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БИОМАРКЕРЫ ЯВЛЯЮТСЯ ПОТЕНЦИАЛЬНЫМИ ПРЕДИКТОРАМИ ДЛЯ РАННЕЙ ДИАГНОСТИКИ И ПРОГНОЗИРОВАНИЯ ПРЕЭКЛАМПСИИ.

BIOMARKERS ARE POTENTIAL PREDICTORS FOR EARLY DIAGNOSIS AND PROGNOSIS OF PREECLAMPSIA.

Abstract. In recent years, biomarkers have been considered among the most promising tools for the early diagnosis and prognosis of preeclampsia, a complex multisystem condition that remains a leading cause of maternal and perinatal morbidity and mortality. Current research shows that disturbances in angiogenic balance, endothelial function, placental perfusion, immune regulation, and metabolic processes arise long before the clinical manifestation of the disease. Therefore, circulating biomarkers reflecting these pathophysiological changes can serve as valuable predictors of the risk of developing preeclampsia in early pregnancy.

The use of biomarkers in clinical practice facilitates the development of a personalized approach to pregnancy management, improves maternal and fetal monitoring, and reduces the likelihood of severe complications. The implementation of biomarker technologies is an important step toward

personalized medicine in obstetrics and more effective preeclampsia management.

Keywords: preeclampsia, pregnancy, risk factor, maternal mortality.

Аннотация. Биомаркеры в последние годы рассматриваются как одни из наиболее перспективных инструментов для ранней диагностики и прогнозирования преэклампсии — сложного мультисистемного состояния, остающегося ведущей причиной материнской и перинатальной заболеваемости и смертности. Современные исследования показывают, что нарушения ангиогенного баланса, эндотелиальной функции, плацентарной перфузии, иммунной регуляции и метаболических процессов возникают задолго до клинического проявления заболевания. Поэтому циркулирующие биомаркеры, отражающие эти патофизиологические изменения, могут служить ценными предикторами риска развития преэклампсии на ранних сроках беременности.

Использование биомаркеров в клинической практике способствует формированию персонализированного подхода к ведению беременности, улучшает мониторинг состояния матери и плода и снижает вероятность развития тяжёлых осложнений. Внедрение биомаркерных технологий является важным шагом на пути к персонализированной медицине в акушерстве и более эффективному контролю преэклампсии.

Ключевые слова: преэклампсия, беременность, фактор риска, материнская смертность.

Introduction. Although great efforts have been made to elucidate the etiology and pathogenesis of preeclampsia in pregnancy, the processes involved in its development remain largely unknown. Most efforts in the last decade have relied on biomarkers for the prediction or diagnosis of preeclampsia, including the antiangiogenic factor sFlt-1 (soluble FMS-like tyrosine kinase-1), the angiogenic factors PlGF (placental growth factor), and PP13 (placental protein-13). These marker proteins have been shown to predict the development of

preeclampsia. are still under debate and their actions have been described separately so far. The three markers mentioned above are said to induce preeclampsia during pregnancy and act synergistically, and when complicated by preeclampsia, it is necessary to protect the mother from harmful effects released from the placenta [7].

Most of these markers indicate impaired placentation, with insufficient development of spiral arteries in the uterus leading to trophoblast invasion and reduced placental perfusion, resulting in ischemia in the placenta, which in turn leads to the release of pro-inflammatory factors, platelet activation, endothelial dysfunction, and maternal renal failure [12].

Studies have shown that maternal plasma markers, pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF), are early predictors of preeclampsia and have high predictive value. The level of β -hCG in plasma increases between 11 and 13 weeks of pregnancy [2].

Placental growth factor (PIGF) is a glycated iron glycoprotein, a member of the vascular endothelial growth factor family. It binds to vascular growth factor receptor-1, which is increased during pregnancy. PIGF is synthesized by villous and extravillous cytotrophoblasts and has vasculogenic (neovascular) and angiogenic functions. It contributes to angiogenesis by changing the vascular phenotype from branched to unbranched and regulating capillary networks. Alterations in the level of placental growth factor or its inhibitory receptors may play an important role in the development of preeclampsia. In the setting of preeclampsia, placental growth factor (PIGF) production by the placenta is reduced, and plasma PIGF concentrations decrease with the onset of clinical signs of preeclampsia [6].

