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Особенности цитокинового профиля у беременных с угрозой самопроизвольного выкидыша на фоне дисбиоза кишечника

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Актуальность. Системная эндотоксинемия, возникающая в результате дисбактериоза кишечника, активирует Th1-иммунный ответ и избыточную выработку провоспалительных цитокинов, что может быть причиной прерывания беременности.

Цель — изучить особенности цитокинового профиля у женщин с угрозой прерывания беременности и его зависимость от состояния микробиоценоза кишечника и уровня эндотоксинемии.

Материалы и методы исследования. В исследовании приняли участие 87 женщин в возрасте от 18 до 43 лет в сроке беременности от 6 до 22 нед. Основную группу составили 50 женщин с угрозой прерывания беременности. В контрольную группу вошли 37 женщин с физиологически протекающей беременностью. Всем беременным проводили качественную и количественную оценку состояния микрофлоры кишечника методом ПЦР в режиме реального времени, исследование уровня эндотоксинемии и цитокинового профиля.

Результаты исследования. У 30 % ($n = 15$) пациентов основной группы был выявлен дисбактериоз кишечника I степени, у 46 % ($n = 23$) — II степени, у 24 % ($n = 12$) — III степени. В контрольной группе нарушения в составе кишечной микрофлоры соответствовали I степени дисбактериоза у 67,6 % ($n = 25$) и II степени у 32,4 % ($n = 12$) женщин; случаев тяжелого дисбиоза в контрольной группе обнаружено не было. Уровень эндотоксинемии у беременных основной группы составил $0,57 \pm 0,02$ нмоль/мл и классифицирован как «повышенный». Уровень эндотоксина в сыворотке крови у беременных контрольной группы составил $0,34 \pm 0,02$ нмоль/мл и соответствовал «низкому» ($p < 0,001$), при этом была установлена прямая сильная корреляционная связь ($r = 0,8$, $p < 0,001$) между степенью дисбактериоза кишечника и уровнем эндотоксинемии. Цитокиновый профиль у пациентов основной группы характеризовался статистически значимым повышением концентрации провоспалительных цитокинов (ИЛ-1 β — $4,9 \pm 1,6$ пг/мл, ИЛ-6 — $4,8 \pm 1,5$ пг/мл) на фоне более низких показателей противовоспалительного ИЛ-10 ($18,0 \pm 4,5$ пг/мл) по сравнению с группой контроля, где показатели составили: ИЛ-1 β — $1,8 \pm 0,2$ пг/мл, ИЛ-6 — $2,1 \pm 0,2$ пг/мл, ИЛ-10 — $30,3 \pm 4,4$ пг/мл. Отмечена статистически значимая средняя по силе положительная связь уровня эндотоксинемии с концентрацией провоспалительных цитокинов и слабая отрицательная связь с показателем противовоспалительного ИЛ-10.

Выводы. Эндотоксинемия, возникающая в результате нарушения микрофлоры кишечника у беременных и активирующая иммунную систему по провоспалительному типу, может служить одним из пусковых факторов в патогенезе невынашивания беременности.

Ключевые слова: невынашивание беременности; дисбактериоз кишечника; эндотоксин; эндотоксин-индуцированный аборт; цитокиновый профиль; цитокины; провоспалительные цитокины; противовоспалительные цитокины.

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Cytokine profile in women with threatened miscarriage and intestinal dysbiosis

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HYPOTHESIS/AIMS OF STUDY: Systemic endotoxemia resulting from intestinal dysbiosis activates the Th1 immune response and excessive production of proinflammatory cytokines, which can cause abortion. This study was aimed at assessing interleukin levels in women with the threat of miscarriage and exploring their dependence on intestinal microbiocenosis and the level of endotoxemia.

STUDY DESIGN, MATERIALS AND METHODS: The study involved 87 women aged 18 to 43 years in pregnancy from six to 22 weeks. The main group consisted of 50 women with a threatened miscarriage. The control group included 37 women with normal pregnancy. A qualitative and quantitative analysis of intestinal microbiocenosis was performed by real-time PCR, with endotoxin and interleukin levels evaluated using conventional methods.

