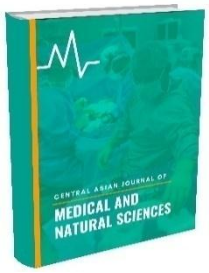
CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES



Volume: 03 Issue: 04 | Jul- Aug 2022 ISSN: 2660-4159

http://cajmns.centralasianstudies.org

Pathogenetic Basis of the Development of Thrombophilia in Preeclampsia

(Overview)

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Received 2nd May 2022,
Accepted 3rd Jun 2022,
Online 13th July 2022

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Resume: In preeclampsia, soluble fibrin monomer complexes (FMFC), fibrin degradation products (PDF) and D-dimer are significantly increased, which indicates the presence of disseminated intravascular coagulation syndrome. The level of D-dimer in the blood is the most favorable prognostic indicator in the assessment of severe preeclampsia. Such a high level of thrombophilia allows us to consider it as the most important etiopathogenetic factor in the development of preeclampsia.

Key words: preeclampsia, D-dimer, thrombophilia, hemostasis.

Preeclampsia (PE), the main cause of perinatal mortality, affects up to 8% of all pregnancies in the Western countries [1,3,25]. This is one of the 4 main causes of maternal mortality and morbidity worldwide, which accounts for 10 to 15% of maternal deaths [2,5]. RE is characterized by new hypertension (arterialnoe davlenie ≥140 / 90 mm rt.st.) in two separate symptoms with an interval of less than 6 hours, which manifests itself after 20 weeks of pregnancy and is associated with clinically significant proteinuria (≥300 mg) in 24 hours [6,7,20].

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. As reported by N. Al. Jameil et al. (2014), PE ranks third in the structure of maternal and perinatal morbidity and mortality, and its frequency in the total number of births ranges from 11% to 16%. Studies by P. James, C. Nelson Piercy show that more than 8 million cases of PE are registered annually in the world, which is the main cause of maternal and perinatal mortality, killing 60 thousand young women annually.

The etiology of PE is still the subject of debate. The leading theories of the development of this complication of pregnancy are based on the processes of defective remodeling of the uteroplacental arteries and ischemia of the placenta, oxidative stress, excessive inflammation; positive response, genetic predisposition and immunological intolerance between mother and fetus[2,8,10].

Preeclampsia is a disease of the mother and the fetus, which leads to several complications on the part of the mother and the fetus. The cause of its origin is still not fully understood, but it is associated with placentation disorders and activation of the coagulation cascade. In the last few years, attention has

been focused on the possible role of hereditary or acquired thrombophilia in the pathogenesis of preeclampsia[16,22].

It is known from research that pregnancy puts the hemostasis system in a hypercoagulable state, which increases during pregnancy and reaches a maximum level throughout the pregnancy. These physiological changes are important to reduce internal blood loss, but increase the risk of thromboembolism during pregnancy and the postpartum period[]. For the mother, this risk begins at birth and continues after delivery, and according to the data, this risk can last up to 12 weeks postpartum [18]. Hemostasis is a complex network of interactions with positive and feedback cycles that unite at least five main components, namely blood vessels, the amount and function of platelets, coagulation factors and their cofactors, inhibitory and fibrinolytic factors. At the same time, pregnancy is associated with profound changes in the coagulation and fibrinolytic system[6,14].

Due to these changes, increased synthesis of coagulation factors, especially fibrinogen, VIII, IX, X factors and increased synthesis of plasminogen activator type 1 and 2 inhibitors, fibrinolysis is significantly reduced, all of which lead to a hypercoagulable state[11].

D-dimer increases in normal pregnancy due to a compensated state of low intravascular coagulation, moreover, this increase indicates that the fibrinolytic system remains functionally active despite a significant deterioration of fibrinolytic potential[].

Hemostatic disorders in preeclampsia are associated with severe and mild forms of the disease. The pathological state of activation of compensated hemostasis associated with thrombocytopenia, the presence of less than 150,000 platelets per mm3 of blood means that 20-25% are complicated by preeclampsia. An early increase in the level of fibronectin, thrombocytopenia, an increase in D-dimer degradation products, and an increase in platelet turnover are signs of endothelial activation. Excessive thrombin production by physiological inhibitors can be seen to increase the level of thrombin-antithrombin complex, which is a characteristic of preeclampsia compared to physiological pregnancy, and a decrease in antithrombin activation[15,23].

Relative hypofibrinolysis of the placenta contributes to the prothrombic state. The activation of erythrocytes and leukocytes leads to a pathological state of coagulation, as a result of which a systemic inflammatory process occurs in the mother's body. The state of pathological activation of blood coagulation can be seen in the thrombotic mode or decompensation beyond the physiological inhibitors of coagulation, or in the thrombophilic context, the silence of these inhibitors can be seen[4].

This is called chronic disseminated intravascular coagulation syndrome or microthrombotic syndrome, in such cases, fetal growth retardation, fetal death in the mother's womb, or maternal renal failure, HELLP syndrome, preeclampsia, eclampsia are observed. Hemostasis is a dynamic phenomenon that changes over time, sometimes hourly, and requires repeated biological assessment[12].

