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# JOURNAL OF REPRODUCTIVE HEALTH AND URO-NEPHROLOGY RESEARCH

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# JOURNAL OF REPRODUCTIVE HEALTH AND URO-NEPHROLOGY RESEARCH

## ЖУРНАЛ РЕПРОДУКТИВНОГО ЗДОРОВЬЯ И УРО-НЕФРОЛОГИЧЕСКИХ ИССЛЕДОВАНИЙ


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### СОВРЕМЕННОЕ ЗНАЧЕНИЕ ПРОГНОСТИЧЕСКИХ МАРКЕРОВ В РАЗВИТИИ ПРЕЭКЛАМПСИИ (ОБЗОР ЛИТЕРАТУРЫ)

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### MODERN SIGNIFICANCE OF PROGNOSTIC MARKERS IN THE DEVELOPMENT OF PREECLAMPSIA (LITERATURE REVIEW)

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### ПРЕЭКЛАМПСИЯ РИВОЖЛАНИШИДА БАШОРАТ ҚИЛИШ МАРКЕРЛАРИНИНГ ЗАМОНАВИЙ АҲАМИЯТИ (АДАБИЙОТЛАР ТАҲЛИЛИ)

Preeclampsia (PE) is a syndrome of polyorganic failure that occurs during pregnancy and is based on an increase in the permeability of the vascular wall and other membranes, resulting in volemic and hemodynamic disorders. Preeclampsia, as a major cause of perinatal and maternal morbidity and mortality worldwide, still remains an important medical and social problem. About 8.5 million preeclampsia cases are reported worldwide each year, accounting for 2-8% of all pregnancies (14% of women die annually) and showing no decreasing trend [7,9]. In terms of maternal mortality, preeclampsia along with its further complications, ranked the second to the fourth. In Uzbekistan, PE is found in about 11-16% of pregnant women, taking the third place among the causes of maternal mortality [2, 11]. Among children born

alive to mothers who have suffered from PE, one in four children lag behind in their physical development [7]. In Russia, according to various sources, PE is found in 5-30% of all pregnancies which makes more than one third of severe obstetric pathology. Over the recent years, an increase in PE cases, has been observed in some of developed countries, particularly in the USA. Specialists believe that the reason for such a growing tendency is the presence of such diseases as diabetes mellitus (AD), obesity, chronic arterial hypertension (CAH). Remote prognosis of women who have experienced PE during pregnancy is also associated with the development of cardiovascular complications later in life.



The World Health Organization reports that in developed countries, hypertensive complications responsible for maternal mortality account for up to 30 per cent of all factors [11]. For many decades, scientists of different specialties (cardiologists, obstetricians, gynecologists, genetics) have been paying close attention to the problem of PE, but despite the results obtained, there is still no accurate information about the causes and pathogenesis of the disease, neither have reliable laboratory methods of diagnosis been developed to provide effective preventive and treatment actions.

Along with early termination of pregnancy, delayed fetal growth retardation and premature placenta abruption detachment, PE refers to the so-called "Great Obstetrical Syndromes" associated with placental pathology, which is due to a different degree of remodeling disorder and obstruction of spiral arteries in the transition zone and myometry. The major risk factors for this complication of pregnancy on the maternal side include: age over 40 years, previous pregnancies with PE, first birth, multiple pregnancies, antiphospholipid syndrome, chronic arterial hypertension, autoimmune diseases, diabetes mellitus, kidney diseases, dyslipidemia and obesity. Preeclampsia is believed to be increasing since the 1990s, possibly associated with an increase in obesity (91). Notably, together with obstetric haemorrhage and infectious complications, PE is the so-called "lethal triad", which causes the overwhelming number of maternal deaths. It is worth mentioning that preeclampsia remains one of the main causes of neonatal morbidity (640-780) and perinatal mortality. Preeclampsia is also associated with stress and subsequent postnatal depression [7,17].