In addition, a decrease in PIGF levels is associated with pregnancy. Clinical signs of preeclampsia also occur in the first and second trimesters [9].

Soluble fms-like tyrosine kinase-1 (sFlt1) is a glycosylated protein with a molecular weight of 90-110 kDa, which is a soluble form of vascular endothelial

growth factor (VEGF) and placental growth factor (PIGF). This protein lacks transmembrane and intracellular domains, and is a “working” cellular receptor specific for the Flt-1 molecule. Normally, sFlt-1 is detected in physiological and pathological pregnancy. The concentration of sFlt-1 increases significantly even before the onset of preeclampsia. In clinical practice, the concentration of the sFlt-1-e5a isoform is used, the expression of which is associated with syncytiotrophoblast and cytotrophoblast [5].

The concentration of sFLT-1 increases with increasing gestational age, which also depends on the mother's age. Its concentration decreases if the mother is overweight, increases with the use of assisted reproductive technologies (ART), and is lower in nulliparous women than in pregnant women [1].

Recent studies have shown that the ratio of soluble fms-like tyrosine kinase-1 (sFLT-1) and placental growth factor PIGF is a very accurate marker for identifying a group at high risk of developing preeclampsia [4].

A number of foreign studies have shown that a study involving 1,149 patients showed that the sFlt-1/PIGF ratio is a clear marker for an increased risk of developing preeclampsia , 20-30 There were more than 85 cases of preeclampsia during the first week of pregnancy and more than 110 cases of preeclampsia during the first week of pregnancy [8].

Currently, a number of anti-inflammatory cytokines (TNFα, IL-1, IL-6), as well as biochemical markers - angiogenesis factors are being additionally studied for the early diagnosis of the development of preeclampsia in pregnant women. These include: PlGF - placental growth factor or vascular endothelial growth factor. Its content increases significantly in the second trimester of pregnancy and remains constant throughout this period, by the end of pregnancy, sFlt-1, soluble PlGF receptors decrease slightly [10].

According to the authors, insufficient increase in PlGF concentration in early pregnancy and increased sFlt-1 concentration are highly likely to cause preeclampsia.

The detection of sFlt-1 is effective in the second half of pregnancy, as well as the sFlt-1/PlGF ratio, which indicates the level of angiogenic activity. In addition to the above data, impaired blood flow in the uterine arteries can play a predictive role in predicting preeclampsia [15].

The aforementioned biochemical markers PAPP-A and PIGF are among the best-studied laboratory parameters in early preeclampsia studies.

At the Fetal Medicine Foundation (UK), a study was conducted to evaluate the construction of a risk model using the Bayesian method, in which anamnesis and instrumental studies (uterine artery pulsatility index (PI)), mean arterial blood pressure, PAPP-A and PIGF are studied at 11-13 weeks of pregnancy, and when these indicators are studied together, it is possible to more accurately identify high-risk groups for the development of preeclampsia [11].

Pregnancy-associated plasma protein-A (PAPP-A) is a glycoprotein produced primarily by placental trophoblast cells and may reflect the degree of placental ischemia or hypoxia.

PAPP-A can regulate the activity of insulin-like growth factors and thus influence the infiltration of placental trophoblast cells, which is therefore very important for normal pregnancy [14].

However, low levels of PAPP-A in plasma early in pregnancy may be associated with preeclampsia. PAPP-A has low plasma concentrations in pregnant women complicated by preeclampsia, and its use alone is not effective in predicting preeclampsia. Some researchers use PAPP-A in combination with Doppler testing to achieve better results in predicting preeclampsia [13].

It is noted that a study of 8839 women showed that PAPP-A levels of five percent or less are associated with a higher risk of preterm birth, intrauterine growth retardation, preeclampsia, and stillbirth. Predictive models for estimating

individual risk of late-term preeclampsia are based on a combination of first-trimester PAPP-A levels and second-trimester sFlt1/PlGF ratios. (Detection rate: 87.5%, false positive rate 5%). With the development of preeclampsia, the concentration of PlGF and PAPP-A in maternal plasma decreases during pregnancy. These proteins are produced by trophoblasts, and their decreased plasma concentration delays the formation of the placenta [14].

