IMMUNE DYSADAPTATION AT PREECLAMPSIA

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ABSTRACT
This review presents the role of immunological and biochemical markers in the pathogenesis of preeclampsia. Preeclampsia is a frequent and serious complication of pregnancy with hypertensive syndrome. Also, the article discusses the modern aspects of forecasting, pathogenesis, mechanisms of its development. It was found that in women who have undergone preeclampsia, chronic kidney pathology and hypertension are formed. With preeclampsia, placental insufficiency and inflammatory changes in the placenta are observed, as a result of which perinatal outcomes worsen. Every fourth child with this pathology has the effects of hypoxia.
KEY WORDS: *preeclampsia; dysfunction of endothelium; inflammation factors, pregnant woman*

DISCUSSION

In the structure of maternal mortality in the world, preeclampsia (PE) is up to 15%, more than 30% in developing countries, up to 23% in Russia, and 26.5% in Uzbekistan [6, 7]. The importance of the problem is also associated with a high percentage of the pathological course of pregnancy, in particular its premature termination. Against the background of arterial hypertension, placental insufficiency and fetal growth retardation syndrome, antenatal fetal death often develop, the risk of placental abruption, retinal detachment, eclampsia, intracerebral hemorrhage, massive coagulopathic bleeding significantly increases [4,5].

PE leads to various obstetric problems: placental insufficiency, fetal growth retardation, premature birth, bleeding in childbirth and the postpartum period [19, 20]. This complication of pregnancy takes one of the leading positions among the problems of modern obstetrics and is quite significant in medical and social terms [16-18, 21]. Hypertensive conditions during pregnancy still occupy one of the leading places in the structure of maternal (second place), as well as perinatal mortality after 20 weeks. pregnancy (from 15 to 30%) [1,12,16]. Most researchers are focused on preventing the development of preeclampsia, which is primarily associated with the identification of factors contributing to the formation of this pathology of pregnancy. The presence of a large number of theoretical premises makes it difficult to determine the primacy of certain factors of occurrence and the paths of progression of preeclampsia.

It is believed that various peak moments lead to the development of this pathology, and preeclampsia itself is defined as a kind of vicious circle, from a large number of pathogenetic links, often manifested by multiple organ failure. Indicators of developing dysfunction in the body of a pregnant woman are changes in the immune, neurohumoral and other systems responsible for regulating vascular tone and the state of microcirculation [2,15] Generalized data from the world literature postulate that PE is the result of insufficient adaptation of the pregnant woman's body to increasing immunological loads insolvency, vascular endothelial lesions with increased aggregation of blood cells and a tendency to intravascular coagulation, dis Balance is a product A2 thromboxane and prostacyclin excessive formation in the mother and fetus biologically active substances (mediators, cytokines, interferons, reactive oxygen species), depletion of functional reserves antioxidant system and the accumulation of lipid peroxidation products [10, 22, 24, 25]

Numerous scientific studies of recent years are devoted to the possibilities of predicting this pathology, identifying high-risk groups for the

development of preeclampsia in order to ensure a more favorable course of pregnancy [15,29]. The pathophysiology of preeclampsia remains unknown, but factors produced by the placenta as a result of oxidative stress and causing an excessive systemic inflammatory response [36] lead to maternal endothelial dysfunction, affecting the clinical features of preeclampsia [13,29]. Improper placentation with abnormal cytotrophoblast invasion and incomplete remodeling of the spiral arteries supplying the placenta, presumably causes a change in circulation and subsequent oxidative stress in the placenta, as well as the associated release of endothelial dysfunction factors into the circulatory system [24,12]. Since the introduction of markers correlating with Down Syndrome into practice, a number of other studies have revealed a correlation of other unfavorable pregnancy outcomes with changes in the level of analyzed markers [16,14]. An increase in α fetoprotein, estriol, and chorionic gonadotropin was noted by different authors [20]. Hypertensive disorders caused by pregnancy aggravate the course of pregnancy at the end of the second and beginning of the third trimester of pregnancy. However, this does not mean that until the 20th week. the gestational process at the same time proceeds without complications.

Starting from the first trimester, in about half of the women examined, pregnancy is accompanied by various complications, often associated with impaired placentation (partial detachment of the chorion and placenta). The analysis of some clinical and immunological parameters in the examined women performed in our work made it possible to obtain fundamentally new information that is important both for understanding the role of the immune system in ensuring a normal gestational process and for developing recommendations for identifying the risk of developing hypertensive conditions in pregnant women. Pathological changes in the serum content of a number of natural autoantibodies are directly related to the mechanisms of development of this pathology [13,40].

