Current Understanding of the Development and Pathogenesis of Preeclampsia

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Annotation: Preeclampsia complicates the course of pregnancy in 2-8% of all cases. According to the literature, preeclampsia is associated with an increase in maternal and perinatal morbidity and mortality, as well as a predictor of the development of chronic diseases in the distant future, which is an important medical and social problem. Of particular interest are the molecular mechanisms of etiopathogenesis and risk factors of preeclampsia, which, unfortunately, are currently insufficiently studied and understood, necessitating further investigation of this formidable complication of pregnancy. This article reviews the current understanding of the etiology, pathogenesis and risk factors of preeclampsia.

Key words: preeclampsia, theories of development, risk factors.

Preeclampsia occupies a leading place in the structure of causes of maternal and perinatal morbidity and mortality in both developed and developing countries (Serov V.N., Sukhikh G.T., 2011; Sidorova I.S., Nikitina N.A., 2013; Khodjaeva Z.S., Kholin A.M., 2013). According to V.N. Serov (2011), preeclampsia is a "disease of adaptation", a severe complication of pregnancy, significantly increasing maternal and infant morbidity and mortality. Perinatal mortality in pre-eclampsia exceeds the average figures by 5 -7 times. According to statistical data, in Russia pre-eclampsia ranks 3rd in the structure of maternal mortality (Serov V.N., Sukhikh G.T., 2011). In the structure of the causes of maternal deaths from pre-eclampsia in the last decade is 18 -25% (Savelyeva G.M. et al, 2013). Preeclampsia is not only a direct cause of maternal mortality, but also an inducer of many cases of massive bleeding and purulent-septic complications (Serov V.N., Sukhikh G.T., 2011; Agapov I.A. et al., 2011; Ailamazyan E.K., Repina M.A., 2013). In addition, while maternal mortality from hemorrhage and sepsis is decreasing, mortality from preeclampsia remains stable. In developing countries preeclampsia is the cause of 40-80% of maternal mortality, and in some developed countries preeclampsia continues to be the main cause of maternal mortality (Makarov O.V., Volkova E.V., 2012; Hutcheon J.A., Lisonkova S., et al. 2011).

Preeclampsia leads to an increased incidence of preterm labor, placental insufficiency, premature detachment of the normally located placenta, to an increased incidence of operative delivery, bleeding in labor and in the postpartum period. Disturbance in the system "mother-placenta-fetus" in this complication leads to hypoxia and growth retardation of the fetus, possible intrauterine infection. Most

In recent years, the incidence of preeclampsia on the background of extragenital diseases has been increasing; if in the 80s it was 7.2-38.8%, in recent years it is 74.5 - 100%. Apparently, this growth is due to the improvement of diagnosis, as well as the deterioration of health of the female population of reproductive age (Serov V.N., Sukhikh G.T., 2011; Makarov O.V., 2011; Ailamazyan E.K., Repina M.A., 2013).

According to M.A. Repina (2012), this theorized classification is very far from practical obstetrics. This classification obviously confuses pre-eclampsia with extragenital diseases, which should be considered according to other criteria than individual symptoms. In addition, Subscribe to DeepL Pro to edit this document. Visit www.DeepL.com/pro for more information.extragenital diseases may be a background for the development of preeclampsia. The presence of detailed symptoms in this classification and the lack of diagnosis complicate the identification of the main cause of the patient's death and prevent mutual understanding between pathomorphologists and obstetricians-gynecologists when dealing with maternal death (Milovanov A.P., 2008).

At the I All-Russian Interdisciplinary Educational Congress "Complicated pregnancy and preterm labor - from the top of science to everyday practice" in 2012, a decision was made to use the unified terminology "pre-eclampsia" instead of "gestosis" (in accordance with the International Classification of Diseases X revision). According to domestic scientists, it is possible to replace the term "gestosis" with "pre-eclampsia", but this is only appropriate when a term replacing "pre-eclampsia" as a condition immediately preceding an attack of eclampsia is found (Savelyeva G.M. et al., 2013).

