ASSESSMENT OF BIOCHEMICAL INDICATORS IN PREGNANT WOMEN WITH THREATING PRETERM LABOR

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Annotation. *It was found that re-pregnancy, re-birth, miscarriage, a history of non-developing pregnancy, medical abortion, inflammatory pathologies of the reproductive system, etc. were also registered in pregnant women at risk of preterm birth. However, in order to identify real risk factors for PR, the activities of the most important components of the homeostasis system were determined, such as the presence of endotoxicosis, activation of lipid peroxidation, antioxidant protection, cytokine intensification, the state of the reactive proteins of the body, the content of the product of purine metabolism, and the stability of the hemostasis system.*

Keywords: *premature birth, antioxidant system, endogenous intoxication syndrome, cytokines.*

ОЦЕНКА БИОХИМИЧЕСКИХ ПОКАЗАТЕЛЕЙ У БЕРЕМЕННЫХ С УГРОЗОЙ ПРЕЖДЕВРЕМЕННЫХ РОДОВ

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Аннотация. *Установлено, что у беременных из группы риска преждевременных родов также зарегистрированы повторная беременность, повторные роды, выкидыш, неразвивающаяся беременность в анамнезе, медикаментозный аборт, воспалительная патология репродуктивной системы и др. Однако для выявления реальных факторов риска развития ПР определяли активность важнейших компонентов системы гомеостаза, таких как наличие эндотоксикоза, активация перекисного окисления липидов, антиоксидантная защита, интенсификация цитокинов, состояние реактивных белков. организма, содержание продуктов пуринового обмена и стабильность системы гемостаза.*

Ключевые слова: *преждевременные роды, антиоксидантная система, синдром эндогенной интоксикации, цитокины.*

ERTA TUG'ILISH XAVFI BO'LGAN HOMILADOR AYOLLARDA BIOKIMYOVIY KO'RSATKICHLARNI BAHOLASH

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Annotatsiya. *Erta tug'ilish xavfi ostida bo'lgan homilador ayollarda ham takroriy homiladorlik, qayta tug'ilish, homila tushishi, rivojlanmagan homiladorlik tarixi, tibbiy abort, reproduktiv tizimning yallig'lanish patologiyalari va boshqalar qayd etilganligi aniqlandi. Shu bilan birga, PR uchun haqiqiy xavf omillarini aniqlash uchun gomeostaz tizimining eng muhim tarkibiy qismlarining faoliyati aniqlandi, masalan, endotoksikoz mavjudligi, lipid peroksidatsiyasining faollashishi, antioksidant himoyasi, sitokinlarning kuchayishi, reaktiv oqsillarning holati. tananing, purin almashinuvi mahsulotining tarkibi va gemostaz tizimining barqarorligi.*

Kalit so'zlar: *erta tug'ilish, antioksidant tizim, endogen intoksikatsiya sindromi, sitokinlar.*

Preterm birth does not raise doubts among scientists around the world, primarily because of the significant contribution to perinatal morbidity and mortality. According to the WHO global report “Born too soon” (2012), about 15 million children are born prematurely in the world every year, 1 million under the age of 5 years die from health problems associated with prematurity [13; 14; 16;]. The stillbirth rate in untimely delivery is 8-13 times higher than in term delivery. The frequency of preterm births on Earth varies from 5 to 18% and has not been decreasing over the past 20 years [9; 10; 15].

An important aspect in solving the problem of PR and their prevention is the identification of non-specific natural reactions of the body that initiate abortion.

Endogenous intoxication syndrome (ESI) develops in all pathological conditions associated with the blockade of the body's detoxification systems [2; 3; 4]. An important pathophysiological mechanism for the development of endotoxicosis is the activation of LPO processes [1]. In the literature, we did not find data on the relationship between lipid peroxida-

tion processes in the placenta of women whose pregnancy ended in premature birth and the formation of endogenous intoxication syndrome in it.

The leading pathogenetic factor of various pathological processes in the body is the increased generation of reactive oxygen species (ROS) as a result of an imbalance of pro- and antioxidant systems and the development of oxidative (oxidative) stress [7; eleven; 12;].

