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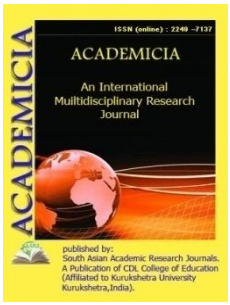

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MODERN VIEWS ON THE ROLE OF THE IMMUNE SYSTEM IN THE DEVELOPMENT OF PREECLAMPSIA (OVERVIEW)

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ABSTRACT

Hypertensive disorders during pregnancy are associated with high maternal and perinatal mortality, so it is very important for obstetricians to recognize severe cases with poor prognosis in time.One of the pathogenesis of preeclampsia is an increase in TNF-alpha and IL-6 levels. In this regard, the researchers wanted to know the expression level of TNF-alpha and interleukin-6 in pregnant women with preeclampsia. In preeclampsia, in contrast to normal pregnancy, the cytokine profile changes - there are higher concentrations of IFN-γ, TNF-α, IL-6, IL-1β, IL-8 and IL-16, and lower concentrations of IL-10.Although the final pathogenesis of this pathology remains to be determined, on the basis of this it will be possible to develop an adequate therapy algorithm to save the life of the mother and child.

KEYWORDS: *Preeclampsia, Interleukin, Pregnancy, Immunology.*

INTRODUCTION

To date, the cause of the development of preeclampsia has not been established. According to the most recognized hypothesis, preeclampsia is a consequence of a disturbance in the formation of the placenta in the earliest stages of pregnancy due to inadequate remodeling of the spiral arteries [1, 2, and 25].

Preeclampsia (PE) is an often fatal pathology characterized by hypertension and proteinuria in the 20th week of pregnancy, which affects 5-10% of pregnant women. This problem is especially important in developing countries, where the incidence of hypertensive disorders of pregnancy is higher and maternal mortality rates are 20 times higher than in developed countries.Risk factors for PE include obesity, insulin resistance, and hyperlipidemia, which stimulate the release of inflammatory cytokines and oxidative stress leading to endothelial dysfunction (ED).However, how all of these clinical manifestations coincide with the development of PE is still not very

clear. Associated poor trophoblast invasion and uteroplacental artery remodeling, described in PE, increase reactive oxygen species (ROS), hypoxia, and ED.

Preeclampsia (PE), the leading cause of prenatal mortality, complicates up to 8% of all pregnancies in Western countries [3, 23, and 24]. It is one of the 4 leading causes of maternal death and morbidity worldwide, causing 10 to 15% of maternal deaths [5,7].PE is characterized by new hypertension (blood pressure ≥140 / 90 mmHg) in two separate indications at least 6 hours apart, which manifests itself after 20 weeks of gestation in combination with clinically significant proteinuria (≥300 mg) for 24 hours [12,15].

Preeclampsia (PE) today continues to be one of the most common complications of pregnancy, leading to serious disorders in the body of the mother and fetus.In the structure of maternal and prenatal morbidity and mortality, PE takes the third place, and its frequency of the total number of births ranges from 11% to 16% [13,24].

Those in the world more than 8 million cases of PE are registered annually, which is the main cause of maternal and prenatal death, claiming the lives of 60 thousand young women annually [4].

The etiology of PE is still a matter of debate. The leading theories for the development of this complication of pregnancy are based on the processes of defective remodeling of uteroplacental arteries and placental ischemia, oxidative stress, excessive sleep; response, genetic predisposition and immunological intolerance between mother and fetus [6, 8].

Over the past few decades, tremendous efforts have been made to decipher the etiology of preeclampsia in the pathology of pregnancy. However, this syndrome has remained as it was fifty years ago: the syndrome of hypotheses.Even today, the pathways and etiology as well as the real origin of the syndrome, all of which lead to clinical symptoms of preeclampsia, remain unclear. With the new definition of preeclampsia, where only hypertension remains constant, it becomes increasingly difficult to compare samples and studies with each other, since each of them may choose different ways of defining the syndrome [20].