RESULTS: In patients of the main group, intestinal dysbiosis of grade I was detected in 30 % ($n = 15$), of grade II in 46 % ($n = 23$), and of grade III in 24 % ($n = 12$) of cases. In the control group, intestinal microflora disorders corresponded to grade I dysbiosis in 67.6 % ($n = 25$) and grade II dysbiosis in 32.4 % ($n = 12$) of cases, there being no cases of severe dysbiosis revealed. The level of endotoxin in pregnant women of the main group was 0.57 ± 0.02 nmol / ml and was classified as "increased". The endotoxin level in the blood serum of pregnant women of the control group was 0.34 ± 0.02 nmol / ml and was characterized as "low" ($p < 0.001$). A strong correlation was found ($r = 0.8$, $p < 0.001$) between the grade of intestinal dysbiosis and the level of endotoxemia. The cytokine profile in patients of the main group was characterized by increased concentrations of pro-inflammatory cytokines (IL-1 β — 4.9 ± 1.6 pg / ml, IL-6 — 4.8 ± 1.5 pg / ml) and a decreased concentration of anti-inflammatory cytokine (IL-10 — 18.0 ± 4.5 pg / ml), when compared to the control group (IL-1 β — 1.8 ± 0.2 pg / ml, IL-6 — 2.1 ± 0.2 pg / ml, IL-10 — 30.3 ± 4.4 pg/ml). There were a statistically significant moderate positive correlation between the level of endotoxemia and the concentration of pro-inflammatory cytokines and a weak negative correlation between the endotoxin level and the concentration of anti-inflammatory IL-10.

CONCLUSION: Endotoxemia, which occurs as a result of intestinal microflora dysbiosis and activates pro-inflammatory pathways, can really be as a triggering factor in the pathogenesis of miscarriage in pregnant women.

Keywords: miscarriage; intestinal dysbiosis; endotoxin; endotoxin-induced abortion; cytokine profile; cytokines; pro-inflammatory cytokines; anti-inflammatory cytokines.

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INTRODUCTION

During pregnancy, the intestinal microbiota in women undergoes a number of structural and functional changes due to the restructuring of the endocrine and immune systems and few anatomical aspects due to an increase in uterine volume. As a result of slowing intestinal motility and reducing the tone of smooth muscles of the intestinal wall, gallbladder, and biliary tract, the exposure of intestinal contents in the terminal sections of the colon increases, leading to reproduction and activation of opportunistic microflora (OM) [1–3]. Conditions are created for the entry of endotoxin, a lipopolysaccharide, into the systemic circulation of the outer cell membrane of gram-negative bacteria, which can cause a complex immune and inflammatory response both through a direct destructive effect on cell membranes and indirect effect through cytokine cascade induction.

During pregnancy, the immune system is known to switch the immune response mediated by T-helper type 1 (Th1) to the immune response mediated by T-helper type 2 (Th2) [4, 5]. Th1 activation leads to the production of proinflammatory cytokines, namely, tumor necrosis factor alpha (TNF- α) and interleukins (IL) such as IL-1 β , IL-2, IL-6, IL-8, and IL-12, which stimulate the proliferation of cytotoxic T-lymphocytes and activate macrophages by participating in inflammatory and immune responses [6]. Th2 produce anti-inflammatory cytokines IL-4, IL-5, IL-9, IL-10, and IL-13, which suppress the processes of embryo rejection and ensure normal trophoblast invasion, preventing inflammatory and thrombotic secondary reactions to trophoblast [7, 8].

In systemic endotoxemia in a pregnant woman, through successive pathobiochemical reactions (Fig. 1), proinflammatory cytokines are produced excessively, which activate apoptosis of trophoblast cells and destruction of the vascular endothelium through an inhibitory effect on the products of growth factors, excessive cytotoxic activation of natural killer cells, and phagocytic activity of macrophages in the endometrium and decidual membrane [9, 10].

Moreover, they increase the production of prothrombinase and activation of coagulation mechanisms and reduce the anticoagulant and fibrinolytic activity of the blood, which results in thrombogenesis in the trophoblast vessels. Damage to the trophoblast and vascular endothelium causes the production of antiphospholipid antibodies and anti-DNA antibodies, the formation of a specific cytotoxic immune response against fetal antigens [4, 7, 11, 12].

An increased amount of proinflammatory cytokines enhances the production of prostaglandins in the amnion and decidual membrane, which leads to stimulation of uterine contractions, desquamation of the decidual membrane, and termination of pregnancy.

Thus, along with the known causes of miscarriage, intestinal dysbiosis may be a source of systemic endotoxemia

and, as a consequence, a cause of the complicated course of pregnancy [13]. The study of this condition is a crucial scientific aspect, the results of which can be widely used in clinical practice.

This study aimed to analyze the aspects of the cytokine profile in women with threatened miscarriage and its dependence on the state of intestinal microbiocenosis and the level of endotoxemia.

MATERIALS AND METHODS

The study included 87 women aged 18–43 years (average age, 28 ± 0.5 years) at a gestational age of 6–22 weeks. The main group consisted of 50 women hospitalized in the gynecological department of the clinic of obstetrics and gynecology of the Kirov Military Medical Academy with threatened miscarriage. The control group included 37 women with normal pregnancies who were registered for pregnancy in the maternity welfare center of the clinic of obstetrics and gynecology. Scientific work was approved by the independent ethical committee of the Military Medical Academy.

The exclusion criteria were pregnancy resulting from the use of assisted reproductive technologies; pregnancy proceeding in presence of confirmed genetic, anatomical, endocrine, immunological, and thrombophilic risk factors for miscarriage; the presence of infections in pregnant women, including sexually transmitted infections; multifetal pregnancy; acute inflammatory diseases; and exacerbation of extragenital pathology.