According to the literature, about 40% of cases of PR are caused by infectious factors [4; 5; 6]. The leading pathogenetic mechanism in such cases is the development of a nonspecific systemic inflammatory response (SIR) of the body to infectious agents. In WIR syndrome, local tissue damage in the area of pathogen inoculation causes a combination of systemic reactions. This process is associated with dysfunction of innate and acquired immunities and is manifested by a violation of the ratio of pro- and anti-inflammatory cytokines. Currently, the role of cytokines in the development of preterm labor is being studied very actively [7]. Thus, there is evidence that an increase in the level of pro-inflammatory cytokines in the contents of the cervical canal indicates a possible risk of PR [8].

One of the key stages in the development of preterm labor is oxidative stress, described in modern literature, its role is reduced to the activation of a systemic inflammatory response, in which metabolic disorders develop in the body of a pregnant woman.

The balance of oxidative/antioxidant status is a process that begins before birth, and premature babies are particularly susceptible to oxidative stress. The combination of hyperoxia, which enhances the production of reactive oxygen species, and low levels of antioxidants causes oxidative stress, inflammation, and even apoptosis, thereby increasing mortality and morbidity. Consistent with the mechanisms of oxidative stress and the lack of research in this area, in this prospective study we aimed to compare serum levels of prooxidant-antioxidant balance in preterm pregnant women.

The aim of our study was, development of a predictive model for the likelihood of preterm birth based on the study of anamnestic risk factors and the results of a comprehensive clinical, laboratory and instrumental study.

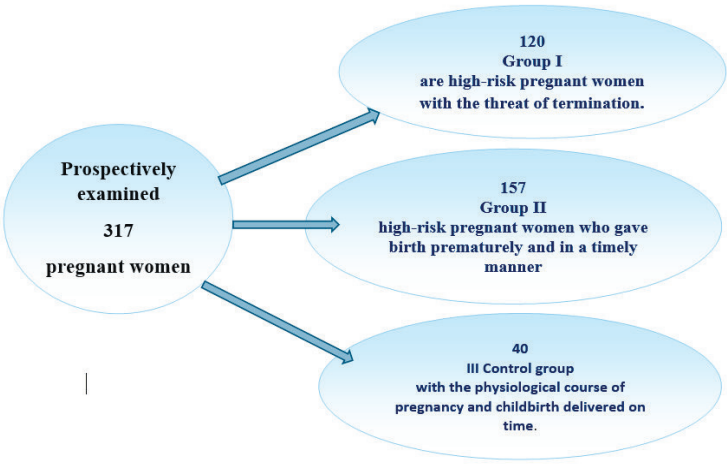
Materials and methods of research: to determine one of the causes of the links in the pathogenesis of PR, we observed 317 pregnant women with threatening PR at a gestational age of 22-34 weeks. Patients were included in the study as they applied and were hospitalized in the department of pathology of pregnant women in the Regional Perinatal Center of Samarkand for the period 2020-2023.

As a result of a prospective study, data such as baseline clinical characteristics, features of the course of pregnancy, as well as its outcomes in 317 pregnant women with threatening and PR were analyzed.

Patients were included in the study as they were referred. According to the data of both clinical, laboratory and functional examination methods, as well as the diagnosis, as well as in accordance with the developed criteria for inclusion in the study, all pregnant women were divided into 3 groups.

The first group (I, n=120) - pregnant women at high risk, with the threat of abortion.

The second group (II, n=157) - high-risk pregnant women who gave birth prematurely and in a timely manner.



The third group - (control, n=40) - examined 40 pregnant women with a physiological course of pregnancy and childbirth, delivered on time. (fig.1)

Figure 1. **Group distribution design**

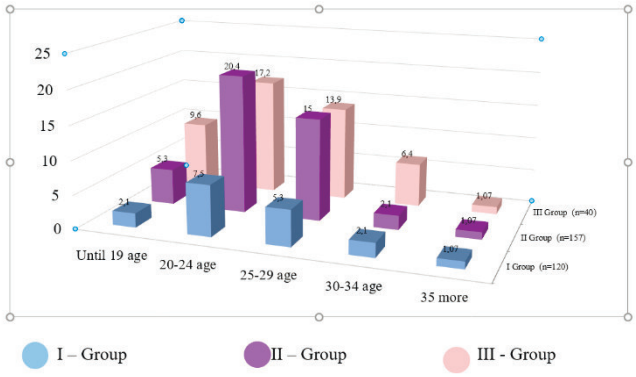


Figure 2. **Distribution of surveyed women by age**

All patients included in the study underwent a standard set of examinations in accordance with the order of the Ministry of Health of the Republic of Uzbekistan dated March 11, 2019 No. ZRU-528 "On the protection of the reproductive health of citizens".