Over the past two decades, a number of very promising hypotheses and theories have been developed, ranging from purely placental origin to purely maternal origin. Most of them are understandable, while others are outdated and already falsified.Nowadays, when data is collected and theories are created on a daily basis, we must keep pace with this development. Therefore, we need to understand and agree that the hypothesis that we have been working on for some time is no longer valid and therefore we need to adapt to the new thinking [2,23].

There are many hypotheses for the development of preeclampsia. However, it is difficult to recognize which mechanisms of occurrence and progression are primary. Many factors have been studied as the basis and root cause of the formation of preeclampsia:

- Genetic;
- Immunological;
- Vascular;
- Humoral factors.

The vascular endothelium is a single-layer specialized layer of cells lining the inner surface of the vessel wall and performing barrier, transport, metabolic and endocrine functions. The endothelium is the largest autocrine, paracrine and endocrine organ [6].

Intact endothelial cells have adhesive and anticoagulant properties, regulate the permeability of the vascular wall [3]. Under physiological conditions, the balance of the production of vasoactive factors by the endothelium is shifted towards maintaining vasodilatation, primarily due to the constant release of the basal level of nitric oxide [8].

Normally, cytotrophoblast cells penetrate into the middle membrane of the spiral arteries, replacing the smooth muscle and connective tissue elements of the wall, and therefore the vessels lose their ability to constriction and acquire a saccular shape and large capacity. This process is called pseudovascularization and it occurs under the influence of endothelial growth factors produced by trophoblast [21, 22].

In case of incomplete replacement of the elements of the vascular wall by cytotrophoblast cells and fibrinoid, the original capacity of the vessel is preserved, as well as its ability to constriction under the influence of endogenous factors. This leads to a narrowing of the lumen of the uteroplacental arteries, insufficient blood flow and, consequently, to placental ischemia. The latter releases into the bloodstream pro-inflammatory cytokines, placental apoptosis products, trophoblast fragments, fragments of cell membranes, a cascade of pathological reactions is triggered in the body [16]. The reason why incomplete invasion of the trophoblast occurs is not completely clear, but the influence of immunological and genetic factors on this process has been determined [18].

This superficial penetration of cytotrophoblast cells leads to poor placenta ion and vascularization (ischemic placenta) in early pregnancy, which ultimately leads to systemic endothelial dysfunction of the mother and activation of immune cells, all of which are believed to be provoking processes leading to clinical manifestations of preeclampsia [9].

Activation and damage of endothelial cells is part of the general inflammatory response and is accompanied by an increase in the functional activity of granulocytes, monocytes, lymphocytes, activation of the complement system, an increase in proinflammatory cytokines in the systemic circulation, and a change in the coagulation properties of blood [14].

There are several factors of microcirculation disturbance in the development of endothelial dysfunction - an imbalance between the factors regulating vascular tone, local hemostasis processes, proliferation and migration of blood cells [19].

It is assumed that proinflammatory cytokines (IL-1a, IL-1R, IL-6, tumor necrosis factors TNF-OS and TNF-R) play a key role in the development of endothelial dysfunction and systemic inflammatory response.Cytokines serve as mediators of all three main tissue processes in inflammation - exudation, alteration and proliferation, and also participate in the development of systemic manifestations of the inflammatory response [10,11].

A pronounced imbalance of cytokines was registered in various types of obstetric pathology (preeclampsia, placental insufficiency with fetal growth retardation syndrome (FGRS), the threat of termination of pregnancy) [17].

In recent years, it has been established that activation of lymphocytes requires the presence of a second signal transmitted through the membrane molecules of antigen-presenting cells and the cytokines secreted by them (IL-1, IL-6, IL-12, IL-15, TNF-α). It is generally accepted that the presence of two activating signals is a prerequisite for the activation of lymphocytes [6].

Medvinsky I.D. (2018) notes that in moderate and severe gestosis, the level of IL-1, IL-6 and TNF-a progressively increased from the 1st trimester to a maximum in the 3rd trimester with severe preeclampsia [5].

Placental macrophages, phagocytizing the products of apoptosis formed as a result of trophoblast reconstruction and programmed cell death, release anti-inflammatory cytokines (for example, IL-10), forming an immunological tolerance to the tissues of the embryo [6].