The modern prediction of PE is reduced to the study of the concentration and ratio of proangiogenic and antiangiogenic factors, as it is well known that the development of this multisystem disorder is based on the imbalance of factors affecting angiogenesis [2,10]. Today, two mechanisms of formation of new vessels are known: vasculogenesis - formation of the primary vascular network *de novo* (embryo cardiovascular system) and angiogenesis - formation of new vessels from existing ones. Both processes occur under the influence of very clear physiological regulation, when stimulators and inhibitors work in balance with each other [2,5,6,10]. Normally, angiogenesis inhibitors predominate over proangiogenic molecules, which prevents angiogenesis, and proliferation of endothelial cells lining the capillary walls is very slow. The processes included in the concept of angiogenesis were studied in detail and highlighted in a number of reviews [2,10] and presented in the following sequence. Angiogenesis begins with vasodilation and increase of vascular permeability. Then, there is the secretion of soluble angiogenic factor that affects the nearby blood vessel and leads to changes in the capillary wall in the form of basal membrane degradation, mitotic division of endotheliocytes, their subsequent migration into the stroma, and proteolytic degradation of the extracellular matrix. At the next stage, vascular endotheliocytes are organized into a tubular structure and the blood flow in the newly formed area is initiated. A huge number of soluble growth factors and inhibitors, cytokines and proteases, as well as proteins of the extracellular matrix and adhesion molecules strictly control this multistage process. The role of tissue hypoxia and increased production of nitrogen oxide in angiogenesis initiation is also widely known.

It is believed that research into factors that are important to preeclampsia will help foresee the severity and extent of pathological changes. Direct study of endothelium structures, which was one of the first to be damaged in preeclampsia, is now available (58). The problem is that meta-analyses are not sufficient to assess biomarkers predicting preeclampsia. It is difficult to compare studies of individual biomarkers.

To date, several dozens of the factors under discussion have been described. It has been established that the following substances deserve special attention:

1. Proangiogenic factors, one of the main representatives of which family is vascular-endothelial growth factor (VEGF);

2. Antiangiogenic factors, including the soluble fms-like tyrosine kinase-1 (sFlt-1);

3. Soluble adhesion molecules: intercellular adhesion molecule 1 (ICAM-1) and vascular adhesion molecule 1 (VCAM-1).

Hypoxia is the main stimulant of angiogenesis. When the action of proangiogenic factors exceeds the action of antiangiogenic factors,

endothelial cells go into an active state, which is called "angiogenesis inclusion". Endometrium, deciduous shell and placenta are sources of angiogenic growth factors that trigger angiogenesis through a complex system of mediators with the involvement of transmembrane receptors with tyrosine kinase activity [10]. It was found that about 20 stimulating and 30 inhibiting angiogenesis factors take part in the process of vascular formation [4,7]. "Survival" and apoptosis of endothelial cells are opposite but necessary processes for angiogenesis, regulated by the balance of proangiogenic and antiangiogenic factors [6, 4]. The list of pathological conditions and diseases characterized by excessive and incorrect angiogenesis includes: oncopathology, retinopathy, arthritis, atherosclerosis, psoriasis, endometriosis and many others. Diseases such as coronary heart disease, diabetes mellitus, arterial hypertension and, finally, PE are characterized by insufficient angiogenesis [10]. The studies have proved the participation of altered production of numerous growth factors in the development of PE, as they are the main carriers of the mitogenic signal of cells, capable of stimulating or inhibiting the growth of tissues and blood vessels [1,3,6]. Since soluble factors involved in the processes of vascular formation are more accessible for research in the maternal bloodstream, and the change in their content in the mother's blood also reflects changes in the circulation and tissues of the fetus, the study of these factors in the blood of a pregnant woman is key to understanding and predicting the disturbance of vascular morphogenesis processes [4,9]. The most studied and of particular interest in studying PE pathogenesis are proangiogenic agents: vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). The role of other growth factors and active substances in the formation of uterine and placental blood flow is insufficiently studied, because the overwhelming mass of studies is performed in late pregnancy, and the fundamental events determining the further course take place at the very beginning of pregnancy [4].

