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The Role of Biophysical and Biochemical Markers in the Early Diagnosis of Preeclampsia

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Abstract This literature review is based on an analysis of more than 40 literature sources that describe current views on the mechanisms underlying the development of early- and late-onset preeclampsia. The review examines the significance of 2 biophysical and 8 potential biochemical markers, which can possibly be studied in the first and second trimesters of pregnancy for the early diagnosis of preeclampsia. The goal was to determine their significance in the diagnosis of this disease. The study found that levels of certain blood markers were significantly higher or lower in women who subsequently developed preeclampsia, compared with a control group of women who had normal pregnancies. However, using these markers alone does not provide sufficiently accurate prognostic information. Future research should focus on identifying combinations of markers that may be effective screening tools for more reliable diagnosis of preeclampsia.

Keywords Preeclampsia, Pregnancy, Biochemical markers

1. Introduction

Preeclampsia (PE) is a multisystem disease, from the group of hypertensive disorders, specific exclusively to pregnancy. According to WHO, hypertensive disorders are registered in 10% of pregnant women and are one of the leading causes of maternal and perinatal morbidity and mortality worldwide [1]. The frequency of developing PE is 3–8% [1–3]. Every year, 8.5 million cases of PE are registered worldwide. In countries with a low level of development, PE is the main cause of maternal mortality, while in economically developed countries it ranks 2–3 in the structure of causes of maternal mortality (15–20% in general). In Europe and the USA, the incidence of eclampsia is 2–3 per 10,000 births, while in developing countries this rate is 10–30 times higher. After experiencing PE or eclampsia, the risk of developing it in a subsequent pregnancy is 25%.

This hypertensive disorder may increase the risk of adverse outcomes for the mother such as placental abruption, kidney failure, liver failure, cerebrovascular accident, HELLP syndrome, as well as infant admissions to neonatal intensive care units (fetal or neonatal death), and may increase the use of additional interventions and hospitalizations.

High rates of early delivery associated with PE also lead to an increase in neonatal mortality, which is 2.7 times higher than in pregnancies ending in urgent birth.

Currently, there is no complete and reliable theory of the etiopathogenesis of PE. Numerous theories about the possible mechanisms of development of PE in most cases turned out to be unfounded. Diagnosis of PE is based on clinical symptoms such as hypertension, edema and proteinuria, which appear after the 20th week of pregnancy.

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Potential biophysical biomarkers of the development of preeclampsia.

Mean arterial pressure (MAP)

One of the first nonspecific biophysical markers is MAP, since blood pressure measurement is most likely to be an indicator of increased susceptibility of maternal blood vessels to PE. Also, hypertension during pregnancy can be a marker of both existing hypertension and developed gestational hypertension. More accurate arterial pressure measurement is achieved through the 24-hour arterial pressure measurement system (ambulatory blood pressure monitoring). Many studies have shown that MAP increased significantly already at the end of the first trimester in patients who subsequently developed PE. High MAP in patients who subsequently develop PE is likely to be caused by decreased maternal arterial elasticity coupled with increased vasoconstriction. Cnossen et al. conducted a systematic review and showed that MAP was a more reliable predictor than systolic and diastolic blood pressure or spontaneous increases in blood pressure, depending on whether it was the first or second trimester [4]. It has been shown that MAP increased significantly already at the end of the first trimester in patients who subsequently developed PE.

Uterine artery Doppler ultrasound. Most algorithms of preeclampsia prediction include uterine artery Doppler ultrasound (UtAD), measured as either pulsatility index (PI) or resistance index (RI). Also, a diastolic notch detected on

ultrasound is used as a sign of increased vascular resistance and decreased elasticity. However, isolated assessment of pulsatility index and/or resistance index in the uterine arteries is not a reliable predictor of preeclampsia and has a relatively low positive predictive value (approximately 21% of PE cases) [5]. In a retrospective comparative randomized study by Sakhautdinova I.V., 588 pregnancy management records were studied, from which 34 records of patients with severe forms of preeclampsia were identified. These patients made up observation group I: I a - patients with early preeclampsia - 10 people, I b - patients with late preeclampsia - 24 people. Group II included 66 patients whose pregnancies were not complicated by preeclampsia. All patients at 11-14 weeks of gestation underwent measurement of pulsatility index (PI) of both uterine arteries.