Currently, there is no single concept that fully reveals the etiology and pathogenesis of preeclampsia, which is rightly called "the disease of theories" (Serov V.N., Sukhikh G.T., 2011; Dobrohotova Y.E., 2013). This is due to the complexity of the mechanisms of development of this complication of pregnancy, which manifests itself in the form of different clinical pictures of its course, since most of the body systems are affected - cardiovascular, urinary, endocrine, hepatobiliary, hemostasis system.

Despite many years and numerous studies, there are still many white spots in the problem of preeclampsia. In terms of etiology, preeclampsia is undoubtedly a multifactorial disease (complication) of pregnancy. In terms of clinical characteristics, preeclampsia is a syndrome manifested by the main triad of symptoms after 20 weeks of pregnancy (edema, proteinuria, hypertension - Zangemeister's triad), as well as many other symptoms resulting from circulatory disturbances in various systems and organs. Tsangemeister triad, which is used by practicing physicians, can not give a true picture of the patient's condition, because its symptom complex is only the tip of the "iceberg" of those deep metabolic disorders that develop in preeclampsia long before the appearance of arterial hypertension, edema, proteinuria. The course of severe preeclampsia can be multifaceted and it is not by chance that it was called "greafimostor" - "the great deceiver" (Serov V.N., Sukhikh G.T., 2011).

According to V.N.Serov (2011), the trigger mechanism for the development of preeclampsia is diffuse-perfusion failure of uteroplacental circulation with the subsequent development of vasospasm, impaired microcirculation, the development of hypoxia, hypovolemia, coagulopathy, immunologic imbalance. In the end, a multi-organ failure syndrome with a different clinical course develops. The
pathological mechanism is activated by a vicious circle in which the uterus and placenta play the main role (Serov V.N., Sukhikh G.T., 2011; Sidorova I.S., Nikitina N.A., 2013; Warrington J.P., George E. M., 2013).

On the basis of further studies, the terms of two waves of cytotrophoblast invasion were outlined - the first one is realized at 6-8 weeks of pregnancy, the second one at 16-18 weeks of normal pregnancy. Implantation, placentation and immune protection of cytotrophoblast and embryo are provided by endometrial protein - glycodelin. A powerful stimulus of the first wave of cytotrophoblast invasion is local tissue hypoxia, which promotes the synthesis of erythropoietins, vascular growth factor. Later, as it moves deep into the endometrium, local regulators of migration, such as insulin-like growth factor, tumor necrosis factor, come to the fore. The latter stimulates the synthesis of metalloproteases in the cytoplasm of interstitial cytotrophoblast and promotes its advancement through the endometrial matrix (Milovanov A.P., 2010; Cohen M., Ribaux P., 2012). The molecular regulation of the second wave of cytotrophoblast invasion has not been studied sufficiently to date, but it has been established that the spread of intravascular cytotrophoblast is preceded by local damage to the endothelium of the involved arteries. In preeclampsia, trophoblast cell invasion is limited to the decidual portion of the spiral arteries only. In the myometrial section it does not occur, smooth muscle fibers remain in the vessel wall, which perceive vasoactive stimuli. The consequence is a violation of capillary blood flow and microcirculation, vascular endothelial damage ((Milovanov A.P., 2010; Sukhikh G.T., Vanko L.V., 2010; Serov V.N., 2011; Sidorova I.S., Nikitina N.A., 2013; Whitley G. S., Cartwright J. E., 2009; Wagner S J., Craici I. M., 2012).

An imbalance between oxidants and antioxidants leads to oxidative stress. Oxidative stress and inflammation are inextricably linked processes. On the one hand, activated leukocytes produce free oxygen radicals. In turn, under the influence of oxidative stress, translocation of the nuclear factor NF-κB occurs and activates the transcription of various factors controlling inflammatory and immune response. This closes a vicious circle that encompasses leukocyte activation, oxidative stress and production of proinflammatory cytokines and, ultimately, leads to clinical manifestations of preeclampsia in the pregnant woman and fetal complications (Vanko L.V., Safronova V.G., 2010; Sukhikh G.T. 2010). Based on numerous studies on preeclampsia, in recent years, views on preeclampsia as a manifestation of the systemic inflammatory response of the body and, as a consequence, the development of endothelial dysfunction have been formed and widely spread. If the regulatory systems are unable to maintain homeostasis, the destructive effects of cytokines and other mediators begin to dominate, which leads to impaired permeability and function of capillary endothelium, the formation of remote foci of systemic inflammation, the development of mono- and multi-organ dysfunction. Systemic inflammatory response syndrome is a symptom-complex characterized by the severity of the inflammatory response in the endotheliocyte system, and, consequently, by the orientation of the inflammatory response to damage.

