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Predicting of Risk Preeclampsia in the Early Stages of Pregnancy

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Abstract: Research objective: to identify objective prognostic criteria for preeclampsia (PE) in the first half of pregnancy.

Materials and methods. A comprehensive dynamic examination of 209 women who had a single pregnancy and gave birth to live, full-term children was conducted. Retrospectively, two groups were formed depending on the results of pregnancy and childbirth. The control group included 84 women with uncomplicated pregnancy and childbirth, and the main group included 125 patients with moderate and severe PE. All participants were determined by the levels of PAPPA, β hCG, PAMG1, echocardiographic examination of central maternal hemodynamics, and the vasodilatory function of the endothelium was assessed.

Results : A prognostic marker of PE is a combination of signs of inadequate trophoblast invasion with abnormal changes in central hemodynamics and impaired vasomotor function of the endothelium.

Conclusion . In pregnant women at 17-20 weeks, an increase in minute volume (MV) of more than 13-14%, a decrease in total peripheral vascular resistance (TPVR) of more than 10-11%, an increase in functional activity. endothelium of 4% or more allows us to predict an uncomplicated pregnancy (without manifestations of PE). At the end of the first half of pregnancy, an increase in MR of no more than 10%, a decrease in TPR of no more than 7% and a decrease or slight increase in functional activity of the endothelium (less than 4%), allows us to predict the occurrence of PE..

Key words: preeclampsia, preclinical diagnosis, prognostic signs.

Preeclampsia (PE) is a life-threatening multisystem disease with complex etiological and pathogenetic components. The causes of PE are considered to be immunological and inflammatory changes that occur during placentation. Placental ischemia caused by insufficient penetration of trophoblasts into the walls of the spiral arteries can lead to an earlier onset and more severe course of PE (early PE), while maternal extragenital diseases can lead to a later clinical manifestation.

Pathological placental dysfunction caused by an imbalance of pro- and anti-angiogenic factors leads to inadequate remodeling of the spiral arteries and placental ischemia [1–4]. Reduced placental perfusion, in turn, leads to the release of harmful factors (LPO products, pro-inflammatory cytokines, anti-angiogenic factors, trophoblast apoptotic debris) into the maternal bloodstream, which contributes to the development of an inflammatory response and oxidative stress.

Under these conditions, the development of pregnancy creates the prerequisites for vasoconstrictor responses by the endothelium, inadequate perfusion of many organs and systems, and increased thrombogenic potential [1, 4-6]. Pre-existing hypertension, metabolic disorders, and autoimmune

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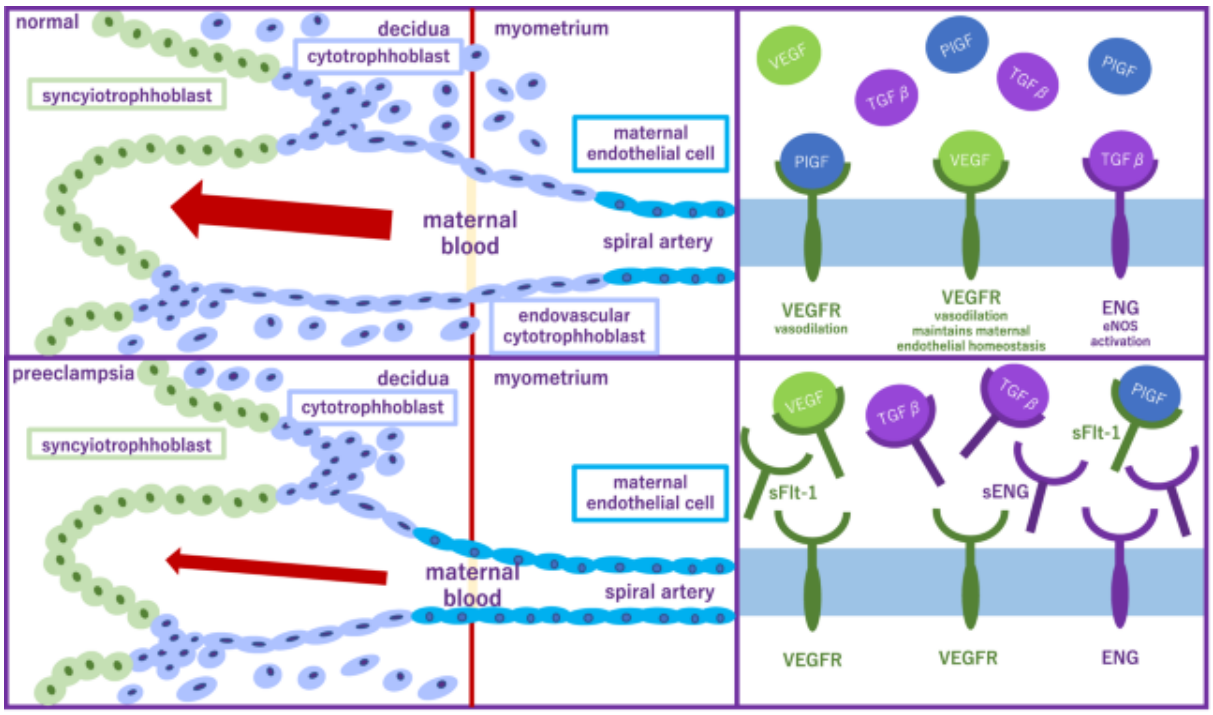
conditions in late PE lead to an overactive inflammatory response during the "normal" period of placentation.



VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; TGF β, transforming growth factor β; ENG, endoglin; sENG, soluble ENG; sFlt-1, soluble fms-like tyrosine kinase-1; PIGF, placental growth factor.

The complexity of pathogenetic processes determines the ineffectiveness of treatment and poor outcomes for the mother and fetus, which makes the problem of prognosis and timely diagnosis of PE particularly urgent. The development of accurate and easily reproducible prognosis of PE allows for timely identification of the risk group and targeted preventive measures.

The aim of the study was to identify objective prognostic criteria for PE in the first half of pregnancy. Materials and methods for 2012–2016. A comprehensive dynamic examination of 209 patients (18–43 years old) who had a singleton pregnancy and gave birth to live, full-term children was conducted in the Kursk City Clinical Maternity Hospital (head physician - KN Ilchenko). Women with multiple pregnancies, heart defects, type 1 diabetes or after IVF were not included in the study. Two groups were retrospectively formed depending on the outcome of pregnancy and childbirth. The control group included 84 women with uncomplicated pregnancy and childbirth, and the main group included 125 pregnant women with moderate and severe PE. The severity of PE was determined in accordance with the clinical guidelines "Hypertensive diseases in pregnancy, childbirth and the postpartum period. Preeclampsia. Eclampsia" 2015 [7].

All patients underwent 2 comprehensive examinations in the first half of pregnancy, corresponding to the periods of the end of the first and second waves of trophoblast invasion (11-13 and 17-20 weeks), which included a standard obstetric examination. Echocardiographic study of maternal central hemodynamics taking into account stroke volume (SV) and minute (MO) volumes, stroke (SI) and cardiac (CI) indices, total peripheral vascular resistance (OPSS), heart rate, blood pressure with subsequent calculation of the types of central hemodynamics (eu, hyper or hypokinetic type).

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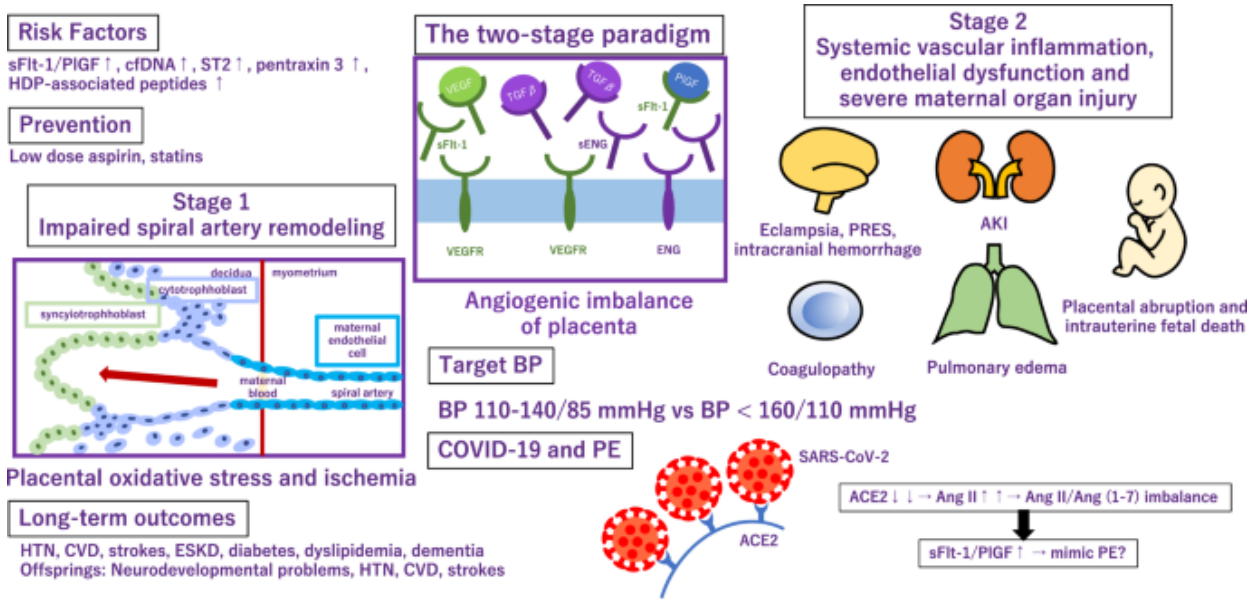

