

# Informatively of the Indicators of Blood Allowing to Predict Premature Water Breaking at Prematurely Born Pregnancy

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**Abstract** The study of the relationship in 47 pregnant women with premature outflow of amniotic fluid of coagulation hemostasis, pro-inflammatory cytokines, complement C3, C4 fractions and insulin-like growth factor-1 in blood serum revealed activation of the prothrombinase internal mechanism of formation, which under conditions of premature outflow of water, due to which local outflow occurs and systemic activation of antigen-stimulated macrophages, NK cells, lymphocytes, neutrophils and activation of the complement system. Determination of serum levels of TIF –a, IL-1 $\beta$ , C3-, C4-complement fractions in pregnant women with ROM can be used to predict the development and timely correction of changes in blood coagulation potential, which will expand the possibilities of successfully choosing an adequate treatment tactic and timely warning development of complications during pregnancy.

**Keywords** Premature water breaking, Prematurely born pregnancy, Pro-inflammatory cytokines, Complement of C3-, C4 fraction, Insulin-like growth factor-1

## 1. Relevance

Currently, the frequency of complications in obstetrics continues to remain at a high level. One of such complications in obstetrics, which make up the difficult obstetric situation and has an undeniable contribution to the formation of the structure of perinatal morbidity and mortality, is the premature discharge of amniotic fluid (ROM) in pregnant women.

According to the definition of the World Health Organization, ROM is understood as a violation of the integrity of the fetal membranes and the outflow of amniotic fluid before the start of labor activity, regardless of the term of pregnancy. The frequency of occurrence of ROM has recently increased 1.5-2 times in the structure of all pregnancies is 2-20% [1,2]. To date, the factors provoking ROM are debatable, despite the progress of medicine and a large number of studies in this area [3,4].

Risk factors for the development of ROM in combination with preterm delivery (PR) may include: extra-genital pathology; bad habits of the mother and adverse factors of the labor process in the workplace; low socio-economic

status; hereditary causes; PR in the anamnesis; transferred viral diseases; isthmio-cervical insufficiency; overstretching and abnormalities of the uterus; surgical operations during pregnancy. Infection is the most common cause of ROM [5,6]. Also, one of the etiological factors of ROM can be considered the activation of lipid peroxidation (LP). LP is activated by microorganisms with the participation of phagocytes and macrophages. Many of scientists put forward a “collagen” theory of the emergence of ROM, namely, the pathology of collagen of the membranes. In modern foreign literature there is evidence that with ROM, metabolic metabolism in plasminogen metabolism occurs. The processes of the influence of progesterin and thrombin on the expression of metalloproteinase-3 in decidual cells with ROM were studied [7,8].

The pathogenesis of ROM is controversial and the existing biochemical aspects of its pathogenesis (clarification or refutation of some of them) will accelerate the solution of a number of obstetric problems related to tactics of conducting pregnancy and childbirth with ROM in practical obstetrics. Until now, there is no systematic information about the pathogenetic relationship of disorders of the blood coagulation potential in the development of ROM.

## 2. The Aim of the Work

The research was conducted to study the relationship of coagulation hemostasis, proinflammatory cytokines, C3-,

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C4-fractions of complement and insulin-like growth factor-1 in the blood serum of women with premature water breaking.

### 3. Materials and Methods

A simultaneous and prospective study of women in 47 patients aged 17 to 26 years with ROM at 22-36 weeks of gestation (main group) was carried out. The comparison group consisted of 12 practically healthy pregnant women, comparable in age with women of the main study group. Assessment of integrative indicators of the state of coagulation hemostasis, fibrinolysis, and cytokine statuses of women of the main group was carried out at the time of their admission to the hospital before treatment against the background of pronounced clinical manifestations of pathology.

Coagulation hemostasis and fibrinolysis parameters were studied by coagulometric methods using a Thrombotimer series coagulometer from Behnk-Elektronik (Germany), as well as conventional manual methods using reagents. The cytokine status was evaluated by the content of IL-1 $\beta$  and TNF- $\alpha$ , as well as the study of C-3 and C-4 fractions of complement and insulin-like growth factor-1 in the peripheral blood serum of patients by enzyme-linked immunosorbent assay using test systems from INNOVA on a COBAS-411 analyzer from ROSH.

