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Original Research

The nature of changes markers of dysfunction of the endothelium in blood of women with premature bursting of amniotic waters

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ABSTRACT:
Traditionally refer vascular and hemodynamic disorders at mother to risk factors of premature detachment of normally located placenta, such as, generalized dysfunction of an endothelium which occurs in the uteroplacental pool, developing at a gestosis and various somatic pathology. Research objective was studying of diagnostic value of definition in blood of a number of markers of a functional condition of an endothelium at women with the premature bursting amniotic waters (PBAW). 72 patients were examined. The main group was made by 48 pregnant women of the full-term with PBOW in the absence of biological readiness for childbirth. The blood analysis on the maintenance of markers of the endothelium dysfunction (ED) was conducted: thrombomodulin, soluble molecules of adhesion (sICAM-1 and sVCAM-1), Villebrand's factor, fibronectin. Results of a research showed on increase in content of thrombomodulin, sICAM-1, Villebrand's factor, fibronectin in a maternal blood-groove at PIOV what demonstrates activation and stimulation of endotheliocytes at this pathology. Thus, determination of content in blood of a number of markers of ED, is diagnostically and predicatively significant in diagnostics of PBOW at pregnant women.
Key words: markers of the endothelium dysfunction, premature bursting amniotic waters, Villebrand's factor, fibronectin.

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INTRODUCTION

Recently, the risk factors for premature detachment of the normally located placenta traditionally include vascular and hemodynamic disorders in the mother, which are observed in various somatic diseases. At the heart of hemodynamic and microcirculation disorders, including in the uteroplacental system, developing with gestosis and various somatic pathologies, is generalized endothelial dysfunction (1,2,3,4,5,).

There are several hypotheses explaining the development of endothelial dysfunction in the pathological course of pregnancy (6,7,8,). The greatest evidence was obtained for the theory of placental ischemia. Absolute or relative placental ischemia can develop primarily as a result of insufficient trophoblast invasion into the spiral arteries of the decidual membrane, or secondarily against the background of diffuse endothelial pathology observed in patients with somatic pathology. As a result of placental ischemia, substances that damage the endothelium enter the bloodstream, there is an imbalance between vasoconstrictors and vasodilators, between the thrombogenic potential of the vascular wall and its thromboresistance, regional blood flow is disturbed, progressive disorders of vital organs and placental functions occur (9, 10). Additional methods for diagnosing PIOT include the determination of fetal hemoglobin in maternal blood, but this method is not sensitive and specific enough. An important indicator is the determination of PDPn and PDPg as markers of intravascular expenditure of blood coagulation factors in this pathology (11). With PIOT, thromboplastic substances of tissue and cellular origin enter the maternal bloodstream, resulting in hyperthrombinemia and intravascular coagulation. Plasma fibronectin

(PFN) is one of the substances with opsonizing ability, due to which it largely determines, regulates phagocytic activity in normal conditions and stimulates this process in inflammation. By now, it is well known that PFN is able to bind and eliminate from the body the products of phagocytosis (particles of tissue detritus, endotoxins of viruses and bacteria) through the macrophage system, as well as immune complexes [2] It acts as a kind of marker of the acute phase of inflammation.

A decrease in the level of plasma fibronectin in plasma is observed: with hepatitis, with sepsis, with physical injuries, in the postoperative period.

The concentration of plasma fibronectin in plasma increases: during a complicated pregnancy (severe preeclampsia, preeclampsia), in violation of the vascular endothelium, in inflammation, in the development of malignant tumors and their metastasis.

The aim of this study was to study the diagnostic value of determining in the blood a number of markers of the functional state of the endothelium in women with premature rupture of amniotic fluid.

MATERIALS AND METHODS

72 patients were examined. The main group consisted of 48 full-term pregnant women with PIOT in the absence of biological readiness for childbirth. The inclusion criterion was premature rupture of amniotic fluid, gestational age 24-36 weeks, insufficient readiness of the soft birth canal for labor induction (uterus: immature, maturing), lack of indications for emergency delivery. Exclusion criteria: signs of ascending infection (leukocytosis, | body temperature), diabetes mellitus, scar on the uterus, large fetus, breech presentation of the fetus, chronic urogenital infection with complications in history (miscarriages, premature birth, endometritis, acute adnexitis). - expectant tactics up to 72 hours of anhydrous period. A comprehensive examination of the condition of the pregnant woman and the fetus was carried out. At 12 hours of anhydrous period, antibiotic therapy was initiated to prevent ascending infection. Preparation for childbirth was carried out with antispasmodics, antioxidants, antigestagens. Miropristone was prescribed after PIOT 0.2 g twice. The first time - immediately after the amniotic fluid poured out. The second - after 6 hours, in the absence of regular labor. When optimal biological readiness for childbirth was achieved or signs of an ascending infection appeared, labor induction was performed. The control group consisted of 24 patients of the same period with timely rupture of amniotic fluid without severe obstetric and somatic pathology of RTI in the absence of biological readiness for childbirth.