HTN, hypertension; HDP, hypertensive disorders of pregnancy; PE, preeclampsia; BP, blood pressure; cfDNA, cell-free DNA; ST2, human suppression of tumorigenesis 2; sFlt-1, soluble fms-like tyrosine kinase-1; PlGF, placental growth factor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; TGF β, transforming growth factor β; ENG, endoglin; sENG, soluble ENG; PRES, posterior reversible encephalopathy syndrome, AKI, acute kidney injury; CVD, cardiovascular disease; ESKD, end-stage kidney disease; ACE, angiotensinogen converting enzyme; Ang, angiotensin.

Endothelial function was determined by the severity of endothelium-dependent vasodilation of the maternal brachial artery (BA) after performing a cuff test with reactive hyperemia [8] using an Aloka SSD 1700 ultrasound device (Japan). The values of vasodilatory endothelial function indicators obtained during the period of 11-13 weeks were taken as initial (initial endothelial function), and during the period of 17-20 weeks - final (final endothelial function). According to the results of two studies, an increase in the vasodilatory function of the endothelium in the dynamics of the first half of pregnancy (FE = FEK - FEI) was assessed (patent for the invention No. 2485894) [9]. In addition, the amount of serum pregnancy markers - PAPRA, bhCG, PAMG1 - was measured during the period of 11-13 weeks.

Statistical processing of the results was carried out using the Statistica 6.0 program (StatSoft, USA). Correlation analysis methods (Spearman coefficient) were used to study the relationship between variables. The significance of the difference between the two means for dependent and independent samples was assessed using the Student's t test. The difference between the mean values in the compared groups was considered significant at $p < 0.05$. To determine the prognostic significance of the studied parameters, univariate and multivariate regression analyses were performed using the Cox proportional hazards model; Multivariate regression analysis included factors that had a statistically significant (or borderline statistically significant) effect on the development of PE. Differences were considered significant at $p < 0.05$. Results The analysis showed that more than half of the respondents (63.6%) were aged 23 to 35 years. When analyzing the course of previous pregnancy and childbirth, it was found that 5.9% of patients in the control group and 23.2% in the main group had previous clinical manifestations of PE ($p > 0.05$). Pregnant women with PE were significantly more likely to have extragenital diseases ($p \leq 0.05$): cardiovascular, inflammatory diseases of the genitourinary organs, metabolic diseases (E70-E90). High blood pressure (R03.0) without a diagnosis of hypertension was diagnosed in 34.4%, hypertension - in 11.2% of women. Chronic pyelonephritis accounted for 20.0% of participants in the main group.

In pregnant women with PE, chronic inflammatory diseases of the uterus and frequent exacerbations were significantly more common than in the control group - 24% versus 6% ($p < 0.05$). Almost every fifth woman with PE had endocrine diseases (polycystic ovary syndrome, hypothyroidism, hyperprolactinemia). 14.4% of participants in the main group were diagnosed with metabolic syndrome and nutritional obesity.