The vascular endothelial growth factor, previously known as the vascular permeability factor (VPR), was first isolated and described in the experiment in 1983 by Senger and belongs to the family of platelet growth factors, its basis is glycoprotein [2,3,5]. At present, several forms of VEGF are known - A, B, C, D, and E [118]; the most studied is VEGF-A. VEGF is the only specific mitogen of endothelial cells, it stimulates their growth, migration, proliferation, and proteolytic activity, increases the permeability of blood vessels in many tissues and promotes vasculogenesis and angiogenesis [4, 5,7], thus playing an important role in the physiological growth of the placenta and the vascular network of stroma naphtha, as well as regulating the invasive properties of the cytotrophblast [7]. One of the main functions of VEGF in the placenta at late stages of pregnancy is to provide increased viability of endothelial cells and stabilization of the vascular channel. In addition, VEGF is essential for maintaining a "healthy" endothelial phenotype of vessels in the kidneys, liver and brain [5,9]. Jović M. et al. have shown that adding VEGF to mouse cell culture stimulates the development of placental tissue and increases the placenta area [1,5]. VEGF is produced by endothelial cells, fibroblasts, smooth muscle cells, and inflammatory cells [1,3,4]. Along with angiogenesis induction it has been found to increase vascular permeability, this ability is approximately 1000 times higher than that of histamine [2,4]. Deciduous NK cells produce VEGF already at early stages of pregnancy, at the stage preceding the invasion of trophoblast cells into mother arteries [4,9]. Its action on cells is mediated by 3 types of specific membrane receptors: VEGF-R1 (fms-like tyrosine kinase-1, Flt-1), VEGF-R2 (Flk-1/KDR) and VEGF-R3 (Flt-4), and the soluble form of the first of them - sFlt-1 - is considered as an antiangiogenic one [2,7]. It is known that the most intensive expression of VEGF-A and VEGFR-2 is observed at early gestational age, and the formation of VEGF-R1 is more intensively closer to the donor term [4].

**Vascular endothelial growth factor receptor 1.** Vascular endothelium growth factor receptor 1 (VEGFR1) is a high-affinity receptor for tyrosine kinase. In patients with PE the serum level of sVEGFR1 was increased, with a correlation between sVEGFR1 concentration and proteinuria level, the number of platelets in the mother and clinical criteria for PE classification [1,2,7]. Both early and late PE are associated with increased sVEGFR1. However, in patients with early PE the serum concentration of sVEGFR1 increases earlier

and to a greater extent than in late PE patients. Moreover, sVEGFR1 is able to predict early PE with greater sensitivity and specificity than late PE.

**Endostatin.** Specific inhibition of endothelial cell proliferation and migration, ability to induce apoptosis, and preclinical increase of endostatin serum concentration in PE have been shown [7,9]. However, studies comparing early and late PE have shown a change in circulating endostatin levels only for early PE and not for late PE [6,7], which supports the view that early PE is associated with pathological placentation.

**Epidermal growth factor.** Epidermal growth factor (EGF) and growth transforming factor- $\beta$  (TGF- $\beta$ ) are two important angiogenic factors that participate in PE pathogenesis. EGF has been shown to be a trigger for trophoblast syncytization, while TGF- $\beta$  inhibits it in vitro [5]. Accordingly, a balance between these two factors is necessary for adequate trophoblast syncytization. Low concentrations of EGF and high TGF- $\beta$  are determined in PE patients [10]; heparin-binding EGF also reduces trophoblast apoptosis, which develops in response to hypoxia; its level is reduced in PE patients [4,9]. TGF- $\beta$ 1 is one of the most studied types of TGF- $\beta$ . Early studies did not find any difference in TGF- $\beta$  levels between PE patients and healthy pregnant women, later studies found an increase in TGF- $\beta$  in women with PE and a genetic predisposition to high TGF- $\beta$  levels in women with PE in the history [1,3]. To date, there are no data on TGF- $\beta$  and EGF concentrations in early and late PE.