Statistical processing of the research results was carried out using the Statistica 6 package.

### 4. Research Results and Discussion

Studies have shown (Table 1) that in pregnant women with ROM, activation of the internal mechanism of prothrombinase formation occurs. This is indicated by the shortening of activated partial thromboplastin coagulation time (APTT) compared with a group of healthy women. At the same time, an increase in the prothrombin index was established, indicating a decrease in the prothrombin coagulation time of the blood plasma of patients compared with the same indicator in the control group, which indicates excessive activation of the external mechanism of prothrombinase formation, in particular, VII plasma factor in ROM. Along with the violation of the first phase of blood coagulation in pregnant women with ROM, a shortening of the thrombin plasma coagulation time was established, which characterizes the final stage of the coagulation process - the conversion of fibrinogen to fibrin under the action of thrombin. It is known that the indicator of thrombin time is largely interconnected with the concentration of fibrinogen in the plasma and the presence of fibrin degradation products.

As it turned out, the activation of procoagulant mechanisms in pregnant women with ROM was accompanied by an increase in the plasma content of fibrinogen, paracoagulation products - soluble

fibrin-monomeric complexes (SFMC), and also D-dimers - the products of the cleavage of cross-linked insoluble fibrin. At the same time, significant changes in the activity of XIIa-kallikrein-dependent fibrinolysis were detected.

From the works of domestic and foreign authors, it is known that pro-inflammatory cytokines have the ability to change the adhesive-aggregation properties of platelets, erythrocytes, and initiate endothelial expression of factors involved in the regulation of blood coagulation and fibrinolysis activity.

**Table 1.** Coagulation hemostasis and activity of the fibrinolysis system in pregnant women with ROM

Indicators	Pregnant with ROM	Control Group
PTT (s)	23,51 $\pm$ 1.34*	30,56 $\pm$ 1,94
PTI (%)	116,83 $\pm$ 8,12	89,34 $\pm$ 7.54
PT (s)	12,85 $\pm$ 0,78*	16,62 $\pm$ 1,34
Fibrinogen (g/l)	4,12 $\pm$ 0,37*	2,77 $\pm$ 0,17
XIIa-kallikrein-dependent fibrinolysis (min)	8,12 $\pm$ 0,65*	5,88 $\pm$ 0,44
SFMC $\times$ 10-2 (g/l)	5,34 $\pm$ 0,45*	3,71 $\pm$ 0,25
D-dimers (ng/ml)	262,75 $\pm$ 9,87*	172,11 $\pm$ 9.87

Note: \* - significance of differences  $P < 0.05$  in comparison with the control group

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From the works of domestic and foreign authors, it is known that pro-inflammatory cytokines change the adhesive-aggregation properties of platelets, erythrocytes, and initiate endothelial expression of factors involved in the regulation of blood coagulation and fibrinolysis activity.

Thus, IL-1 $\beta$ , which inhibits the formation of disintegrin, metalloproteinases by endothelial cells and hepatocytes, increases the content of aggregation stimulants, procoagulants, fibrinolysis inhibitors, in particular, von Willebrom factor and platelet activating factor, is the most important regulator of vascular-platelet hemostasis, blood coagulation and fibrinolysis. IL-1 $\beta$  and TNF- $\alpha$  activate the blood coagulation process, stimulating the expression of tissue factor on endotheliocytes and monocytes, preventing the formation of thrombomodulin, reducing the activating effects on protein C.

In this regard, it was advisable to find out whether pro-inflammatory cytokines do not play the role of mediators that ensure the realization of procoagulant effects in ROM. To partially resolve this issue, the content of IL-1 $\beta$ , TNF- $\alpha$  in the peripheral blood of pregnant women with ROM was studied. As the results showed, in pregnant women with ROM a significant increase in the content of

pro-inflammatory cytokines in the blood plasma was found. So, the level of IL-1 $\beta$  exceeded the same indicator of blood plasma of women in the comparison group by 3 times, the level of TNF- $\alpha$  - by 2.6 times (Table 2). The increase in IL-1 $\beta$  and TNF- $\alpha$  level found in the blood of pregnant women with ROM that we found indicates that local and systemic activation of antigen-stimulated macrophages, NK cells, lymphocytes, neutrophils and other proinflammatory cells occur under conditions of premature discharge of water. cytokines.