To achieve this goal, a blood test was carried out for the content of endothelial dysfunction markers: thrombomodulin, soluble adhesion molecules (sICAM-1 and sVCAM-1), von Willebrand factor, fibronectin.

Blood for the study was taken from the cubital vein into a plastic or siliconized tube containing a 3.8% solution of 3-substituted sodium citrate (sodium citrate), the ratio of blood volume to sodium citrate was 9: 1. The blood was centrifuged at 3000-4000 rpm (1200 g) for 15 minutes. As a result, platelet-poor plasma was obtained, which was transferred to another tube, where it was stored until the study. Analysis of plasma with clots, hemolysis, excess sodium citrate and obtained more than 2 hours ago was not allowed. Frozen plasma samples were stored at temperatures from -20 to -16 ° C for no more than 1 month.

To determine the blood levels of sVCAM-1, sICAM-1 and thrombomodulin, the reagents "humansVCAMELISA", "humansICAMELISA" and "humansCD141 ELISA" manufactured by Diaclon (France) were used. To determine fibronectin, avntithrombin-III, we used the ELISA-Fn kit manufactured by NVO Immunotex. To determine the deficiency of protein C, we used the Parus-test kit produced by Technology-Standard. Specific semi-quantitative determination in plasma of cross-linked fibrin derivatives containing the D-dimer domain was carried out by latex agglutination immunoassay.

Statistical processing of the material was performed using the standard statistical software package Statistica10.0 (StatisticaforWindowsv. 6.0).

RESULTS AND DISCUSSION

One of the most important methods for diagnosing endothelial dysfunction is to assess the content of various substances in the blood that are formed in the endothelium. Not all indicators have the same diagnostic value, since a significant part of the markers of the functional state of the endothelium, in addition to endothelial cells, are formed in other cells. Thrombomodulin and soluble adhesion molecules ICAM-1 and VCAM-1 are highly specific markers of endothelial dysfunction. Thrombomodulin is a glycoprotein in the endothelial membrane and a cellular receptor for thrombin. It converts protein C into its active form, performing an anticoagulant function. The content of thrombomodulin in the blood increases with damage to the endothelium.

The adhesion molecules, ICAM-1 and VCAM-1, belong to the superfamily of immunoglobulins and bind to leukocyte membrane integrins. They are expressed by endotheliocytes and partially pass into the blood when the endothelium is activated. An increase in the content of soluble adhesion molecules in the blood is a highly specific marker of endothelial dysfunction. Increased adhesiveness of the endothelium is of great importance in the pathogenesis of atherosclerosis, systemic inflammatory response syndrome and other pathological conditions. A highly specific marker of the functional state of the endothelium is also the von Willebrand factor, which promotes platelet adhesion to the damaged endothelium. Platelets are another

source of von Willebrand factor. Fibronectin is a subendothelial extracellular glycoprotein that is also found in platelets and plasma and is an important factor in platelet adhesion at the site of vascular injury. Unlike the above markers, fibronectin is not a strictly specific marker of endothelial dysfunction, since it is synthesized not only by endothelial cells, but its content in the blood increases in pathology accompanied by damage to the vascular wall. Thus, X. Wang et al. fibronectin was determined at 24-34 weeks. In those women who subsequently developed IGRP, the level of fibronectin was significantly higher. In our studies, presented in Table 1, it is shown that an increased level of plasma fibronectin in the control group occurs in 13% of cases, while in the group with PIOI it is increased in 25% of cases.