The reason for the development of preeclampsia is a pathological change in the processes of implantation and placentation, the first manifestation of which is a violation of the migration of cytotrophoblast cells at the beginning of pregnancy, which subsequently causes pathological changes in the function of the vascular endothelium. Various growth factors and cytokines are involved in the regulation of the invasion of cytotrophoblast into the wall of the spiral arteries of the uterus [41].

The system of placental growth factors regulates the growth and function of the vessels of the placenta. Placental growth factors, on the one hand, are stimulants of angiogenesis and increase vascular permeability inside the placental uterine bed. On the other hand, through the autocrine mechanism, the invasion, differentiation and metabolic activity of the cytotrophoblast during placentation are regulated. The most informative in assessing the severity of gestosis is the determination of the levels of vascular endothelial growth factor (VEGF), placental growth factor (PIGF) with their receptors (sf1t-1). There is convincing evidence of increased expression of sflt-1 in the placenta and a decrease in the circulation of VEGF and PIGF during preeclampsia[6].

Endothelin acts as an angiogenesis inhibitor that competes with TGF-b. A marked increase in soluble endoglin was found in patients with preeclampsia [27]. However, soluble endoglin is not only a marker of preeclampsia, according to various other placental pathologies [8]. Of great importance is the increase in the level of extracellular fetal DNA by 2-5 times, starting from 17 pedals and 3 pedals before the clinical debut of preeclampsia [9]. Markers of endothelial dysfunction are nitric oxide, angiotensin converting enzyme, thrombomodulin, and von Willebrand factor [10]. In the development of endothelial dysfunction, endothelin is of great importance, capable of both directly and indirectly through the generation of nitric oxide and the formation of angiotensin-P to affect the change in vascular tone [11].

The study of the mechanisms of formation of endothelial dysfunction opens up new possibilities in understanding the pathogenetic mechanisms of the development of preeclampsia. However, studies of the role of these factors in the development of preeclampsia are few and contradictory. Determination of the critical parameters of these markers during the development of preeclampsia would prevent its transition to a more severe form [29, 34]. Currently, great importance is attached to immune and genetic factors, which can manifest themselves by the features of placentation. Inhibition of trophoblast migration and the absence of transformation of the muscle layer of the spiral arteries as pregnancy progresses predispose to their spasm, decrease in villous blood flow and hypoxia. Subsequently, the complex of hemodynamic disturbances becomes generalized, causing endothelial damage [12].

Hypoperfusion of tissues, hypoxic and ischemic changes in them lead to the development of multiple organ pathology syndrome. In the pathogenesis of the occurrence of preeclampsia, the rheological properties of blood play a special role: hyperaggregation of red blood cells, platelets, dysproteinemia, hypercoagulation, with the development of chronic disseminate intra vascular folding syndrome [28,34]. Against the background of developing hypoxic changes in the tissues, an autoimmune lesion of the central nervous system of

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the fetus arises due to a violation of the blood-brain barrier. As a result of a significant increase in BBB permeability, neurospecific proteins enter the fetal peripheral blood stream after chronic intrauterine hypoxia. They, in turn, contribute to the death and sclerosis of neurons, disruption of the formation of the vasculature of the brain and structural relationships "capillary - glia neuron", as important components.

This indicates the adverse long-term consequences of perinatal cerebral lesions in children whose mothers suffered preeclampsia [3]. In this regard, the study of brain neutrophic factor (BDNF) in the umbilical cord blood of newborns born to mothers undergoing preeclampsia as a marker of brain tissue damage is relevant. It has been shown that many features of late toxicosis can be caused by inadequate activation of the maternal inflammatory cellular response [15]. Using flow cytometry, inflammatory markers (SG) Pb, SG) 64, CD62L, HLA-DR and intracellular reactive oxygen species) were analyzed in leukocytes of women with physiological pregnancy and in women with preeclampsia.

Although the latter showed lower CD62L expression and significantly higher levels of reactive oxygen production compared to healthy pregnant women, the differences between pregnant women with gestosis and healthy women were in many ways smaller than those between control groups of pregnant and non-pregnant women. Compared with samples from non-pregnant women, leukocytes from healthy pregnant women showed significantly higher levels of CT b +, SG) b4 + cells and oxygen radicals. The authors confirmed and expanded the concept that with preeclampsia there are generalized changes in circulating leukocytes characteristic of inflammation. In addition, it was found that normal pregnancy itself is characterized by a similar response [7,32].