The course of the first half of this pregnancy in patients with PE was characterized by signs of early abortion (60.0%), chorionic detachment (43.2%), as well as the risk of repeated abortion during

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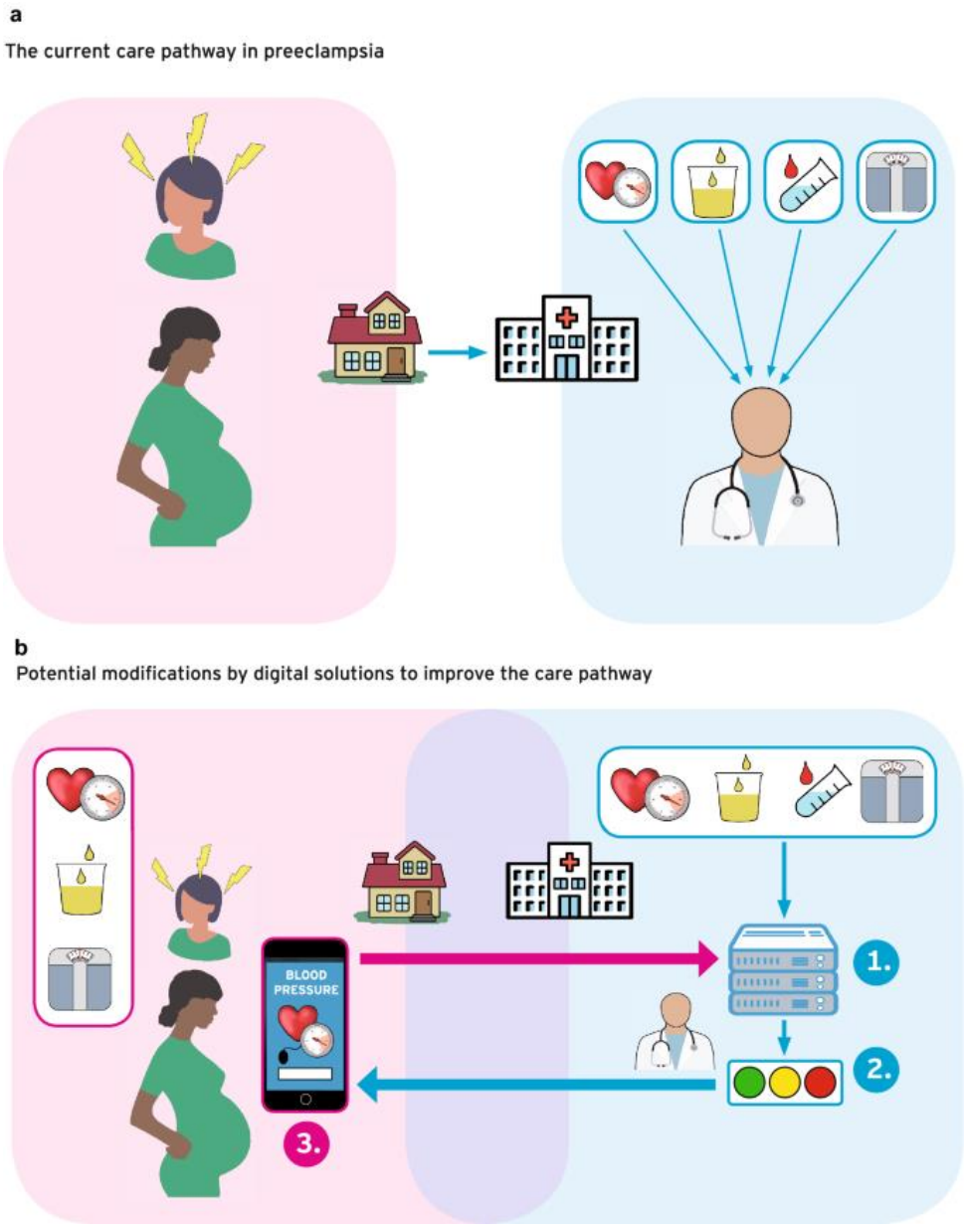
pregnancy (33.6%). The combination of relative polyhydramnios with the presence of echo-positive inclusions in the amniotic fluid, interpreted as ultrasound signs of amnionitis, was detected in 36.8% of women with PE and in 19.0% of pregnant women in the control group. Ultrasound and Doppler signs of placental insufficiency were observed in 48.8% of patients with PE.