Results of the study. We did not detect a statistically significant difference in the PI of the uterine arteries in the studied groups; we concluded that an isolated assessment of the pulsatility index in the uterine arteries is not a reliable predictor of preeclampsia [6].

Proangiogenic and antiangiogenic markers. According to numerous research data, the leading theory for the development of PE is impaired placentation. Poor trophoblast invasion of the spiral arteries is hypothesized to result in the release of oxidative stress, antiangiogenic, or proinflammatory factors into the maternal blood flow. The release of these factors by the ischemic placenta plays a key role in endothelial damage, which is one of the leading signs of PE. In this regard, many biomarkers have been proposed for the prediction and diagnosis of preeclampsia - proangiogenic and antiangiogenic factors, placental proteins, free fetal hemoglobin (HbF), markers of kidney and endothelial dysfunction, metabolic status, oxidative stress, hemolysis. Proangiogenic factors, such as placental growth factor (PlGF), endothelial growth factor (VEGF), play a fairly important role in the formation of new blood vessels and the normal course of pregnancy [7]. Along with antiangiogenic factors such as soluble tyrosine kinase 1 (sFlt1), they are important regulators of early placental development. Impaired trophoblast invasion results in the cytotrophoblast being unable to suppress the expression of adhesion molecules characteristic of epithelial cells and unable to increase the expression of adhesion molecules characteristic of endothelial cells. As a result, pseudovasculogenesis is disrupted. PE is believed to occur due to an imbalance of proangiogenic factors and antiangiogenic factors. Studies have shown that exogenous soluble tyrosine kinase 1 (sFlt1) inhibits cytotrophoblast invasion in vitro [8].

VEGF is a potent angiogenic protein that promotes vasodilation, thereby inducing the synthesis of nitric oxide and prostacyclin by endothelial cells [9]. The function of VEGF is to ensure the viability of endothelial cells, the stability of the process of their migration, differentiation, and stimulate an increase in vascular permeability [10]. VEGF acts through two receptor tyrosine kinases: VEGF receptor-1 (FMS-like tyrosine kinase) and VEGF receptor-2, which are selectively expressed on the surface of vascular endothelial cells. The VEGF-1 receptor has 2 isoforms: a transmembrane isoform and a soluble isoform (sFlt).

PIGF is an angiogenic growth factor that enhances VEGF signaling by displacing VEGF from the VEGF-1 receptor and allowing it to bind to the more active VEGF-2 receptor [11]. An increase in sFlt-1 during PE is associated with a decrease in free VEGF and free PIGF in the blood [12]. The main source of PGIF is the trophoblast, and it is expressed in several different isoforms that bind only to the VEGF receptor -1. Inadequate modification of the spiral arteries of the uterus leads to increased production of the antiangiogenic factor sFlt-1.

sFLt-1 is a circulating soluble receptor for both VEGF and free PIGF. High levels of sFlt-1 in maternal plasma bind the two above-mentioned factors, thereby effectively reducing their concentrations in blood. The ability of VIGF and PIGF to interact with their receptors on the cell surface of cells is lost. This in turn leads to suppression of receptor signaling, which makes it impossible to stimulate angiogenesis and maintain endothelial integrity [13]. sFlt-1 is an antagonist of the proangiogenic factors VEGF and PIGF, attaching to their receptor-binding domains. [14]. In the kidney, this inactivation of free VEGF is thought to cause endotheliosis and proteinuria [13]. It has been proven that in PE there is an abnormally high expression of endogenous sFlt-1 [14].

