the placenta and fetus), which is not rejected due to the functioning of a whole complex of immunological mechanisms of gestation, where natural cytotoxic cells (NK cells) are the most significant [32]. In the early stages of pregnancy, >70% of neutrophils in the endometrium are uterine NK cells with the CD56hi and CD57lo phenotype (uNK), which ensure successful implantation of blastula, and then participate in vascular remodeling through the secretion of cytokines and angiogenic mediators, their number is significantly reduced by the third trimester of pregnancy [33]. Human leukocyte antigen (HLA)-G, presented on the surface of trophoblast cells, which interact with KIR receptors (inhibitors) of uNK cells, reduces the cytotoxicity of NKs and limits their migration across the placenta, thus protecting the fetus from adverse immunological reactions from the mother's body. Therefore, defects in the placental expression of HLA-G and KIR receptors may be associated with an increased risk of pregnancy complications, which are based on impaired uteroplacental circulation [34]. According to S.A. Robertson et al. (2018),

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T-lymphocytes makeup 10%–20% of decidual immune cells at the onset of the first trimester and are significant in the processes of implantation and placentation [35]. An imbalance between the regulatory (Treg) and effector (Teff) T-lymphocytes (bias toward Teff) may also be one of the potential immunological mechanisms for the development of PE [36]. Teff negatively affects placental development through the release of proinflammatory cytokines and the activation of antigen-dependent cytotoxicity of the trophoblast. Decidual Tregs secrete IL-10 and TGF-β and express CD25 and PD-L1, which inhibits the effector T-lymphocytes and neutralizes their effects, and also have potent anti-inflammatory, immuno-, and vasoregulatory properties [37].

One of the components of the pathogenesis of PE is the deregulation of the complement system, which is most often associated with the presence of mutations in genes that control the biosynthesis of complement activation regulators, namely factor H, membrane cofactor, factor I, component C3, etc. The complement system disruption leads to endogenous damage to the tissue structures, endothelium, blood cells, and platelets with the subsequent formation of microthrombi, and the development of endothelial dysfunction and systemic impairment of fetal tolerance [38].

The main component of the arterial hypertension pathophysiology in PE is the biologically imbalanced active substances produced by endothelial cells, which are involved in vascular tone regulation. Placental ischemia stimulates the release of mediators that cause systemic endotheliosis, which leads to decreased vasodilator synthesis (prostacyclin, nitrogen monoxide [NO], and endothelium-dependent hyperpolarization factor). Concurrently, the production of endothelin-1 and thromboxane A_2 increases, which has a powerful vasoconstrictor effect. The disorders cause an increased total peripheral vascular resistance and, accordingly, blood pressure [39]. Female patients with PE have increased angiotensin II and norepinephrine sensitivity due to the activation of AT2R1. Heterodimerization of AT2R1 and bradykinin B_2 receptors and placental ischemia-induced production of autoantibodies to AT2R1 receptors also enhance the pressor effects of angiotensin II [40]. Immune mechanisms also contribute to the development of hypertension in PE. An imbalance between two subpopulations of $CD4^+$ T-lymphocytes (Th1/Th2), Tregs and Teff, and excessive secretion of IL-17 contribute to increased production of vasoactive mediators and autoantibodies to AT2R1 receptors, thereby aggravating endothelial dysfunction, which also leads to increased blood pressure in PE [41].

To date, a large number of studies have been conducted that comprise the information about 130 possible PE risk factors, covering a large list of comorbidities, biomarkers, environmental factors, and genetic determinants [42, 43]. Thus, S. Rana et al. (2019) studied the risk factors for PE development that are ranked according to the value of the relative risk (RR) and divided into several categories, where the main group of risk factors (RR > 2.5) includes a history of PE, CAH, DM, multifetal pregnancy, body mass index (BMI) of >30 kg/cm^2 in the pregravid period, and antiphospholipid syndrome; group 2 of the risk factors (RR 1.8–2.5) include systemic lupus erythematosus, stillbirth, history of infertility and premature placental detachment, use of assisted reproductive technologies, chronic kidney disease, maternal age of over 35 years at the time of pregnancy, and polymorphism of candidate gene (rs4769613 of the FLT_1 gene, rs9478812 of the $PLEKHG_1$ gene, etc.); the last group of less significant risk factors (RR < 1.8) includes a family history of PE and fetal trisomy of the 13th pair of chromosomes (Patau syndrome) [44].