However, activated macrophages also secrete cytokines that initiate 19 inflammatory responses, in particular IL-1, IL-6, IL-12 and tumor necrosis factor α (TNF-α).These cytokines, activating lymphocytes, have a pro-inflammatory effect and mediate the formation of a systemic inflammatory response. In preeclampsia, in contrast to normal pregnancy, the cytokine profile changes - there are higher concentrations of IFN-γ, TNF-α, IL-6, IL-1β, IL-8 and IL-16, and lower concentrations of IL-10 [8] .

In addition, some cytokines, acting as chemo attractants, further enhance the activation and mobilization of leukocytes. It is important to note that macrophages under the influence of T-helper lymphocytes lymphokines (interleukin-1 and interleukin-2, interferon-gamma or its combination with TNFα, TNFβ and lipid A) are able to produce nitric oxide, regulating this process through inducible nitric oxide synthesis [15].

During pregnancy, the balance of T helper1 (Th1) (cellular immunity) and Th2 (humoral immunity) cytokines is characterized by an initial prevalence of Th2 cytokines, followed by a gradual shift towards a predominance of Th1 in late pregnancy.Interleukin-2 (IL-2), interferon-gamma (IFN-gamma) and tumor necrosis factor-alpha (TNF-alpha) are cytokines produced by Th1 cells. IL-4, IL-5, IL-6, IL-10 are Th2 cytokines [10].

Nitric oxide, in turn, stimulates the synthesis of prostaglandins by activating cyclooxygenases, enhances antioxidant protection, activating the production of glutathione and superoxide dismutase, and directly contributes to vasodilatation by activating guanylate cyclase [11].

Thus, any imbalance of regulatory processes can predispose to the development of preeclampsia, since their excessive or insufficient influence can lead to decompensation of the immunological adaptation of the mother's body.

The role of cytokines in the development of preeclampsia is confirmed by a number of studies, the authors of which note an increase in the release of pro-inflammatory fractions into the bloodstream - IL-2, IL-6, IL-8, TNFα, and IFNγ [].The decreased ability of peripheral blood mononuclear cells to produce the immunosuppressive cytokine IL-10 in women with preeclampsia may indicate a shift in the cytokine profile in favor of pro-inflammatory fractions [9, 15].

Cytokines, interacting with specific receptors of target cells, implement intracellular signaling pathways and activation of transcription and thus act as gene regulatory proteins [10].

With the onset of pregnancy at the systemic level, the production of pro-inflammatory cytokines by cells of the phagocytic series sharply increases, at the end of pregnancy the secretory activity of peripheral phagocytes decreases.At the local level, the opposite direction of the activity of macrophages is noted: at the beginning of pregnancy, the synthesis of proinflammatory cytokines and chemokines is inhibited, and at the end of gestation it is increased.At the same time, an excessive increase in the level of pro-inflammatory cytokines has a direct embryotoxic effect, disrupts placentation processes, embryo formation, and can lead to thrombosis and ischemic necrosis in the placenta.High sensitivity of the embryo to these mediators was noted. As a result of their interaction in the endometrium, a pathological type of immune response to trophoblast antigens is formed and the following cascade of reactions leading to miscarriage [16,17].

During normal pregnancy, the induction of reactions aimed at suppressing inflammation is noted, which is facilitated by a high level of the receptor antagonist of IL-1 and the soluble form of the IL-1 receptor, which prevents the interaction of cytokines with the receptor on the surface of effectors cells [16].

Induction and maintenance of gestational immunosuppression occurs as a result of a complex interaction of cytokine-mediated and cellular mechanisms of regulation of immunity in pregnant women [5]. At the same time, the development of immune dysfunctions, according to the literature [10], is associated with a complicated course of pregnancy. According to a study by B. La Marca et al. [6], IL-6 plays a role in the development of hypertension during pregnancy.

One of the pathogenesis of preeclampsia is an increase in TNF-alpha and IL-6 levels. In this regard, the researchers wanted to know the level of expression of TNF-alpha and interleukin-6 in pregnant women with preeclampsia [19].