A fairly large number of studies indicate that there is indeed a decrease in the level of serum VEGF and PIGF with a simultaneous increase in the level of sFlt-1 in PE compared with indicators in normal pregnancy [14,15,16]. 80 pregnant women took part in the period from 2008 to 2012 in a study by Masoura et al.: 40 women with PE before treatment (study group) and 40 women with normal arterial pressure without any pathology during pregnancy (control group). The levels of VEGF and PlGF in blood were significantly lower in women with PE than in the control group: VEGF 90 (mean range 90-211) pg/ml vs. 90.55 (mean range 90-521) pg/ml and PIGF 13.62 (mean range 8-532) pg/ml vs. [239.86 (median range 61-685)] pg/ml. However, serum levels of sFlt-1 were significantly increased in the study group than in the control group 21297 (mean range 690-32637) pg/ml vs 846.45 (mean range 363-2867) pg/ml [19]. Therefore, measuring these factors early in pregnancy may be of great prognostic value for women at high risk of developing PE. The ratio of sFlt-1/PIGF is considered a more reliable indicator of angiogenic activity and can be used as a screening test for the development of early PE [17].

Soluble endoglin (sEng). sEng is another antiangiogenic factor that, together with sFlt-1, causes severe PE. Endoglin is an isoform of the co-receptor transforming growth factor (TGF)-β1 and TGF-β3, which is expressed on the cell membranes of the vascular endothelium and on the syncytiotrophoblast [18]. This factor is involved in angiogenesis and regulation of vascular tone [19]. TGF-β is a pro-angiogenic molecule, so when sEng levels increases, it loses its properties and is inactivated. Soluble endoglin (sEng) acts as a potential antiangiogenic factor by interfering with the binding of TGF-β1 to its receptors, which ultimately affects nitric oxide

(NO) production, vasidilation and capillary formation by endothelial cells [19]. Like the levels of sFlt-1, the levels of sEng are significantly high in women with PE. The level of sEng is 4 times higher in patients with PE compared to women with a normal pregnancy [20]. In a study by Akolekar et al, in women who subsequently developed PE, the levels of sEng were already high at 11–13 weeks [21]. Levine et al. conducted a study in which 72 women with PE and 120 women from the control group with normal arterial pressure took part. The levels of circulating soluble endoglin increased markedly 2–3 months before the onset of PE. After the onset of PE, the average level in the blood of women with PE was 46.4 ng/ml compared to 9.8 ng/ml in the control group [22].

Pregnancy-associated plasma protein A. Pregnancy-associated plasma protein (PAPP-A) is a large glycosylated protein that is produced by the developing trophoblast and plays an important role in implantation [23]. As a result, it may reflect the degree of placental ischemia and hypoxia. PAPP-A regulates the activity of insulin-like growth factors (IGF) by cleaving insulin-like growth factor binding proteins. Thanks to this, free IGF can perform its biological functions. PAPP-A is secreted from the placenta into the blood. Its indicator is often used to screen for aneuploidy in early pregnancy. Reduced level of PAPP-A indicates a high risk of the existence of trisomy in fetus [24], which, consequently, is used as a biomarker for Down syndrome. There is evidence that in chromosomally normal pregnancies, low level of PAPP-A in maternal serum is associated with an increased risk of subsequent development of PE. In studies by Poon et al. first trimester screening was carried out in 8051 women with a live fetus at gestational ages from 11 + 0 to 13 + 6 weeks. 156 women (1.9%) developed PE, including 32 (0.4%) women who delivered before 34 weeks (early PE) and 124 (1.5%) who delivered at 34 weeks or later (late PE); 7895 (98.1%) cases were pregnancies (in the control group with normal course). The median PAPP-A was 1.002 (0.685 –1.411) MoM in the control group, 0.555 (0.463–0.922) MoM in the preterm delivery group, and 0.911 (0.580–1.247) MoM in the 34-week delivery group [25]. The results of this study confirm the results of previous findings that in pregnancies with the development of PE, the concentration of PAPP-A in maternal serum is reduced from 11 + 0 to 13 + 6 weeks of gestation [54]. Additional findings from the study were that PAPP-A levels were significantly lower in those who delivered preterm (early PE) compared to those who delivered after 34 weeks (late PE). However, PAPP-A measurement is not a sufficiently effective stand-alone tool for diagnosing PE. When combined with Doppler ultrasound, PAPP-A is a powerful prognostic biochemical marker for PE with a 70% predictive rate and a 5% false-positive rate.