Our data on the simultaneous activation of the external and internal pathways of prothrombinase activity formation, as well as the conversion of fibrinogen to fibrin and an increase in the plasma levels of IL-1 $\beta$  and TNF- $\alpha$  in pregnant women indicate that these pro-inflammatory cytokines stimulate procoagulant blood counts. At the same time, the activation of the complement system was detected, which was confirmed by a significant increase in the content of the complement component C3 in the serum of patients by 1.9 times and complement component C4 - 2.1 times compared with similar indicators of healthy pregnant women.

**Table 2.** The content of pro-inflammatory cytokines and C3, C4 fractions of the complement system in the blood serum of pregnant women with ROM

Indicators	Pregnant with ROM	Control Group
Interleukin -1 (IL -1) (pg/ml)	4,31 $\pm$ 0,34*	1,43 $\pm$ 0,14
Tumor Necrosis Factor (TNF- $\alpha$ ) (pg/ml)	4,03 $\pm$ 0,32*	1,54 $\pm$ 0,12
Component of complement C3 (g/l)	2,25 $\pm$ 0,18*	1,15 $\pm$ 1,34
Component of complement C4 (g/l)	0,57 $\pm$ 0,03*	0,27 $\pm$ 0,03
Insulin-like Growth Factor-1 (ng/ml)	151,24 $\pm$ 10,49*	276,45 $\pm$ 11,92

Note: \* - significance of differences  $P < 0.05$  in comparison with the control group

As is known, the activation of the complement system, due to the inclusion of the classical and alternative cascades, is closely interconnected with the activation of the XII Hageman factor, kallikrein-kinin system, platelets, the formation of immune complexes and metabolic acidosis, which is accompanied by activation of the C3 fraction and increased blood coagulation by the internal mechanism. Moreover, the expression of IL-1 and TNF- $\alpha$  support complement activation processes, providing the release of plasminogen activator inhibitor, tissue factor, from monocytes, macrophages and endothelial cells, which is accompanied by platelet aggregation. Proteolytic enzymes of the complement system stimulate the release of biologically active substances from platelets, micro-, macrophages, mast cells, cause retraction of endothelial cells, which contributes to the adhesion and aggregation of platelets on exposed collagen of the vascular wall. Activated platelets and leukocytes close the vicious circle, inducing the formation of new portions of active complement fractions, in particular C3a. The results of the studies suggest a pathogenetic

relationship between the increase in the levels of pro-inflammatory cytokines IL-1 $\beta$  and TNF- $\alpha$ , C3-, C4-fractions of complement and procoagulant shifts in pregnant women with ROM.

The nature of changes in the content of insulin-like growth factor (IGF1) in the blood serum of pregnant women with ROM is shown in Table 2. The maximum levels of IGF-1 were observed in pregnant women with a physiological course - 276.45  $\pm$  11.92 ng / ml. The minimum concentration of IGF-1 was detected in pregnant women with ROM and amounted to 151.24  $\pm$  10.49 ng / ml. Thus, when considering the dynamics of changes in the content of IGF-1 in the blood serum of pregnant women with ROM we found significant changes in the indicator, manifested in its significant decrease. A decrease in the level of IGF-1 by 28% with an increase in serum insulin concentration by 164% reliably predicts conditions that threaten the life of the fetus. IGF-1 stimulates the proliferation of cells of all tissues, primarily cartilage, bone, muscle, has a pronounced anti-apoptotic effect. The synthesis of IGF-1 is stimulated by growth hormone and depends on many factors, including good nutrition.

## 5. Findings

A pathogenetic relationship between the accumulation of IL-1 $\beta$ , TNF- $\alpha$ , C3-, C4-fractions of the complement system and activation of procoagulant mechanisms in the blood of pregnant women was revealed. The complement system can act as a connecting pathogenetic link between shifts of the cytokine status and activation of coagulation hemostasis mechanisms at the stage of pronounced clinical manifestations of acute inflammatory lesion of the uterine appendages. Determination of serum levels of IL-1 $\beta$ , TNF- $\alpha$ , C3, C4 complement fractions in pregnant women with ROM can be used to predict the development and timely correction of changes in blood coagulation potential, which will expand the possibilities of successfully choosing an adequate treatment tactic and timely prevention of developing complications during pregnancy.

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