Endoglin is mainly expressed on the endothelial cell surface as well as on the placenta syncytiotrophoblast and is a coreceptor for TGF- $\beta$ 1 and TGF- $\beta$ 2. The increase in the level of the soluble form of endoglin (sEng) was studied as a prognostic marker of PE, as a noticeable increase in sEng concentration in women with PE was shown in some cases 2-3 months before the signs of pathology appeared [9]. There are conflicting data on sEng levels in early and late PE. Thus, some authors noted the absence of reliable differences [10], while others reported a significant increase in sEng concentration in women with early PE compared to late PE [1,4]. Increased sEng and sFlt1 levels were also shown in the first trimester in women who subsequently developed late PE [5]. According to the researchers, a combination of sEng and sFlt1 can be a reliable prognostic marker of PE, especially for the development of early PE with a sensitivity of about 100% and specificity of about 95% [2,5] in a study at 13 and 20 weeks of pregnancy.

**Placental Protein 13.** Placental Protein 13 (PP-13) is a placental-specific marker that plays a role in normal implantation, placental vessel development and spiral artery remodeling. Normally, the level of PP-13 increases during pregnancy, and in women who subsequently develop PE, its level is abnormally reduced [5]. Studies have shown that the serum level of PP-13 in combination with the average pulsation index of the uterine artery with high accuracy can be a predictive marker of PE. Moreover, it has been shown that serum level PP-13 itself in the first trimester, as well as its combination with the pulsation index of the uterine artery according to ultrasound Doppler in the second trimester,

better predict the development of early PE than the late form of the disease [4].

**Plasma pentraxin 3.** Pentraxins is a superfamily of proteins, which are mandatory components of the humoral immune system. Plasma pentraxin 3 (PTX3) is expressed by a number of cells, including endothelial cells of vessels, monocytes, macrophages and fibroblasts. It is believed to bind the antigens of apoptotic cells in order to limit their risk of initializing the immune response. An association between PE and an increase in plasma RTX3 concentration has been shown [7,9]. Moreover, serum RTX3 levels in 11-13 weeks of pregnancy are significantly higher compared with controls, although they do not differ in patients with subsequent development of early or late PE. In addition to those discussed above, analysis of biochemical and placental determinants revealed that "early" PE is characterized by an increased ratio of plasminogen inhibitor of the first type to the second (PAI-1/PAI2) - a marker of trophoblast dysfunction; a higher concentration of 8-iso-prostaglandin F $2\alpha$  in the placenta - a marker of oxidative stress [4,8]; higher concentration of elastase - a soluble marker of neutrophil activation [1,5]; increased concentration of retinol binding protein-4 - adipokine, involved in pathogenesis of insulin resistance and inflammation [1,8]. At the same time the increase of adiponectin - adipokine with anti-inflammatory action in blood was revealed only in patients with late PE [3,7,8].

**Soluble Fms-like tyrosine kinase.** Taking into account the connection between PFR and SEFR and the development of the trophoblast, it can be assumed that antiangiogenic factors play an important role in the development of PE, which inhibit their functions. PFR and SEFR bind to the receptor fms-like tyrosine kinase, which undergoes an alternative splicing from Flt-1 to soluble Fms-like tyrosine kinase (sFlt1), inducing endothelial dysfunction. Placental expression of sFlt1 is increased in PE, in some works it is associated with the degree of disease severity [4]. There are data that reliable changes in PFR level in PE are observed already in the first or in the beginning of the second trimester. The sFlt1 level rises 2-3 months before clinical symptoms of PE occur [9]. Both early and late PE are associated with changes in sFlt1 serum concentrations, with more pronounced disorders in early disease development.

At present, in the conditions of practical obstetrics, the most important measures to diagnose and prevent hypertensive disorders in pregnancy, and especially PE, are carefully collected anamnesis, identification of reliably associated with PE risk factors, early and adequate laboratory diagnostics, including the study of the most important parameters: proteinuria, hemostasis system, indicators of clinical and biochemical blood tests, including hepatic enzymes, determination of reliable prognostic markers of PE development in the blood. Complex laboratory diagnostics, dynamic monitoring of the patient under the control of instrumental methods of research, timely and rational tactics of management of pregnant women with hypertensive disorders will contribute to the effective reduction of maternal and perinatal morbidity and mortality, as well as improve the remote prognosis for mother and fetus.

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