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Hemostasis Alterations and Placental Outcomes in Preeclampsia: Perubahan Hemostasis dan Kondisi Plasenta pada Preeclampsia

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General Background: Pregnancy induces profound physiological changes in the hemostasis system, balancing procoagulant and fibrinolytic mechanisms to ensure maternal and fetal survival. **Specific Background:** Preeclampsia disrupts this balance, leading to hypercoagulation, endothelial dysfunction, and compromised placental circulation. **Knowledge Gap:** Despite numerous studies, the specific patterns of coagulation system alterations and their diagnostic value in preeclampsia remain incompletely characterized. **Aims:** This article aims to analyze the dynamic changes in coagulation and fibrinolysis during normal pregnancy and to compare them with the pathological shifts occurring in preeclampsia. **Results:** Findings demonstrate increased procoagulant activity, elevated D-dimer levels, reduced fibrinolysis, and decreased antithrombin III activity in preeclampsia. These changes contribute to placental insufficiency, fetal growth restriction, and heightened maternal risk of thrombohemorrhagic complications. **Novelty:** The study highlights the prognostic importance of D-dimer levels and platelet indices as accessible markers to monitor hemostasis dysfunction in preeclampsia. **Implications:** Early identification of coagulation markers offers prospects for improving diagnostic precision, guiding therapeutic strategies, and preventing severe maternal-fetal complications in preeclampsia.

Highlight:

- Altered coagulation and fibrinolysis in preeclampsia drive maternal and fetal risks.
- D-dimer and platelet indices emerge as practical prognostic markers.
- Early detection of hemostasis dysfunction enables better clinical outcomes.

Keywords: Preeclampsia, Coagulation Cascade, Fibrinolysis, D-Dimer, Hemostasis

The endothelium of blood vessels provides an anticoagulant surface, which constantly serves to keep the blood in a liquid state, but if the endothelium is damaged, the components of the subendothelial matrix communicate with the blood, and some of these components activate the process of clot formation, consisting mainly of platelets and fibrin. Based on the control of this

process, it is activated within a few seconds after injury, and the damaged vascular endothelium is localized [7], [16], [2].

The development of physiological pregnancy is accompanied by an increase in the content of procoagulants and a decrease in the activity of factors in the fibrinolytic system. During childbirth, the levels of fibrinogen, prothrombin, proconvertin, and Hageman factor double. At the beginning of pregnancy, prothrombin levels do not undergo significant changes. At the end of the third trimester of pregnancy, a prolongation of prothrombin time (PT) is observed, which indicates an increase in thrombin generation and activation of the extrinsic blood coagulation pathway. This process gradually intensifies with the progression of pregnancy, remains elevated during childbirth, and decreases within the first few days after delivery [8], [17], [25].

The placenta is a rich source of tissue plasminogen activator inhibitors that suppress fibrinolytic activity, the levels of which increase especially during the third trimester of pregnancy and during childbirth [19], [23].

By the end of pregnancy, a sharp decrease in fibrinolytic activity is observed; however, as the pregnancy progresses, the level of the main factor of fibrinolysis - plasminogen - increases. The increase in plasminogen levels occurs as a result of a decrease in the amount of its activating factors. A reduction in the synthesis and release of plasminogen activators leads to a decrease in fibrinolysis.

Changes associated with plasma and fibrinolysis inhibitors reflect the processes occurring in other parts of the hemostasis system. The main inhibitors are AT III, alpha-2-antiplasmin, alpha-1-antitrypsin, protein C. All inhibitors are proteins capable of blocking 2 or more fibrinolysis factors and the complement system. AT III has the greatest activity. With the development of pregnancy, a gradual decrease in the activity of AT III is observed [4], [12], [26].

An increase in the content of fibrinogen and fibrinogen degradation products indicates an intensification of intravascular coagulation processes. The level of D-dimer in blood serum increases with increasing gestational age during childbirth and persists for 3-4 days after delivery [1], [14].

Activation of the hemostasis system in preeclampsia (PE) creates a premorbid background for thrombohemorrhagic complications. Such a disruption of hemostasis increases the risk of bleeding during labor. The same is observed with a deficiency of coagulation factors [2], [5], [11].

Activation of the hemostasis system, leading to the development of thrombosis, is accompanied by the appearance of specific signs reflecting the degree of increase in the hemostatic potential of blood in the bloodstream. There are markers of platelet activation (platelet factor 4, beta-thromboglobulin) and the coagulation cascade. The coagulation cascade includes a marker of activity (prothrombin proteolysis product), a thrombin-antithrombin complex, a fibrin monomer, fibrinopeptide A, and D-dimer. However, identifying almost all of them, except for D-dimers, is difficult for obtaining results. Detection of D-dimers of fibrin degradation products interacting with plasmin is an exception.