To date, the molecular mechanisms that regulate the activity and migration of lymphoid cells have not been completely studied, among which an important role is given to CD27 + molecules in the differentiation and migration of T-lymphocytes. The macrophages of the decidual tissue of the placenta and trophoblast (SG) 14+ are practically poorly understood. It has been suggested that placental macrophages are capable of providing local regulation of the processes occurring in the tissue of the developing placenta during normal pregnancy, and act as the initiator of a cascade of reactions leading to its termination. Decidual macrophages not only provide the barrier function of the placenta, but also produce a wide range of growth factors that regulate trophoblast growth, angiogenesis, and endometrial decidualization [16]. Mononuclear phagocytes represent one of the largest populations of immunocompetent cells in the placental tissue, in the chorionic villi they are actually the only representatives of immunocompetent cells.

It is believed that maternal and fetal macrophages block the path of infection, thereby ensuring the preservation of pregnancy. They also participate in protecting the fetus from local maternal immunity. However, to what extent local regulation of processes is changed during preeclampsia, the fact remains unclear [17.38]. In pregnancy complicated by preeclampsia, an imbalance develops between maternal antibodies and fetal antigens. Aggressive immune complexes, deposited on the surface of the vascular endothelium, not only violate the ability of the vascular wall to prevent vascular spasm, but also damage endothelial cells. The subsequent development of immune vasculitis is accompanied by choriodecidual lesions, the release of tissue thromboplastin, fibrinogen, fibrin and the development of DIC. Severe endothelial damage extends to the entire system "mother - placenta - fetus." Deficiency of utero-placental blood flow is possible with blockade of the spiral arteries, which can be caused by genetic or acquired thrombophilic disorders.

Acquired thrombophilic disorders, such as antiphospholipid syndrome (APS), are combined with placental vascular pathology and with abnormal blood coagulation in the bloodstream of the placenta. Two types of antiphospholipid antibodies (lupus coagulant and anti-cardiolipin antibodies) most often lead to the development of preeclampsia in two ways: damaging the implantation of the embryo and causing thrombosis of uterine-placental vessels [19]. The study of the role of cytokines in the pathogenesis of preeclampsia is given special attention. An increase in IL-2 production due to decreased expression of placental llLA-G leads to a decrease in trophoblast invasiveness in women with preeclampsia. In addition, T-10 deficiency may contribute to an increased inflammatory response induced by TNF-a and TNA-g against trophoblast cells. A decrease in T-10 expression by villous trophoblast is associated with a possible increase in the maternal immune response to fetal antigens and inadequate placenta development during preeclampsia. Produced mainly by macrophages and dendritic cells, IL-12 may be the dominant factor in the genesis of preeclampsia participating in damage to the vessels of the placenta [21,42].

Similar markers of inflammation are found in preeclampsia and in the amniotic fluid, which indicates perinatal damage to the fetus. It is these links of the pathogenesis of preeclampsia that are currently the most actively studied, and the number of publications devoted to the role of cytokines, adhesive molecules, leukocytes, inflammation in the pathogenesis of preeclampsia and perinatal pathology

is constantly growing. Considerable attention was paid to the study of the role of cytokines in the pathogenesis of preeclampsia. Serum concentrations of IL-2 and TNF-a are higher in the trimester of pregnancy in those women who later develop preeclampsia [22]. Apparently, a violation of immune regulation takes place much earlier than its clinical manifestation. A study of decidual tissue in patients with preeclampsia revealed strong tissue staining for IL-2 compared with very weak staining in healthy pregnant women. It is believed that IL-2, detected in the decidual tissue of pregnant women with preeclampsia, affects placenta angiogenesis [23,36]. IL-2 activates cellular cytotoxicity.

It is able to disrupt vascularization by activating lymphokine conjugated cells. These data are consistent with those obtained by D. T. Rein et al. [24]. They evaluated the balance of IL-2 and V1 (DH-g) and IL4 cytokines in pregnant women with preeclampsia. An increased expression of IL-2 was found in peripheral blood MNCs in the III trimester of pregnancy. These data confirm the hypothesis that women with preeclampsia do not have immunoregulatory changes that occur during normal pregnancy [17].