In pregnant women with moderate PE, swelling of the lower extremities was first noted at 28-31 weeks, followed by hypertension after 2-3 weeks. In severe PE, clinical symptoms were noted 2-4 weeks earlier, first with increased blood pressure, then edema syndrome and proteinuria. Surgical delivery according to fetal or maternal indications was performed in 68.0% of pregnant women, 12.0% of whom had symptoms of severe PE.

The average body weight of the fetus in mothers with PE was 2874 ± 294 g, and the Apgar score at birth was 5.6 ± 2.6 points, which were lower than in the control group (3357 ± 310 g and 8.3 ± 0.4 points). . In the early neonatal period, hypoxic-ischemic lesions were detected in 51.2% of newborns of the main group.



Univariate and multivariate regression analysis performed did not reveal the prognostic significance of anamnestic data, the presence of extragenital diseases, and the course of previous pregnancies for predicting PE.

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Assessment of the functional activity of the main elements of the fetal egg and decidual tissue showed that patients with PE had lower concentrations of PAPPA and bhCG (0.89 ± 0.19 MOM versus 1.49 ± 0.15 MOM and 0.87 ± 0.31 versus 1.6 ± 16, OM, respectively) and higher levels of PAMG1 (23.1 ± 4.2 ng/ml versus 12.6 ± 3.4 ng/ml) than the control group ($p \leq 0.05$ for all parameters).

Analysis of the initial types of central hemodynamics showed that with the development of PE, the hypokinetic (21.4%) type was twice as high as in the control group, and the hyperkinetic (39.3%) type was three times higher ($p < 0.05$ for both indicators).

The dynamics of SI and SI in both groups do not reflect the nature of changes during pregnancy, since they largely depended on changes in the patient's body weight during this period of pregnancy.

Analysis of changes in echocardiographic parameters in the control group from 11-13 to 17-20 weeks revealed a significant increase in SV and MO, as well as a significant decrease in OPSS (table, Fig. 1). In pregnant women with PE, the increase in SV and MO by 17-20 weeks was less than 10% (see table, Fig. 1), TPR slightly decreased. Table Indicators of central maternal hemodynamics and vasodilatory function of the endothelium in the examined women (M ± m) * Differences from the indicators at 11-13 weeks were significant ($p < 0.05$). Rice. 1. Changes in indicators of central maternal hemodynamics in the first half of pregnancy in the study groups, % Changes in endothelial function showed that in uncomplicated pregnancy, the diameter of the VA at 11-13 weeks after the cuff test exceeded 3.5 mm. 4.3 mm (average 18-24%), blood flow velocity increased by 11-13% (see table). After the compression test, the expansion of the VA diameter at 17-20 weeks of gestation was more pronounced with a parallel increase in blood flow velocity (25-26%). In the control group, the total increase in the functional activity of the endothelium during the dynamic observation period (from 11 to 20 weeks) was 4.7 ± 0.4% (Fig. 2). Rice. 2. Changes in the vasodilatory function of the endothelium in the study groups during pregnancy * Differences from the indicators at 11-13 weeks are significant ($p < 0.05$) Assessment of the vasodilatory function of the endothelium at 11-13 weeks of gestation in patients with PE did not reveal differences with the control group ($p > 0.05$). After the cuff test, the diameter of the VA increased by 18-22%, and the blood flow rate by 12-14%. Significant differences in the functional activity of the endothelium from those in the control group were detected in the period of 17-20 weeks. After the cuff test, the diameter of the VA changed slightly - from 33 mm to 37 mm (no more than 11-12%), the blood flow rate increased by about 9-10% (see table). It should be noted that the vascular response detected in response to the compression test was multidirectional. In the main group, 28.8% of women responded adequately to the test in the form of an increase in the diameter of the VA, 40.0% did not change the vascular diameter over time, and 31.2% had a paradoxical reaction in the form of a decrease in the diameter of the VA after the compression test. The overall increase in endothelial vasodilatory activity during the first half of pregnancy was 3.2 ± 0.2% ($p \leq 0.05$) (see Figure 2). Discussion Currently, there are no realistic options for the prevention and treatment of PE, so early identification of pregnant women at high risk of developing this complication may help improve pregnancy outcomes [10].