The age of women ranged from 19 to 38 years. The youngest age at the onset of preterm birth is 18 years, and later - at 38 years, inaveraging 27+2.9 in all groups. (fig.2)

In the analysis of the social position, city dwellers prevailed.According to the social status among the surveyed were: students - 18.2%, working -40.3%, housewives -41.5%.

When studying the parity, the highest frequency of multi-pregnant women was observed in the second group, primigravidas - in the first. In group 3, both primigravidas and recurrent pregnancies occurred with approximately equal frequency. Primiparous - to a greater extent noted in the second, multiparous - in the first.

The frequency of induced labor was 21 (17.5%) of the first group and 77 (49%) of the second, and spontaneous - 99 (82.5%) and 80 (51%) (Table 1).

According to the anamnesis, it was revealed that the number of primigravidas and re-pregnant women in the first group were 78 (65.0%) and 42 (35.0%), and the second - 62 (39.4%) and 95 (60.5%). Primiparous and multiparous were 89 (74.1%) and 31 (25.8%) women of the first group and 70 (44.5%) and 87 (55.4%) of the second.

Obstetric and gynecological history showed that miscarriage was 74 (61.1%) and 43 (27.3%), respectively. Non-developing pregnancies - 32 (26.6%) and 25 (15.9%), Hypertension - 51 (42.5%) and 69 (43.9%), and medical abortion - 30 (25.0%) and 33 (21.0%) respectively.

It is important to note that inflammatory diseases such as salpingoophoritis, endometritis, endomyometritis, etc., of the pelvic organs were recorded in 57 (47.5%) women of the first group and 41 (26.1%) in the second (Table 1).

Thus, it was noted that high risk factors threat of termination of pregnancy and premature birth are primigravida, first childbirth, miscarriage, various kinds of abortions (spontaneous, medical), HPPT. They can negatively blame the course of pregnancy.

One of the most important issues that concerns obstetricians around the world is the optimal tactics of delivery in PR. Taking into account that at present there is no single concept of conducting PR.

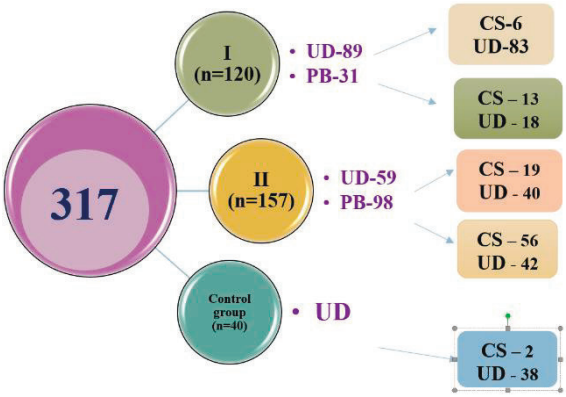


Figure 3. **Indicators of birth outcomes of the study group**

UD – urgent delivery
PB – premature birth
CS – cesarian section

According to the results of analyzes of timely and PR, it was revealed that among all the studied groups (n=317), childbirth ended more often through the natural birth canal (Fig. 3).

According to the analysis of the outcome of childbirth in the prospective group, in group I, SR was 74.1% (89) of cases, and PR was 25.9% (31), in the second group, SR was 37.5% (59), and PR was 62, 5% (98) of cases.

In recent years, the systemic inflammatory response syndrome (SIRS) and oxidative stress have played an important role in the pathogenesis of PR development. The development of oxidative stress is due to an imbalance between the generation and elimination of reactive oxygen species (ROS). Our research results, presented in the table, showed that the content of lipid peroxidation products in the blood plasma of pregnant women in the control group was 41.54±3.67 μmol/l. It was noted that with the progression of the disease, the content of TBA-active products significantly increases, 78.14±6.89 μmol/l in pregnant women of group II versus 41.54±3.67 μmol/l in healthy pregnant women ($p<0.05$).

Simultaneously with the activation of oxidative processes, there is an increase in the activity of blood catalase in pregnant women of group I up to 13.57±1.56 cat/l, group II up to values of -11.32±1.27 cat/l, against 7.98±0 ,81cat/l to the control group, which indicates an increase in the antioxidant activity of the blood. An increase in the activity of blood catalase in patients of group II indicates the depletion of the antioxidant defense system, which is indirectly confirmed by the activity of SOD and the content of TBA-active products in this group, compared with the control. There is a decrease in SOD activity in group I by 45%, in group II by 64% compared with healthy pregnant women. There are also suggestions that it is the consequences of decompensation of antioxidant protection that contribute to the accumulation of LPO products.