According to modern data, CAH is recorded in 1%–5% of all pregnant women, with an incidence of PE of up to 75%. A. Syngelaki et al. (2018) revealed that CAH before pregnancy is associated with a high risk of PE (odds ratio [OR] 5.76; 95% confidence interval [CI] 4.93–6.73), stillbirth (OR 2.38; 95% CI 1.51–3.75), and small for gestational age newborns (OR 2.06; 95% CI 1.79–2.39) [45]. In addition, D. Nzelu et al. (2018) noted that despite the correction of hypertension with drugs and maintaining the control blood pressure values at <140/90 mm Hg. from the first trimester of pregnancy in pregnant women with CAH, the risk of developing PE and the birth of children with developmental retardation is >2 times higher. This is associated with progressive endothelial dysfunction, arteriole remodeling, and muscle wall thickening, followed by vasoconstriction and decreased sensitivity to vasodilation [46].

The most common modifiable risk factor for PE is overweight (BMI ≥ 25 kg/m^2), as >10% of all pregnant women are obese. A meta-analysis of 19 cohorts conducted by X.J. He et al. revealed that obesity and overweight are associated with an increased risk of PE (OR 2.48; 95% CI 2.05–2.90) [47]. An increased BMI by 1 kg/m^2 leads to a statistically significant increase in the OR of PE by 15%. The probability of this pregnancy complication increases by 30% in women who are overweight at the time of pregnancy [48]. O.B. Kalinkina et al. (2012) revealed that an increased BMI is associated with an earlier onset of PE, as in patients with normal body weight, clinical manifestations of PE were manifested at a term of 30.25 ± 0.38 weeks and manifested at a term of 26.00 ± 2.35 weeks of gestation at BMI of 35 kg/m^2 or higher (p < 0.001). A direct correlation was also found between BMI and blood pressure indicators (systolic, diastolic, mean, and pulse) [49].

Hereditary thrombophilia causes the occurrence of blood clots in the placental blood vessels, which is associated with an increased risk of placenta-associated pregnancy complications [50]. G. Mello et al. (2005) revealed that the presence of at least one of the mutations *FV* Leiden, *MTHFR* C677T, and *Pt* G20210A is associated with a more severe course of PE (OR 4.9; 95% CI 3.5–6.9) [51]. The most significant congenital defects of hemostasis components in PE development are considered mutations in the *MTHFR* gene (15%–40%), type 1 plasminogen activator inhibitor (5–8%), Leiden (3%–6%), and prothrombin II (1%–4%). The combination of hyperhomocysteinemia and *FV* Leiden mutation was established to increase the risk of thrombotic complications by a factor of 10–20 [52]. Literature data revealed that the mutation of the methylenetetrahydrofolate reductase C677T gene is an independent risk factor for higher blood pressure during pregnancy and PE [53].

The contribution of DM and insulin resistance to the formation of PE is undeniable. According to the literature, PE is diagnosed in 25%–40% of pregnant women with type 1 DM and in 20%–24% with type 2 DM [54]. S. Lisonkova et al. (2013) found that DM that developed before pregnancy is a risk factor for both an early manifestation of PE (up to the week 34, OR 1.87; 95% CI 1.60–2.81) and its late development (OR 2.46; 95% CI 2.32–2.61). This is associated with the development of systemic diabetic vasculopathy and the frequent combination of DM with preexisting CAH [55]. K. Bramham (2017) notes that diabetic nephropathy in pregnant patients with DM is associated with a higher risk of PE (35%–66%) compared with female patients with DM without nephropathy (9%–17%) [56]. In addition, insulin resistance is often associated with other risk factors for PE (obesity, CAH, metabolic syndrome, etc.) and has the same mechanisms of PE development, which is confirmed by identical disorders in the expression of various biomarkers (PAI-1, leptin, intercellular adhesion molecules, etc.) in these two pathological conditions [57].