With the development of preeclampsia, at the same time as activation of platelet binding, disturbances in the procoagulant binding of the hemostasis system are also formed [12,24]. Signs of intravascular activation of the hemostasis system are soluble fibrin monomer complexes (RFMC), thrombin-antithrombin III complex, fibrin breakdown products, D-dimer, which are much higher in preeclampsia than in uncomplicated pregnancy[17].

According to a large number of researchers, D-dimer is one of the main markers predicting preeclampsia[]. An increase in the D-dimer fraction is observed in women complicated by preeclampsia[5].

An increase in the level of the D-dimer fraction indicates hemostatic potential, that is, an increase in blood clotting within the vessel. This, along with high blood pressure, may reflect a tendency toward an increased risk of cardiovascular thrombotic events later in life[13].

The study of the hemostasis system during pregnancy allows to identify important patterns of adaptive changes in the blood coagulation system. In the first and second trimesters of physiological pregnancy, it was found that there were significant changes in general evaluation tests describing blood coagulation factors, thrombocyte aggregation properties and their number[2,14].

True hypercoagulation - a decrease in the activity of fibrin-stabilizing factor, an increase in fibrinogen, a decrease in activated thromboplastin time, prothrombin time, D-iron, thrombin time occurs in the third trimester and is a preparation mechanism for childbirth [17].

Thus, with the development of disseminated intravascular coagulation syndrome, which is one of the main causes of intravillous thrombosis in preeclampsia, continuous activation of platelets and procoagulant connections of the hemostasis system was noted, and blood flow in the placenta led to organ failure [21].

As a result of general spasm of arterioles and the formation of thrombocyte-fibrin microthrombi, microcirculation, transcapillary metabolism is disturbed and hypoxia develops. These processes lead to the formation of organ damage [25].

Fibrin deposition is observed in the microcirculation of pregnant women complicated by preeclampsia, which in turn leads to impaired placental perfusion, delayed fetal development, and impaired maternal organ function[7].

It is noted that soluble fibrin monomer complexes (RFMC), fibrin degradation products (PDF) and D-dimer are significantly increased in preeclampsia, which indicates the presence of disseminated intravascular coagulation syndrome. The D-dimer level in the blood is the most favorable prognostic indicator in the assessment of severe preeclampsia[19].

According to the literature, there is a correlation between diastolic blood pressure and D-dimer level and an inverse relationship between birth weight of babies with D-dimer[5,7].

Another characteristic hemostasiological sign of disseminated intravascular coagulation in preeclampsia is microangiopathic anemia, which is caused by mechanical destruction of erythrocytes in terminal vessels partially or completely blocked by fibrin deposits.

Currently, it is found that as the severity of preeclampsia increases, the level of hyperfibrinogenemia also increases[10,16].

According to the data of researchers in the world, as well as according to our data, thrombophilia was found in 80% of women complicated by preeclampsia[9]. Such a high level of thrombophilia allows us to consider it as the most important etiopathogenetic factor in the development of preeclampsia.

According to many researchers around the world, a new era of studying the etiopathogenesis of preeclampsia began with the discovery of new genetic defects of the hemostasis system and antiphospholipid syndrome in the most common thrombophilia in the general population, the role of thrombophilia in the pathology of the implantation process and placentation, and later utero-placental circulation disorders[16,24]

According to the general information of the world literature, complications such as venous thrombosis, placental insufficiency, preeclampsia, fetal growth retardation, fetal death in the mother's womb are observed in 30-75 percent of pregnancies in various forms of thrombophilia[15,21].

Many studies have shown that with increasing severity of preeclampsia, there was a proportional increase in fibrinogen, a protein that ensures blood viscosity, participates in platelet and erythrocyte aggregation, adhesion, and activation, as well as other factors that indicate hypercoagulation and thrombinemia, such as soluble fibrin monomer complexes (RFMC).), platelet count, partially activated thromboplastin time decrease[9].

In response to disseminated intravascular coagulation, the processes of fibrinolysis are activated, which causes an excess concentration of fibrin and fibrinogen breakdown products[22].

Many researchers have studied the hemostasis system in pregnant women complicated by preeclampsia, in which an increase in signs of vascular platelet activation (FV, R-TG, 4- PF), changes in the coagulation (TAT, RFMK) and fibrinolysis (D-dimer) systems have also been found in preeclampsia. directly depends on the output[19,22].

Progressive changes are noted in mild and severe forms of preeclampsia: activation of platelets increases (aggregation indices increase), endothelial damage, hypercoagulation, hyperfibrinogenemia, thrombonemia and reactive hyperfibrinolysis, D-dimer increase, and natural anticoagulant activity increase [22].

Thus, when pregnancy is complicated by labor and preeclampsia, it is necessary to recognize the role of thrombophilia in their pathogenesis and optimize the management of high-risk pregnant women, taking into account the "thrombophilic component".

It should be noted that early (prenatal) diagnosis, pathogenetic prevention and its differentiation with trobophilia can prevent the development of obstetric complications, as well as improve maternal and perinatal mortality rates.

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