Table 1.

Analysis of LPO-AOS indicators in pregnant women with premature childbirth

Indicators	1 group (n=41)	II group (n=42)	III-group (n=35)
TBA-active products, μmol/l	67.23±5.78	78.14±6.89*	41.54±3.67
Catalase activity cat/l	13.57±1.56*	11.32±1.27*	7.98±0.81
SOD activity IU/1 mg of protein	3.46±0.29*	2.31±0.21*	6.34±0.58

Note: * - the difference is significant when compared with the control group, p<0.05;

The physiological course of pregnancy is accompanied by a certain restructuring of the immune system, which ensures the tolerance of the mother's body to the antigens of the fetal egg and gestation. It has now become apparent that the defense of the fetus against a damaging maternal immune response is based on a complex mechanism and that communication between different steps in the cascade of events is mediated by cytokines.

It has been established that during the normal course of pregnancy, the cytokine status shifts towards immunosuppressive cytokines (IL-4, IL-10, TGF-β), which inhibit cellular immunity reactions and stimulate the production of blocking antibodies. In our study, the level of anti-inflammatory cytokines IL-4 and IL-10, respectively, was significantly lower by 1.6 and 2.5 times than in the control group. In this situation, the most informative indicators were IL-10, low values of which can serve as a marker of the risk of developing PR.

Table 2.

Indicators of cytokine status in pregnant women with threatened preterm labor

Index	1 group (n=41)	II group (n=42)	III-group (n=35)
IL-1 c, pg/ml	3.31± 0.27*	4.35±0.38 *	2.15±0.18
IL-2, pg/ml	9.53±0.84	7.54± 0.64*	11.14±0.91
IL-4, pg/ml	2.24± 0.17*	2.15± 0.13*	3.58±0.19
IL-6, pg/ml	3.78±0.35*	4.83±0.39*	2.38±0.19
IL-8, pg/ml	8.51± 0.79*	10.98± 1.03*	5.42±0.51
IL-10, pg/ml	9.01±0.82*	7.36±0.62*	22.48±1.96
TNF-a, pg/ml	2.68± 0.27*	3.14± 0.23*	1.76±0.14

Note: * - the difference is significant when compared with the control group, p<0.05;

Therefore, in pregnant women at risk of preterm birth, significant disturbances occur in the cytokine system, which may be accompanied by the penetration of pro-inflammatory cytokines into the systemic circulation, which, in our opinion, contributes to the pathogenesis of PR. In addition, an increase in TNF-αand cytokines can serve as markers of inflammation of the endothelium of the uterine vessels, and also indicate a high permeability of the membranes of the membranes, which, in our opinion, is one of the reasons for the mechanisms of preterm labor and amniotic fluid rupture.

Particular attention is given to pregnant women at high risk of PR, in which the level of ceruloplasmin was lower than the control group.

As the results of the study showed, in the first group the level of ceruloplasmin was 12.6 g/l, in the second group it was reduced to 10.4 g/l in the control group 20.2 g/l.

In a comparative analysis of the level of another protein S100 in the serum of pregnant women, a tendency to its decrease was noted in groups I and II compared with patients in the CG. The average content of S100B protein in the blood serum of women in the control group was 60.9±5.08 mc/ml, while in the first group bql was reduced to 32.80±13.41 mc/ml, in the second group 33.90±10 .21 μ/ml (>0.05). In women who experienced PR after a threat of miscarriage in the period from 22 to 34 weeks, a decrease in the level of S100B protein was found compared to pregnant women in the control group (33.48±7.3 and 60.9±5.08 mc/ml, <0.01).

Table 3.

The content of S-100 protein in women of the studied groups

Index	1 group (n=41)	II group (n=42)	III-group (n=35)
S-100 protein	32.80±13.41	33.90±10.21	60.9±5.08

Note: *-significance of differences P <0.05

Serum content of S100B, equal to or less than 43.66 μg/ml, is also a new prognostic criterion for AR and increases the risk of their onset after a threatened abortion at 22–34 weeks by 3.15 times.