An aggravated obstetric and gynecological history with PE is the most significant risk factor for this pregnancy complication. M. Lewandowska et al. (2020) established that females with a PE history have a significantly increased risk of hypertensive disorders during pregnancy (OR 27.54; 95% CI 5.8–130.8; $p < 0.001$ for PE and OR 22.90; 95% CI 7.3–72.4; $p < 0.001$ for gestational arterial hypertension) [48]. A direct relationship was established between the same periods of manifestation of clinical symptoms of PE in previous and present pregnancies. Early-onset PE in the history increased the risk of the corresponding form of PE by 25.2 times (95% CI 21.8–29.1), and, accordingly, the manifestation of this pathology after week 34 of gestation increased the risk of late PE by 10.3 times (95% CI 9.85–10.9). The authors attribute this to the predominant influence of genetic factors on the development of early PE and the most significant contribution of environmental agents to the formation of late PE [58].

The available literature provides data on the relationship between ethnicity and race with the epidemiology and course of PE. Thus, A.B. Caughey et al. (2005) found that the risk of PE is significantly higher in African Americans (OR 1.41; 95% CI 1.25–1.62) and lower in the Asian population (OR 0.79; 95% CI 0.72–0.88) compared with the Caucasians [59]. In addition, black women have significantly higher rates of maternal mortality from complications associated with PE compared to Europeans (121.8 cases per 100,000 deliveries, 95% CI 69.7–212.9 and 24.1 per 100,000 deliveries, 95% CI 14.6–39.8, respectively, $p < 0.01$) [60]. The ethnicity of the father also influences the risk of PE, as the risk of this pregnancy complication is significantly increased in couples that belong to different ethnic groups, compared with parents of the same race (OR 1.13; 95% CI 1.02–1.26) [61].

A hereditary predisposition is significant in PE formation. According to various sources, the presence of hypertensive disorders in combination with proteinuria during pregnancy in females with a family history in first-degree relatives (mother, sisters) increases the risk of PE by 24%–163% [62]. A study by N.C. Serrano et al. (2020) revealed that the risk of this pregnancy complication in females whose close relatives had PE history is significantly increased (PE in a sister increases the risk by 2.43 times [95% CI 2.02–2.93]), that in the mother by 3.38 times (95% CI 2.89–3.96), and that in the mother and sister by 4.17 times (95% CI 2.60–6.69)] [63]. History of CAH in the mother (OR 1.41, 95% CI 1.04–1.90), sister (OR 2.48, 95% CI 1.31–4.69), or all female relatives (OR 3.65, 95% CI 1.65–8.09) increases the risk of PE development by >2 times [64], and the presence in the family history of two family members or more with cardiovascular diseases (including cerebral infarction) leads to a more than threefold (OR 3.2, 95% CI 1.4–7.7) increase in the probability this complication to occur [65].

Therefore, as studied in the international and Russian literature, we can conclude that, firstly, despite numerous studies, no consensus was found on the molecular mechanisms of PE etiopathogenesis. Secondly, the key role in the development of this pregnancy complication is attributed to the processes of placentation disturbance, immune maladjustment of the mother's body, endothelial dysfunction, angiogenic imbalance, and others; however, their significance in the formation of early and late PE is considerably different. Thirdly, >130 different risk factors were identified for

PE development (family history of PE, DM, CAH, hereditary thrombophilia, etc.), but the available data are often ambiguous and vary depending on the studied population. Thus, the existing contradictions and insufficient consensus of certain biological processes involved in PE development necessitate a further study of this pregnancy complication.

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