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INFLUENCE OF PREECLAMPSIA DEVELOPMENT MARKERS ON PLACENTAL MORPHOLOGICAL CHANGES (LITERATURE REVIEW)

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ABSTRACT

Research of the placental bed began in the late 50s of the last century, and was conducted by two independent groups of researchers who used various biopsy techniques. Histological confirmation that the biopsy material was taken from the placental bed was based on the presence of trophoblastic cells, villi, or altered spiral arteries. However, the absence of these morphological components did not indicate that the sample was not taken from the placental bed.

KEY WORDS: ***Cytotrophoblast, placental bed, placental site, preeclampsia, spiral arteries, myometrial segments.***

DISCUSSION

Basic information about the role of cytotrophoblast invasion in the utero-placental area (placental site) and insufficient gestational restructuring of the endo - and myometrial spiral arteries in PE was obtained in the 80's and described in classic studies [95]. There are two types of cytotrophoblast-interstitial (ICT) and invasive, which penetrates the lumen of endometrial arteries-intravascular CT (IVCT). The maximum invasive activity of ICT and IVCT is realized at the 5th-8th week of gestation, when their combined action leads to arose of the spiral arteries and the formation of their mouth opening into major since space of placenta. As a result, during the first trimester, several dozens of utero-placental arteries are formed in the endometrium, which increases the flow of oxygen to the intensively growing organs of the embryo. After a certain decline in cytotrophblastic invasion at the end of the first trimester, probably due to the disappearance of the hypoxic stimulus, a new rise in invasive activity begins — its second wave, reaching a maximum at the 16th— 18th week. It spreads mainly in the arteries of in the artery of adjoining myometrium. A number of authors believe that the main mechanism of endothelium and elastomuscular components of the walls of myometrial segments of spiral arteries destruction is intravascular invasion, when the CT moves against the flow of maternal blood. Absence of gestational restructuring of the myometrial segments of the spiral arteries is a significant link in the pathogenesis of preeclampsia. This is due to the superficial or shortened cytotrophblastic invasion during its second wave. The progress of biomedical researches has significantly expanded our knowledge of the placental bed. It is known that in PE there is no physiological reconstruction (remodeling) of spiral arteries, which consists of decidual and trophoblast-dependent stages. These processes occur in the decidual and transitive junction zone (TJZ) of arteries myometrial segments. In decidua, early vascular remodeling is at least partially performed by leukocyte infiltration, including uterine NK-cells that appear during early endometrial decidualization in the late luteal phase of the cycle and cluster around spiral arteries at the beginning of the remodeling process [46]. NK-cells play an important role in trophoblast invasion and remodeling of spiral arteries. Uterine NK-cells are an important source of angiogenic growth factors and, unlike peripheral blood NK-cells, do not have cytotoxic activity, especially in relation to trophoblast cells, but they produce high levels of cytokines: γ-interferon (IFN-γ), interleukin (IL)-10, granulocytmacrophagal colony-stimulating factor (GM-CSF), leukemia-inhibiting factor (LIF), tumor necrosis factor (TNF-α) [27].

Human trophoblast cells don't have the so-called classical human leukocyte antigens of class I of the main histocompatibility complex (HLA-A and HLA-B), which are targets for the cytotoxic action of NK cells of peripheral blood. At the same time, trophoblast cells express HLA-C, HLA– E, and HLA

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– G, which interact with NK cells of the endometrium and decidual tissue and are involved in the development of pregnancy. Early vascular smooth muscle disorganization also occurs in PJZ of myometrium, where NK cells are absent. Thus, NK cells play an important role in trophoblast invasion and remodeling of spiral arteries. NK cells help replace endothelial cells in the spiral arteries with trophoblast cells, which allows the spiral arteries to provide ever-increasing blood flow needs in a physiologically developing pregnancy. However, in PE, expression on decidual NK cells of the AA variant the killer cell immunoglobulin-like receptors (KIR AA) and on trophoblast cells - HLA – C2 is often found, which leads to insufficient NK cell function, decreased production of vascular endothelial growth factor (VEGF) and IFN-γ, and impaired remodeling of spiral arteries. In contrast to decidual tissue, vascular remodeling in myometrium is enhanced by the presence of interstitial trophoblastic cells and angiogenic growth factors localized in them, which contribute to the process of early vascular remodeling [1,5,11]. Only after this stage of vascular disorganization, endovascular trophoblasts appear in the spiral arteries, followed by their inclusion in the vessel wall. During this process, the endothelium seems to disappear, while the smooth muscle and elastic layers of vessels are further fragmented due to trophoblast-induced apoptosis of endothelial and smooth muscle cells [1,4,8]. In PJZ of myometrium, there are 3 different types of spiral artery transformation disorders: partial transformation, no transformation, and no transformation with obstructive damage [1,12]. The described features of trophoblastic invasion, taken as a basis, provide important information about the formation of defective placentation in future.