Assessment of this marker is of great importance in clinical practice for the diagnosis of D-dimer thrombosis. Moreover, among all markers of hemostasis activation, D dimer has the longest lifespan, which allows their detection [3], [15], [21].

In healthy individuals, the concentration of D-dimer in the blood does not exceed 500 ng of FEU (equivalent units of fibrinogen) /ml. An increase in the concentration of D-dimer indicates activation of fibrinolysis [6], [24].

From the early stages of pregnancy, the level of D-dimer gradually increases, and in women with

complicated pregnancy, a high level of D-dimer is observed. A significant increase in D-dimer levels is observed, especially in pregnancies accompanied by preeclampsia, gestational diabetes, and kidney disease. At the beginning of the second trimester of pregnancy, more than half of the pregnant women had a D-dimer content of more than 0.50 mg/l (or 1.0 fibrinogen of an equivalent unit), and in the third trimester, more than 90% of women had a D-dimer content of >0.50 mg/l.

Currently, there is no direct evidence in the medical literature to determine the D-dimer level threshold (or trimester-divided thresholds) in pregnant women at risk of developing thrombosis and thromboembolism. To solve this problem, it is necessary to measure the level of D-dimer in many pregnant women [9].

It is known that preeclampsia, a complication of pregnancy, is accompanied by endothelial dysfunction and a multisystem response of the maternal organism, resulting in chronic placental ischemia. Cardiovascular, infectious-septic, immune, metabolic, and genetic factors, as well as generalized microangiopathy, underlie placental circulatory disorders [22].

In preeclampsia, profound and complex changes in the hemostasis system, activation of the coagulation cascade, and fatigue of the anticoagulant system are observed, which, in turn, leads to placental insufficiency and fetal growth restriction. Existing "screening" tests for assessing the hemostasis system do not allow for a complete assessment of changes in the blood coagulation system, but these changes are the main cause of the development of serious fatal complications for the mother and fetus [3], [10].

Thrombin time and fibrinogen levels tend to reverse during pregnancy. From the conducted scientific studies, it is clear that the level of fibrinogen in pregnant women with preeclampsia was lower than in patients without PE, and, conversely, it was higher in the PE group compared to healthy pregnant women.

To this day, PE is interpreted as a very pronounced state of hypercoagulation. Depending on the level of blood pressure, PV, fibrinogen, and D-dimer, we can determine that in pregnant women with PE, not only increases the level of procoagulants, but also complex changes occur in the fibrinolytic and procoagulant systems. With increasing gestational age, the level of D-dimer constantly increases, but in patients with PE, the level of D-dimer is especially high [8], [11], [19].

During pregnancy complicated by preeclampsia, pronounced changes in the vascular-platelet system of hemostasis are revealed, which depends on the time of early or late onset of the pathological process and is characterized by multifaceted reactions. With increased platelet activity and preeclampsia, intravascular aggregates are formed, blocking the microcirculatory channel, including the mother-placenta-fetus system. In the clinical blood test, an increase in platelet indices is observed, such as the average platelet volume, which is inversely related to the platelet count. This, in turn, indicates a decrease in platelets in peripheral blood and constant activation of synthesis in bone marrow [13], [20].

In addition, an increase in von Willebrand factor is detected, which indicates endothelial dysfunction. Similar changes are detected in newborns of pregnant women with preeclampsia. Changes in the function of the hemostasis system during preeclampsia are characterized not only by an increase in the coagulation capacity of the blood, but also by dysfunction of the fibrinolysis system and weakening of the anticoagulant system, which, on the one hand, leads to an exacerbation of this condition, and on the other - to a deterioration in the condition of the fetus and newborn [9], [15], [23].

In preeclampsia, profound and complex changes in the hemostasis system are observed, leading to the activation of the coagulation link of the hemostasis system and fatigue of the anticoagulant system, which, in turn, causes placental circulatory insufficiency and fetal growth restriction, exacerbation of preeclampsia and its complications, and the development of multiple organ failure.

Thus, due to the incomplete study of clinical, laboratory, and functional studies in the development of preeclampsia, the identification of markers assessing changes in the biochemical, inflammatory, and coagulation systems, the close relationship of preeclampsia with bleeding, septic diseases, the development of antenatal and perinatal pathologies in them, changes in the fetoplacental system, early detection of these markers assesses the prospects for preventing complications of the disease.

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