AFP (alpha-fetoprotein) is a major plasma protein produced by the fetal liver and gallbladder. AFP is similar to the fetal analogue of serum albumin—they have similar physical properties and are inversely proportional to each other. Elevated levels of AFP in the second trimester of pregnancy are a good predictor of preeclampsia [5].

Human chorionic gonadotropin (HCG) is a hormone produced by trophoblast cells from 10-12 weeks of pregnancy. It has been shown that HCG stimulates angiogenesis, so today, according to clinical indications, its concentration in the second trimester of pregnancy is considered to be a basis for suspecting the presence of preeclampsia if it is > 3 MoM [8].

As a test for predicting PE in the third trimester of pregnancy, high AFP levels (>2 MoM) have been shown to have a sensitivity of 11% and a specificity of 96% [7].

sFlt-1 binds to both VEGF-A and PlGF, inactivating their functions, so an increase in its blood concentration leads to various pregnancy complications, especially preeclampsia [1].

Studies have shown that in patients with preeclampsia, sFlt1 is increased and PlGF is decreased, and the increase in Flt1 may be associated with a decrease in VEGF and PlGF in the blood. sFlt1 and PlGF have shown high sensitivity in predicting the onset of PE from the second trimester of pregnancy [13].

In the literature, it has been found that an increased sFlt:PlGF ratio may be of some importance in predicting PE [6]. Due to the potential role of sFlt1

and PlGF in the pathogenesis of PE and their predictive role, they have become high-ranking biomarkers for PE, especially randomized trials, although further studies are still required to assess their value.

Thus, the levels of angiogenic proteins (sFlt-1, PIGF, and sEng) in the blood of pregnant women change several weeks before the onset of clinical signs and symptoms of the disease, which allows their quantitative parameters to be used for early non-invasive diagnosis of PE [3]. In the second trimester, the ratio of angiogenic factors PIGF/sEng and PIGF/sFlt is the best prognostic indicator.

At the same time, impaired placental angiogenesis is accompanied not only by PE, but also by other pathologies of pregnancy: premature birth, premature placental abruption, low-lying placenta, intrauterine fetal death. To increase the accuracy of predicting PE, a number of researchers have used complex parameters - the concentration of sFlt-1 / PIGF, PIGF / sEng, sFlt-1 / sEng, sFlt-1 / PIGF + sEng, and other combinations of these factors [10].

Such combinations allow for effective differentiation of PE from each indicator separately and in combination with Doppler data from the second trimester - with sensitivity reaching almost 100%, specificity reaching 98-99%.

Many studies have shown that excess sFlt-1 production is associated with an increased risk of PE. It has been proven that excessive amounts of this factor are released from the placenta under the influence of proteases. Plasma sFlt-1 levels are significantly higher in pregnant women with preeclampsia compared to women with normal pregnancies in the first and second trimesters[13].

Thus, the placentally secreted marker sFlt-1 may be a prognostic or diagnostic marker for preeclampsia. Developing a precise assay for these variants could significantly improve early and late disease screening (in combination with PlGF and alone) .

The right test could significantly accelerate obstetric care worldwide without increasing the economic burden on financially challenged health

systems. In addition, a better understanding of the pathways involved in the release of antiangiogenic factors from the placenta and the role played by different splicing variants may help improve therapeutic design and evaluate drug efficacy.

Thus, high levels of antiangiogenic factors and low levels of proangiogenic factors are useful biomarkers for early detection and prognosis of preeclampsia.

Thus, the search for markers that contribute to the diagnosis and differentiation of hypertension in pregnant women is currently an urgent problem in obstetrics. Timely diagnosis and determination of the nature of the identified pathology can have a decisive impact on the tactics of managing pregnant women and the timely initiation of treatment, pregnancy outcomes, and the health of newborns.

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