Spiral artery remodeling can be described as a multi-stage process that occurs at the beginning of pregnancy [11,25]. Two main factors are being determining in the blood flow from mother to placenta: the size of placental bed, which depends from the number of spiral arteries communicating with interstitial space, and the degree of physiological transformation of spiral arteries, which is most expressed in the center of the placental bed. Studies of the placental bed using biopsy confirm that most of spiral arteries undergo a complete change in PJZ of the myometrial segment, which is consistent with the results of ultrasound studies. Studies in the second trimester of pregnancy using pulse-Doppler method with staining showed that the resistance of blood flow in the central region of the placental bed is less than in the periphery. The results of three-dimensional ultrasound Doppler screening study with the determination of the placental bed vascular index in the first trimester in 4325 pregnant women in comparison with the data of blood flow in the uterine arteries at 12 and 22 weeks, the volume of placenta and the concentration of PAPP-A revealed a high prognostic significance of determining the placental bed vascular index in the development of severe pregnancy complications, including PE [8,4].

In severe PE, only some of spiral arteries in the center of the placental bed are completely transformed into PJZ of the myometrial segment. In addition, obstructive artery damage (such as thrombosis, acute atherosis) can lead to or contribute to incomplete placentation. The placental bed of patients with PE is characterized by decreasing the number of spiral arteries with a transformed myometrial segment. This segment preserves the hypertrophied structure of the smooth muscle layer, despite the presence of interstitial trophoblasts, sometimes even in excess amount [1,3,8,16]. The determined changes are more pronounced in myometrial than in decidual segments. The placental area in patients with PE and fetal growth restriction (FGR) is similar to that described in patients with PE. It is characterized by a large number of untransformed spiral myometrial arteries, which often have obstructive damage, such as acute atheroma and thrombosis. Acute atheroma is not only a characteristic damage of small decidual arteries, but also a typical damage of spiral myometrial arteries in PE and FGR. Impaired deep placentation in PE and FGR leads to the appearance of central zones with transformed arteries. The number of interstitial extra villous trophoblastic cells is reduced in PE and, conversely, increased in the cases of fetal growth restriction(FGR) [7,14,22]. The extent of the impaired transformation of spiral arteries of myometrium and the presence of its obstructive vascular damages explain the frequent combination with placental infarctions. 90% of spiral arteries in PJZ myometrium of the placental area are completely transformed in the normal course of pregnancy. Comparison of certain clinical situations and the degree of severity of spiral artery remodeling disorders suggested that the process of cyclic decidualization and subsequent menstruation serves as a mechanism for preparing the uterus for deep placentation. Both menstruation and implantation are inflammatory conditions that cause certain physiological ischemic-reperfusion tissue stress. According to the authors, regular menstruation can be crucial in protecting the uterine tissue from deep inflammatory and oxidative stress associated with deep placentation. This process is called "preconditioning" [11]. The lack of adequate "preconditioning" may explain why the first pregnancy in young women under 20 years of age is associated with a significant risk of adverse outcomes (preterm birth, FGR and PE), compared to the first pregnancy in women after 20 years of age who have experienced "preconditioning". On the other hand, placental abnormalities even at preclinical stages are present in patients with PE and FGR. In such