Cystatin – C. Cystatin-C is a 13-kDa cysteine protease inhibitor continuously produced by all nucleated cells. It is freely filtered through the glomerulus, where it is broken down by the cells of the proximal tubules. It is also not subject to tubular secretion. Therefore, it can be used as a biomarker of kidney function. Normal pregnancy is associated with an increase in serum cystatin-c levels in the third trimester, followed by a significant decrease in the postpartum period [26]. In vitro studies have shown that cystatin-c expression is regulated by extravillous trophoblastic cells in the ischemic placenta. This finding suggests that cystatin-c is involved in placentation [27]. In their study, Thiganthan et al. measured the level of Cystatin-C in maternal blood samples during early pregnancy in two groups. The first group included women who subsequently developed PE. The second group included women who had a normal pregnancy outcome. High concentrations of cystatin-c in blood were associated with an increased risk of developing PE several weeks after the study. This observation supports the hypothesis that the balance between proteases produced by trophoblasts and inhibitors produced by the decidua plays a major biological role in trophoblast development. Violation of this balance can lead to defective development of the trophoblast and the subsequent development of PE.

The measurements of cystatin C levels in the blood of the mother were made in 30 women who subsequently developed PE (the study group) and in 90 women with normal pregnancy outcomes (the control group). The concentrations of Cystatin C in early pregnancy were significantly higher in the study group (0.65 mg/L, mean range 0.59 - 0.75 mg/L) than in women in the control group (0.57 mg/L, mean range 0.50 - 0.63 mg/l) [28]. Since the levels of cystatin C are high in women with PE 5 months before this complication becomes clinically apparent, cystatin C alone or in combination with other markers may be useful as a marker of this disorder.

Fetal hemoglobin (HbF). (HbF) causes oxidative stress, which plays a huge role in the pathogenesis of PE. Therefore, in recent years, researchers have studied the relationship between HbF and PE [29]. In a study by Centlow et al. It was found that the level of HbF in the placenta of patients with PE was significantly increased. HbF was released into placental vessels, causing endothelial damage with subsequent inflammation [29]. Therefore, HbF may play a role in the progression of PE by damaging the placenta, kidneys, and other tissues, although the mechanism of damage requires further study. Particularly, the levels of α1-microglobulin (A1M), an antioxidant, were increased in patients with PE, which may be a consequence of oxidative stress caused by HbF. A1M has a compensatory effect on tissue damage. Therefore, I would suggest that further research on A1M as a potential treatment for PE is needed [88]. HbF may be released into the blood of patients with PE because oxidative stress damages the blood-placental barrier, accordingly, the level of HbF in the blood serum of patients with PE was increased already in early pregnancy. This suggests that HbF has the right to be considered an early diagnostic marker of PE [30]. In a recent meta-analysis study by Bellos et al., it was confirmed that increased values of HbF and A1M were directly associated with the development of PE. However, larger-scale clinical studies are needed [31].

Insulin-like growth factors (IGF). (IGF-I) is a potent mitogen that promotes cell proliferation and differentiation and plays a critical role in many aspects of placental

development, regulation of fetal growth and subsequent postnatal development. It enhances the differentiation of cytotrophoblast into syncytiotrophoblast and extravillous trophoblast. Moreover, it also enhances the proliferation of placental fibroblasts and trophoblast, enhancing trophoblast invasion [32]. The actions of IGF-1 in the blood circulation and extracellular matrix are regulated by the presence of IGF-binding proteins (IGFBPs), mainly 1 and 3 (IGFBP-1 and IGFBP-3). Insulin-like growth factors I and II regulate the trophoblast life cycle in the developing placenta [32]. In non-pregnant women, IGFBP-1 is produced in the liver under strict insulin regulation. During pregnancy, IGFBP-1 is also produced by the placenta, which leads to higher concentrations of this protein in the maternal body [33]. The blood is enriched with IGFBP-3 more than other IGFBP, although both IGFBP-1 and 3 increase the plasma half-life of IGF and provide a depot of IGF for target tissues. Sifakis et al. conducted 2 studies and reported that in pregnant women at 11-13 weeks' gestation who subsequently develop PE, the levels of circulating IGF-I and IGFBP-1 are significantly reduced already in the first trimester of pregnancy [34,35].