Studying the dynamics of endothelial dysfunction markers is important for understanding the role of endothelial dysfunction in the pathogenesis of RTI. 1, the content of such markers of endothelial dysfunction as thrombomodulin, soluble adhesion molecules, von Willebrand factor and fibronectin, had a peculiar dynamics during PIO. The results of our study showed an increase in the content of thrombomodulin, sICAM-1, von Willebrand factor, fibronectin in the maternal bloodstream during PIOT, which indicates the activation and stimulation of endothelial cells in this pathology. In women with PIOT, a statistically significant increase in the content of fibronectin in the blood was observed, which, apparently, is associated with damage to the trophoblast. The source of the increase in the content of thrombomodulin in the blood in these women, apparently, is also trophoblast. As you know, as pregnancy increases, the degree of thrombinemia increases, detected by an increase in the content of soluble fibrin-monomer complexes (RFMK), fibrinogen degradation products (PDF) and fibrin (D-dimer). These changes are associated with the intensification of the processes of intravascular blood coagulation, including in the uteroplacental blood flow. To date, the D-dimer test is the most accessible, often performed in domestic laboratories and quite informative. During pregnancy, due to an increase in the total coagulation potential of the blood, a thrombophilic state almost always develops. Such changes in the hemostatic system during physiological pregnancy are considered necessary for the normal formation of the fetoplacental complex. Their development is associated with such morphofunctional changes in the spiral arteries of the uterine mucosa as the invasion of trophoblast cells into the arterial wall, replacement of the internal elastic membrane and internal media with a thick layer of fibrinoid, disruption of the integrity of the endothelium and exposure of collagen structures, as well as the formation of Developing changes, as a rule, are not accompanied by pathological hyperthrombinemia and intravascular disseminated blood coagulation (DIC), however, they can lead to hypercoagulation, which is the result of imbalance in the hemostatic system under conditions of hereditary and / or acquired changes in it with various extragenital diseases. Thrombophilic status can lead to a disruption of adaptive mechanisms during pregnancy and childbirth and cause the development of obstetric complications - fetal growth and development retardation, placental insufficiency, late toxicosis (gestosis), fetal death, etc. , coagulation, fibrinolytic and anticoagulant links of hemostasis is determined by the peculiarities of the course of pregnancy and the initial state of the coagulation system. These factors are interrelated and interdependent; their violations often lead to termination of pregnancy at different times, which makes timely diagnosis of intravascular thrombus formation and its therapy with the use of specific and non-specific methods that affect individual links of pathogenesis.

It is extremely important to study the blood content of pregnant women with PIOT of indicators of the anticoagulant potential of blood, in particular, the content of the main anticoagulant - antithrombin III. With PIOT, its amount was 85.15 ± 5.31 mg / l, which is significantly lower than in women with the physiological course of pregnancy, which indicates the important role of antithrombin III deficiency in the development of these formidable complications of pregnancy.

Table 1. Content of markers of endothelial dysfunction in the blood of pregnant women with PIOT

Examined group	Indicator				
	Thrombomodulin ng / ml	**Von Willebrand factor ng / ml**	**Fibronectin ng / ml**	**sICAM-1 ng / ml**	**sVCAM-1 ng / ml**
Physiological course of pregnancy n = 12	6,76 ± 0,38	109,45 ±5,07	233,14 ±9,67	998,92±14,6	742,34±9,78
Pregnant women at risk for PIOT n = 72	8,96 ± 0,53	169,45 ± 6,37	503,23±10,24	1308,92±51,6	797,51±12,45

Note: * - reliability of differences P <0.05

Considering that the coagulation potential according to the APTT, PT and RFMK tests in women with PIOT had a tendency to increase, it can be assumed that the decrease in antithrombin activity in our studies is associated with depletion of the anticoagulant system and may cause the development of gross shifts in the hemostasis system

Table 2. Content of markers of endothelial dysfunction in the blood of pregnant women with PIOT

Examined group	Protein C %	D-dimer ng / ml	Antithrombin%
Physiological course of pregnancy n = 12	84,76 ± 6,38	179,23 ±9,07	109,45 ±7,33
Pregnant women at risk for PIOT n = 72	128,58 ± 9,53	317,45 ±10,37*	85,15 ±5,31*

Note: * - reliability of differences P <0.05

We also screened violations in the protein C system of pregnant women with premature rupture of amniotic fluid, which revealed a statistically significant increase in the amount of protein C. high values of thrombomodulin. In order to identify the activation of intravascular coagulation in women with premature rupture of amniotic fluid, the blood content of D-dimer was examined. In 49.8% of women with premature rupture of amniotic fluid, an increase in the content of D-dimer in the blood above 300 ng / ml was revealed. This indicates the processes of cross-polymerization of fibrin in the process of intravascular blood coagulation, which is observed at the time of the expanded clinical picture by premature rupture of amniotic fluid. Consequently, with PIV, there is a deficiency of natural anticoagulants (antithrombin III) and activation of intravascular coagulation (an increase in the content of protein C and D-dimer). It is not excluded that an important pathogenetic factor of premature rupture of amniotic fluid may be the presence of congenital defects in the hemostatic system, which create an unfavorable premorbid background and contribute to the manifestation of hypercoagulation in the intervillous space.

CONCLUSION

Thus, based on the obtained research results, it can be indicated that the detection of an increase in the content of D-dimer, protein C, antithrombin III in the blood has the highest specificity, positive and negative predictive value and diagnostic accuracy, and the highest sensitivity is an increase in the content of thrombomodulin.

Therefore, the determination of the content in the blood of a number of markers of endothelial dysfunction, such as thrombomodulin and fibronectin, as well as a marker of intravascular coagulation D-dimer, protein C is diagnostic and prognostically significant in the diagnosis of premature rupture of amniotic fluid in pregnant women.

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