Sources of TNF-α production in preeclampsia, in addition, are neutrophils, monocytes and possibly the placenta. One possible mechanism in preeclampsia was that factors derived from the placenta are stimulated by monocytes and neutrophils to produce TNF-α leading to endothelial disruption. Hence, it seemed that the increase in serum TNF-α may be part of the pathology of preeclampsia. At the same time, interleukin-6, commonly identified as a B-cell differentiating factor, is a multifunctional cytokine in various tissues and cells. Interleukin-6 is a pleiotropic cytokine mainly involved in the regulation of inflammation, immune response, and hematopoiesis [21].

Endogenous bioregulators, including immunomodulatory cytokines, play a decisive role in the interaction of the nervous and immune systems. Pro inflammatory cytokines IL-1, IL-6 and tumor necrosis factor α (TNF-α), discovered as mediators of intercellular interactions in the immune system, are considered as the main mediators of neuroimmune interactions [].A decrease in the level of pro-inflammatory cytokines (TNF, IFN, IL-1, IL-2) and an increase in the level of anti-inflammatory cytokines (IL-4, IL-10, etc.) slows down viral replication, prevents demyelination, the development of gliosis, thereby preventing a persistent neurological defect []. IL-1 plays an important role in the regulation of the body's defense functions, initiates a cascade of innate and acquired defense reactions [16, 19].

In the last decade and a half, it has been established that IL-1 is expressed by receptors not only of immunocompetent and related cells, but also of cells of various structures of the brain,

including neurons, and also activates the glucocorticoid function of the hypothalamic-pituitary-adrenocortical system [22].

Preeclampsia is not only associated with an increase in pro-inflammatory cytokines, but is also associated with a decrease in anti-inflammatory cytokines. The most important pro-inflammatory cytokines are interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α) and pro-inflammatory interleukins (IL): IL-1, -2, -6, -8 -15, -16 and - eighteen [9].In fact, preeclampsia patients may have genetic polymorphisms from TNF-alpha and IL-1, resulting in increased levels of these cytokines [11]. In addition, acute phase reagents (C-reactive protein) are higher in preeclampsia than in normal pregnancies [13].

It has been suggested that IL-12 is involved in damage to placental vascularization, leading to restriction of fetal growth, which is usually found in women with hypertension during pregnancy [5, 9].

Investigated the effect of tumor necrosis factor alpha (TNFα) on apoptosis of placental endothelial cells (PEC) in the context of uterine artery Doppler with high or normal levels; They demonstrated that placental endothelial cells (PECs) from the high resistance index (RI) group exposed to TNFα had a half-life of 40% less than those from the normal RI group exposed to TNFα [9].

The trophoblast itself produces a factor that inhibits the expression of the T-cell receptor for the antigen. In addition, progesterone promotes the development of type 2 T-helper cells, which secrete IL-4 and / or IL-10, and IL-4 is a cytokine that inhibits the development of T cells. IL-10 is a possible inhibitor of Th1 cells, NK and macrophages and can also be produced directly by trophoblast.In samples of the placenta with preeclampsia, an increased level of expression of IL-1β, TNF-α, IL-10 is shown. It is believed that this may be related to placental hypoxia and contribute to global endothelial dysfunction in preeclampsia [14].

In women with severe preeclampsia, an increase in serum levels of TNF-a and IL-6 is determined, which correlates with the concentration of leptin, a hormone that regulates metabolic efficiency, energy expenditure and food intake.It is produced mainly by adipose cells, but its mRNA is also expressed by cells of the placenta. It has been shown that with preeclampsia, the concentration of leptin in the blood plasma and the level of production by the placenta cells increase.Serum leptin concentration increases progressively during the first 2 trimesters of pregnancy, correlating with maternal weight and mass index. In women with preeclampsia, serum levels of TNF-α, IL-6 and TGF-β1 also increase.A significant correlation was found between inflammatory cytokines and leptin in the third trimester in women with physiological pregnancy and in women with preeclampsia. It is assumed that increased levels of TNF-a and other inflammatory cytokines (IL-6) may contribute to the pathogenesis of preeclampsia [8].

Thus, the study of the immunopathophysiological mechanisms acting in the mother-placenta-fetus system contributes to the improvement of methods for the early diagnosis of preeclampsia and the selection of path genetically justified therapy to prevent this formidable complication of pregnancy.

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