In the first study, blood samples were taken from 18 women who subsequently developed early-onset PE, 35 women who subsequently developed late-onset PE, and 106 pregnant women from the control group who did not experience PE. The results were as follows: the level of IGF-1 MoM was 0.53 (mean range 0.40-0.75); 53.8 (mean range 40.6-73.9) ng/ml in women with early PE; 0.55 (mean range 0.42-0.86); 69.9 (mean range 41.6-93.8) ng/ml in women with late PE, compared with the control group, whose level of IGF-1 MoM was 1.04 (mean range 0.59-1.49); 104.4 (58.2–134.5) ng/ml [34]. In the second study, the levels of IGFBP were measured in 20 women at 11–13 weeks' gestation who subsequently developed early-onset PE (Group 1), 40 women who developed late-onset PE (Group 2), and 120 women from the control group who did not have PE (Group 3). The results were as follows: the level of IGFBP MoM was 0.63 (mean range 0.37–0.92); 40.9 (mean range 23.9–61.4) ng/ml in women with early-onset PE; MoM was 0.67 (mean range 0.37-0.92); 48.8 (mean range 24.8-67.7) ng/ml in women with late-onset PE, compared with the control group, where MoM results were 1.01 (0.72 –1.27); 78.6 (54.9–99.4) ng/ml. Both studies also found that PI of uterine artery increases in early PE [34,35]. These data confirm that the decrease in circulating levels of IGF-I and IGFBP in the first trimester of pregnancy is most likely to be associated with the pathogenesis of PE.

Vitamin D (25OH). The active form of vitamin D (25OH) regulates the transcription and function of genes associated with trophoblast invasion, normal implantation, and angiogenesis [36]. Also, vitamin D is a potent endocrine suppressor of renin biosynthesis and is able to prevent hypertension through suppression of the renin-angiotensin system [37]. It reduces the level of insulin in the blood, improves endothelial-dependent vasodilation, and also reduces the anticoagulant activity of the blood [38-40].

In the study by Maltsev L.I., 174 patients aged from 19 to 41 years were examined. The 1st group included 35 women at 34-37 weeks of pregnancy with PE of varying severity, the 2nd group included 109 pregnant women with a high risk of developing PE, who were followed by cohort observation from the end of the first trimester of pregnancy until delivery. Determination of vitamin D content in blood in women with PE showed a pronounced decrease in its level. On average, its value was 10.7±0.6 ng/ml, while in patients with a physiological pregnancy it was 19.82±1.5 ng/ml ($p<0.01$). It was important to note that the levels of vitamin D were equally low in both moderate and severe PE. A decrease in the levels of vitamin D was accompanied by an increase in the amount of vitamin D-binding protein in the blood; this was most pronounced in severe PE. The severity of PE was reflected by an increase in the level of endothelin in the blood - twofold compared to healthy people in moderate PE and twentyfold in severe forms.

2. Conclusions

Accurate prognosis of PE is important for early identification of those women who require more careful antenatal monitoring. It is quite important to learn how to diagnose PE even before its clinical debut. This will allow timely initiation of preventive measures for those at risk, reduction of maternal and perinatal mortality, and prevention of perinatal complications. A good screening test for PE should reflect either a high positive probability or a negative probability of developing PE, and it should also be rapid and available in early terms of pregnancy. This will undoubtedly help reduce morbidity rates. This review article highlights potentially valuable prognostic biomarkers in the development of PE, which may become markers that we can introduce into the practice of an obstetrician-gynecologist. Despite the large number of different markers indicating impaired placental circulation and insufficiency of the maternal circulatory system, their isolated use alone does not provide an adequate predictive picture. Subsequent research should focus on developing predictive models that combine several biochemical and biophysical markers. For example, the use of biochemical markers of the first, second and third trimesters in combination with uterine artery Doppler examination can predict pregnancy outcome with greater accuracy. All future scientific studies should focus on finding the necessary combinations of markers, which can then be used as powerful screening tools for a higher probability of diagnosing PE [41].

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