Analysis of anamnestic data and the results of objective studies in the early stages of pregnancy (10-13 weeks) showed that no single parameter or combination of several parameters considered separately can be considered a prognostic predictor of PE due to its low prognostic significance. . At the same time, there is a direct relationship between placental complications of pregnancy associated with diseases of the cardiovascular system, kidneys, diabetes, chronic inflammatory diseases, and placental diseases.

Pathogenetically, diseases of the cardiovascular system are accompanied by significant changes in maternal hemodynamics and microcirculation, which are mainly manifested by arteriolospasm and hypovolemia, which creates a favorable premorbid background for the development of PE. Somatic inflammatory diseases (chronic bronchitis, tonsillitis, pyelonephritis) increase the risk of negative effects of bacterial and viral infectious agents on the formation and development of the mother-fetus-placenta complex. Toxic substances can cause various effects and reactions both at the level of

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cellular structures and at the intersystem and interorgan levels (activation of the kallikrein system, coagulation and fibrinolysis, etc.) [1]. As a result, such changes lead to a violation of vascular tone, capillary perfusion, rheological properties of blood, water and electrolyte balance, hypovolemia, thrombosis, etc. Concomitant hypoxia leads to damage to the vascular endothelium with a violation of its thrombotic and vasoactive properties. release of mediators (endothelin, serotonin, circulating eclampsia factor, thromboxane) that play a key role in regulating hemostasis and vascular tone.

According to the modern theory of the development of PE, the development of this disease is divided into two stages: the first - placental, asymptomatic in the early stages of pregnancy, the second - maternal, with clinical symptoms manifested in the second half of pregnancy. . The first stage occurs as a result of a violation of the immune adaptation of the mother's body in response to the effects of various agents of the fetal egg from the early stages of pregnancy and is manifested by insufficient penetration of trophoblasts into the spiral arteries. This leads to the formation of primary placental insufficiency, impaired placental perfusion, hypoxia, increased apoptosis and necrosis of placental tissues.

The severity of negative processes in the trophoblast affects the development of all embryonic and extraembryonic structures of the fetal egg, which is reflected in the level of expression of pregnancy proteins, growth factors, hormones and other biologically active substances [2, 11, 12]. In our study, we analyzed the relationship between changes in the concentration of bhCG and pregnancy proteins PAMG1 and PAPPA in patients with PE and during physiological pregnancy. In PE, a significant decrease in the level of bhCG and PAPPA and a 1.8-2-fold increase in the content of PAMG1 compared to normal values (0.8-1.0 MOM) were noted, which indicates the first pathological course. wave of trophoblast invasion and disruption of early placental formation.

It was also noted that in all cases of early PE, the levels of PAPPA and bhCG were significantly lower than 0.8 MOM, and the concentration of PAMG1 exceeded 18 ng / ml. In pregnant women with late PE, no clear correlation was found between the results of the first biochemical screening and the characteristics of the pregnancy process. Therefore, it is impractical to use the levels of the hormone bhCG and pregnancy proteins to predict all types of PE.

The development of the second (maternal) stage of PE is associated with placental hypoxia, impaired perfusion, which is formed in the early stages of pregnancy. The clinical manifestation of PE in the second half of pregnancy occurs when endothelial dysfunction develops, micro- and macrocirculation is impaired, and inflammatory reactions in the mother’s body are activated [13]. It should be noted that the presence of severe primary placental insufficiency does not always lead to the development of PE, but can also lead to premature birth, as well as fetal growth retardation [2, 5, 12]. It is known that only disturbances in placental blood flow with genetic, environmental, constitutional characteristics of the mother, the presence of predisposing factors for cardiovascular diseases, and endothelial dysfunction can lead to PE.

Accordingly, the search for objective prognostic criteria for uncomplicated or complicated pregnancy should be carried out in accordance with the characteristics of the functioning of the fetoplacental complex, taking into account the severity of changes in the maternal cardiovascular system during pregnancy. Given that the clinical manifestations of PE occur after 20 weeks of gestation, we evaluated the pregnancy-related changes in maternal central hemodynamics during the second wave of trophoblast invasion (from 11-13 to 17-20 weeks).

The study found that during uncomplicated pregnancy, adequate adaptive restructuring occurs in maternal hemodynamics aimed at meeting the increasing needs of the growing fetus. During the second wave of trophoblast invasion, SV and MO values increase by approximately 17-19%, while TPR decreases by 11.7% and systolic and diastolic blood pressure remain stable.

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