Recently, the immunologic theory of preeclampsia onset has attracted increasing attention of researchers. The hypothesis of immune etiology of preeclampsia is based on a large number of epidemiologic observations. High frequency of preeclampsia is characteristic of first-born women, when transferring a foreign egg in IVF program, in hyperplacentation, there is some protection in repeat pregnancy from the same partner, and, most importantly, rapid improvement of the woman's condition after delivery. All this indicates the antigenic role of the placenta (Sukhikh G.T., Vanko L.V., 2010; Torchinov A.M., Tsakhilova S.G., 2010; Lamarca B., 2010). According to the immune theory, the basis for the development of preeclampsia is the coexistence of two organisms differing in antigenic structure - mother and fetus. It has been established that the maternal immune response to antigenic stimuli is genetically determined. The fetus differs from the maternal organism due to the information it receives with the father's genes. The only system in the body that recognizes the foreign
is the immune system. Therefore, in the development of pre-eclampsia in pregnant women, the most important point is the reaction of this system.

The immunologic theory views preeclampsia as an immunobiologic conflict between the antigenic systems of mother and fetus. The leading role in this conflict is attributed to impaired permeability of the placental barrier and decreased immunologic tolerance. The immune system is the only system capable of recognizing foreign protein and, therefore, the most significant component in the development of preeclampsia is the reaction of this system to foreign antigens.

In addition, the immune system of the pregnant woman is in a strict physiological framework of immunosuppression, due to the clear work of immunoregulatory mechanisms. But it is the immune mechanisms that are the first to react to the impact of any destabilizing factor of both exogenous and endogenous nature. Thus, immunostructural homeostasis provides adaptation mechanisms in pregnancy (Sukhikh G.T., Vanko L.V., 2010; Torchinov A.M., 2010; Makarov O.V., 2012; Dobrohotova Y.E., 2013; Sidorova I.S., Nikitina N.A., 2013; Hodjaeva Z.S., Kholin A.M., 2013; Shahbazova N.A., 2013; Uzan J, 2011).

Preeclampsia may result from an imbalance between maternal antibodies and fetal antigenic structure. An association between antiphospholipid antibodies and severe preeclampsia has been suggested. This is confirmed by the high titer of antiphospholipid antibodies, which is observed in many women with this pathology. According to A. D. Makatsaria (2011), 70% of preeclampsia detected in the first pregnancy, arise against the background of congenital thrombophilia. In repeat pregnancies, if preeclampsia occurred in previous pregnancies, the presence of thrombophilia occurs in 100% of cases.

There are numerous observations indicating the important role of the hereditary component in the etiology and pathogenesis of preeclampsia. Preeclampsia is a typical heterogeneous disease, in the genesis of which an important role belongs to both the genetic component and various unfavorable exogenous factors that provoke this disease (Hodjaeva Z.S., Kholin A.M., 2013). The emergence of national projects on preeclampsia, which are supposed to combine the results of biochemical, clinical and molecular genetic studies into a single search program, gives some optimism about the rapid progress in our understanding of the pathogenetic mechanisms of this disease (Baranov V.S., 2010).

Thus, despite the large number of hypotheses, there is no unified theory of preeclampsia. However, there is no doubt that this obstetric pathology is caused by the development of the fetus and placenta in the maternal body.

LITERATURE


34. Ульянина Е.В., Фаткуллин И.Ф., Хайруллина Г.Р. Маркеры ангиогенеза и ультразвукового исследования в оценке степени тяжести синдрома задержки развития плода // Вестник современной клинической медицины. — 2016. — Т. 9, вып. 5. — С. 79-82.