When studying the analysis of hemostasis, it was demonstrated that preterm labor is characterized by changes in coagulation and fibrinolytic activity in the form of hypercoagulability and hypofibrinolysis.

In women of the main group, a shortening of the APTT time and PT by 33.3% and 31.2% (p<0.05) relative to the control group was noted.

In high-risk pregnant women who gave birth prematurely, APTT and PT were lower than the control group by 20.1 and 25.4% (p<0.05).

In the group where pregnant women at high risk of PR who gave birth in a timely manner, the time of APTT and PT was reduced by 15.6 and 17.1% (p<0.05) (Fig. 4).

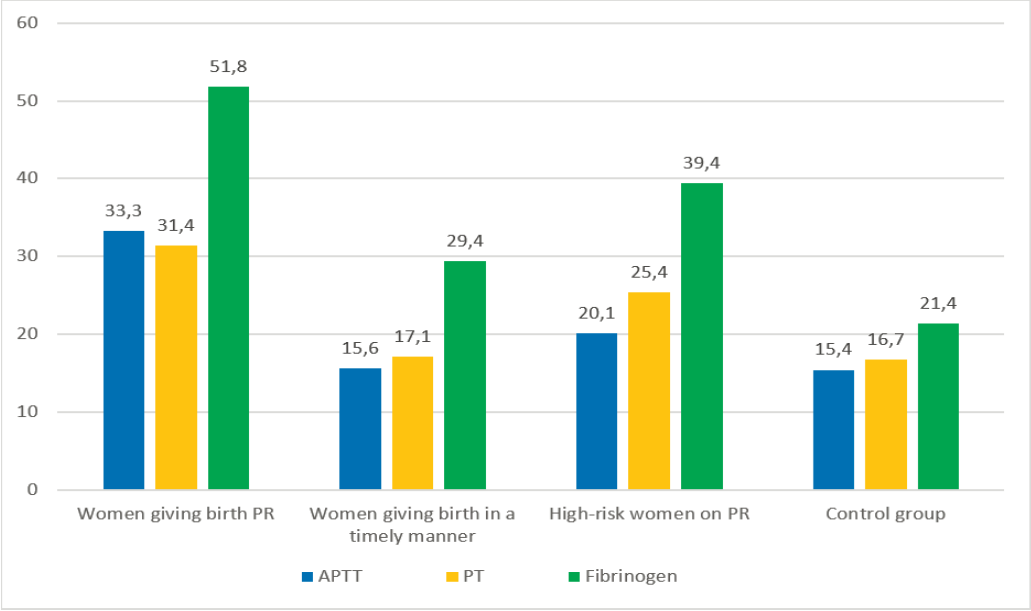


Figure 4. **Study of the hemostasis system in the studied groups**

APTT - activated partial thromboplastin time
PT – Prothrombin time

When studying the process of fibrinolysis in PR, it was found that the amount of fibrinogen was exceeded in the main group by 51.8, 39.4 and ($p<0.05$) when compared with the control group

So, the development of preterm labor is accompanied by the formation of endogenous intoxication in pregnant women. With a high risk of PR and the threat of interruption, the intensity of toxemia was recorded to the greatest extent relative to other women who gave birth prematurely and in a timely manner.

Thus, one of the pathogenetic factors of PR is the activation of the processes of free-radical destabilization of biological membranes, accompanied by an excessive increase in the content of peroxide compounds in the blood, as well as malondialdehyde, diene conjugates and catalase with a pronounced universal cytopathogenic effect and a decrease in the amount of SOD.

Thus, our results of the study allow us to state that the study of the cytokine balance is significant for assessing the direction of the immune response, as well as the outcome of pregnancy for the mother and fetus.

Therefore, the results of our studies indicate that the study of the dependence of endothelial dysfunction on the profile of factors affecting the endothelium is a promising direction in the development of methods for the prevention and treatment of preterm birth.

Summing up the results of these study groups, it was found that re-pregnancy, re-birth, miscarriage, a history of non-developing pregnancy, medical abortion, inflammatory pathologies of the reproductive system, etc. were also recorded in pregnant women at risk of preterm birth. However, in order to identify real risk factors for PR, the activities of the most important components of the homeostasis system were determined, such as the presence of endotoxicosis, activation of lipid peroxidation, antioxidant protection, cytokine intensification, the state of the reactive proteins of the body, the content of the product of purine metabolism, and the stability of the hemostasis system.

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