It is suggested that IL-12 is involved in damage to placental vascularization, leading to fetal growth restriction, which is usually found in women with hypertension during pregnancy [25]. It is known that IL-12 is able to direct the development of the T-cell response according to the Thl type. IL-12 is absolutely critical for the development of TU-T cell response to foreign antigens. With a mild degree of preeclampsia, the level of IL-12 was comparable to that of healthy non-pregnant women, and in severe cases exceeded it. Increased expression of antigens and reduced CD14 with a constant number of monocytes suggested the activation of monocytes in pregnant women with preeclampsia.

It was concluded that a decreased production of IL-12 by peripheral blood cells may contribute to the dominance of the TU-type immune response, and an increased T-type response [39]. Angiogenic factors — soluble FMS-like tyrosine kinase-1 (sFlt1), also called receptor-1 vascular endothelial growth factor receptor-1 (VEGF-R1) —was well studied as a possible endothelial damaging factor in preeclampsia [9]. An increase in sFlt1 in the second trimester predicts the development of preeclampsia; it is the best predictor of early preeclampsia. A low concentration of sFlt1 in the first trimester, which predicts an early onset of preeclampsia, was confirmed in J.P. Kusanovic and O.Erez studies taking into account BMI, a history and absence of childbirth in history [31,37]. Most studies have shown that a low concentration of PlGF in the second trimester predicts the late development of preeclampsia [27,41], but others could not confirm

this relationship [21]. Other studies have linked a low serum concentration of PAPP-A (pregnancy-associated plasmaprotein) [13.39]. Inhibin A and activin A are also glycoprotein hormones from the β-group of TGF (transforming growth factors). The placenta is the main source of these circulating proteins, their concentration increases in the third trimester in uncomplicated pregnancies.

A simultaneous increase in activin A and inhibin A is often found, possibly due to the fact that activin A stimulates the secretion of hCG (human chorionic gonadotropin), while hCG, in turn, stimulates the production of inhibin A [9]. Placental protein-13 (PP-13) is another marker that predicts not only preeclampsia, but also fetal growth retardation. In the serum of patients with the development of preeclampsia, the concentration of PP13 increases, despite a decrease in its excretion by the placenta. Perhaps the discharge of PP13 into the mother's blood is due to an expanded syncycotrophoblastic membrane [32,40] A study of the course of pregnancy in the third trimester showed that premature placental abruption is more than 3 times more frequent with hypertensive conditions caused by pregnancy and almost 7 times more often, intrauterine growth retardation occurs compared with pregnant women whose gestational process was not complicated by hypertensive disorders. The urgency of the problem is also caused by severe consequences. E of this disease. In women who have undergone preeclampsia, chronic kidney pathology and hypertension are formed.

Every fourth child with this pathology has the effects of hypoxia [14,17,18,20,23]. The study of immunopathophysiological mechanisms operating in the system "mother - placenta - fetus" helps to improve methods for the early diagnosis of preeclampsia and its complications. The selection of pathogenetic substantiated therapy to prevent this formidable complication of pregnancy. Conclusions Thus, the negative impact of hypertensive disorders on the health status of a pregnant woman, perinatal morbidity and mortality is now generally recognized. In this regard, the problem of protecting the health of mothers and children in hypertensive conditions requires the intensification of scientific research aimed at improving the assessment of the risk of developing hypertension during pregnancy, establishing the role of immunological mechanisms in the genesis of preeclampsia, and developing methods for its prevention and treatment. At the same time, early detection of prognostic immunological markers will make it possible in the first trimester of pregnancy to identify among pregnant women a risk group for the development of hypertension.

Further in-depth examination of these women makes it possible to begin the prevention of hypertensive disorders from the beginning of

pregnancy and to monitor the hemostatic system, the condition of the fetus and improve pregnancy outcomes. The developed prognostic criteria will allow predicting the development of preeclampsia in late pregnancy, which makes it possible to identify a cohort of patients requiring observation and threatened with the development of this complication of pregnancy. Timely diagnosis will allow to start the prevention of intrauterine suffering of the fetus on time and, as a result, reduce the percentage of resuscitation care for newborns if early delivery is necessary, reduce the rates of perinatal, maternal morbidity and mortality. All of the above dictates the need to search for new markers and highly sensitive methods for the diagnosis of preeclampsia and its complications to prevent disability of women and their children and, accordingly, to improve quality.

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