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conditions, impaired deep placentation is characterized by the presence of untransformed spiral arteries of the PJZ, which can be affected by obstructive vascular injuries. Arterial injuries such as intima hyperplasia, acute atheroma, and thrombosis can develop in these arteries in a very short period of time, even with slight hypertension. The combination of obstetric complications and various vascular diseases in the connective zone of myometrium indicates that "preconditioning" in this zone during fertilization can be a crucial factor for successful implantation and normal placentation. Currently, there is strong evidence that the pathology of the placental bed due to ischemia and immunologically mediated processes leads to various complications of pregnancy (PE, FGR, premature birth, premature rupture of fetal membranes in premature pregnancy, placenta abruption). And the development of one of these complications depends on genetic factors, environmental factors, pregnancy, duration and prevalence of the ischemic zone. In addition, the determination of the clinical phenotype and the severity of its manifestations depend on the state and interaction of mother-placenta-fetus system [1,6,9]. The limited number of studies and reviews, and the lack of established criteria for separating early and late PE, suggests that additional research is needed to determine whether these two forms are separate diseases or stages of the same process. Also, most of the researches in this direction belongs to placental research, but only a few studies are devoted to the study of placental site tissues. In this regard, taking into consideration the close relationship of the placenta and placental bed, the lack of detailed data on changes in the tissues of the placental bed and placenta's condition, depending on different variants of the course of PE, the presence or absence of accompanying fetal growth restriction syndrome, further researches in this direction are required.

Prevention of severe preeclampsia / eclampsia.

Scientists of different specialties (cardiologists, obstetricians, gynecologists, geneticists) have been paying much attention to the problem of PE for many decades, but despite the results obtained, there is still no accurate information about the causes and pathogenesis of the disease, reliable laboratory methods of diagnosis have not been developed yet, so there are no effective measures of prevention and treatment. It is clear that interventions should be taken as early as possible, ideally before pregnancy. Despite the fact that there is strong data on risk factors for PE, there is still no information in literature about simple, safe, non-invasive and inexpensive screening methods that would be preventive for severe PE. In the past, such methods as strict bed rest and a salt-free diet were indicated, which later proved to be ineffective. Then there were works on the role of ascorbic acid (vitamin C) and other vitamins in the prevention of PE. It was found that a decrease in blood plasma of vitamin C, E and β-carotine is associated with severe PE [5,7,17]. However, these phenomena were explained by the body's response to oxidative stress, but not by a lack of nutrients. Supplements of fish oil or omega-3 polyunsaturated fatty acids showed a decrease in prostacyclin levels (an increase of this indicator occurs in PE) [23,25]. However, it has not been established whether mild or severe PE can be prevented by these additives. The supplementation of certain minerals (zinc, magnesium, cadmium, selenium, zinc) in the prevention of PE has conflicting data. For example, the concentration of zinc in plasma, red blood cells and placental tissues in pregnant women with PE decreases. One large randomized clinical trial showed that magnesium supplementation does not affect the development of PE. This was due to the fact that oral magnesium intake does not have a good absorption effect [4,6,8,17]. Studies have shown that the concentration of calcium in plasma of patients with PE is significantly lower than in plasma of healthy women. A series of randomized controlled clinical trials showed the benefits of calcium supplementation in 4500 women at low risk of PE [7,10,18].

Several randomized placebo-controlled double-blind clinical trials have been conducted since 1993, involving 22,000 women who have demonstrated the benefits of low doses of aspirin in preventing PE and the absence of adverse effects on mother and fetus [5,9,22]. However, the literature does not support the view that low doses of aspirin are used to prevent PE in low-risk women. In women at high risk for PE, preventive aspirin administration can reduce PE development by 13%. [3,5,9,27].

Since PE is associated with coagulation disorders, it was suggested to treat with anticoagulants in order to prevent PE. Research results have shown that in a group of women at high risk of PE, combined administration of aspirin and low-molecular-weight heparin (LMWH) can improve pregnancy outcomes (low birth weight and perinatal outcomes) [3,8,13]

In 2019, a multicenter randomized controlled trial was conducted in Uzbekistan [7,14,24] showed that timely treatment of women with chronic diseases complicated by placental dysfunction and the risk of pre-eclampsia with inclusion of L-arginine in the treatment regimen in the second and early third trimester of pregnancy improves perinatal outcomes, improves utero-placental blood circulation, reduces the progression of mild to severe PE, which allows to prolong pregnancy until delivery.

Summarizing the literature review, it should be noted that there are no clinically significant methods for predicting and preventing PE. The only successful method of treatment is the timely termination of pregnancy. In this regard, in modern

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conditions, the only real way to reduce severe forms of PE and its complications is prediction, early diagnosis, development and implementation of a clear algorithm for monitoring and treatment, depending on the severity of PE.

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