The qualitative and quantitative composition of the intestinal microflora in all pregnant women was assessed

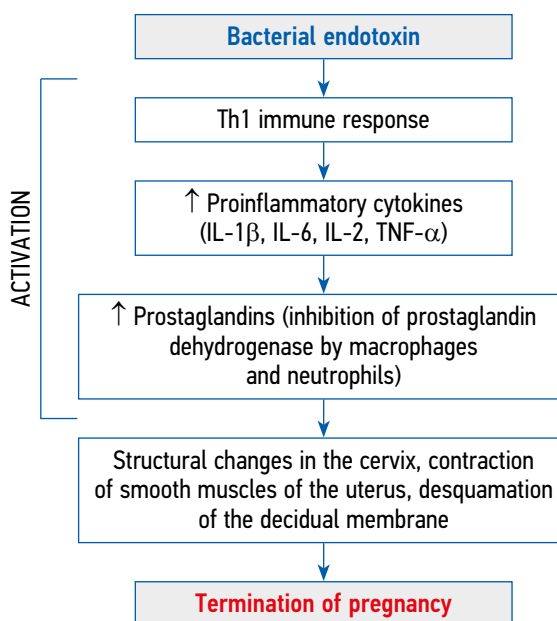


Fig. 1. The mechanism of the bacterial endotoxin effect on the uterus

by the method of polymerase chain reaction (PCR) in real time. *Bacteroides* spp., *Prevotella* spp. (type *Bacteroidetes*), *Parabacteroides* spp., *Clostridium leptum* group (including *Faecalibacterium prausnitzii* and some species of *Eubacterium* and *Ruminococcus*, type *Firmicutes*), *Blautia* spp., *Bifidobacterium* spp., *Lactobacillus* spp., *Akkermansia* spp., and *Methanobrevibacter* spp. were determined from a number of commensal microorganisms in the study. Opportunistic species of microorganisms, namely, *Campylobacter* spp., *Clostridium dif.*, *Enterobacter* spp., *Streptococcus* spp., *Pseudomonas* spp., and *Staphylococcus* spp., were studied.

The grade of abnormality of the intestinal microflora was assessed according to the classification based on the bacteriological method of research and approved by the order of the Ministry of Health of the Russian Federation No. 231 of June 9, 2003, considering the current information on the species composition of the intestinal microbiocenosis, as well as the working instructions for the study of the colon microbiota by PCR with fluorescence detection in real time "Colonoflor" (RF, RU No. RZN 2019/9479).

Grade I (mild) is manifested by deficiency of representatives of normal biota (decrease in the number of microorganisms by one order of magnitude), the amount of OM $<10^4$ /L.

Grade II (moderate) is manifested by the presence of OM ($>10^4$ but $<10^6$ /L) with a deficiency of normobiota (with a decrease of less than two orders of magnitude).

Grade III (severe) is manifested by the excessive growth of OM ($>10^6$ /L) with a pronounced deficiency of normobiota (with a decrease of more than two orders of magnitude).

In order to assess the possible systemic effect of intestinal dysbiosis on the body of a pregnant woman, the level of endotoxemia was studied in 62 women (32 women from the main group and 30 women from the control group). The blood was examined using the method of gas chromatography — mass spectrometry [14]. The results

of endotoxemia were assessed in accordance with the classification of J. Marshall (2004). The endotoxin index from 0 to 0.39 nmol/ml was considered low, that from 0.4 to 0.59 nmol/ml was considered increased, and that from 0.6 to 1.0 nmol/ml was considered high.

The cytokine status was determined in 50 women examined (main group, 30; control group, 20); the levels of IL-1, IL-6, and IL-10 in the blood serum were assessed by the method of enzyme-linked immunosorbent assay (Vector-Best-Baltika, Russia) on the immunochemical analyzer LisaScan EM (Erba Mannheim, Germany). In this study, venous blood was taken on an empty stomach in the morning.

Statistical data analysis was performed using the IBM SPSS Statistics 22 software package (Armonk, NY, USA). The work used methods of variation statistics with a differentiated assessment and methods of statistical analysis depending on the type of distribution of attributes in the samples. Differences were considered statistically significant when determining the probability of 95% ($p < 0.05$).

RESULTS

Assessment of intestinal microflora by real-time PCR confirmed the diagnosis of intestinal dysbiosis in 100% of the pregnant women examined.

In patients of the main group, grade I intestinal dysbiosis was revealed in 30% ($n = 15$) of cases, grade II in 46% ($n = 23$), and grade III in 24% ($n = 12$). Moreover, in the control group patients, disorders in the intestinal microflora composition were revealed, corresponding mainly to grade I dysbiosis (67.6%, $n = 25$) and, to a lesser extent, to grade II (32.4%, $n = 12$); no cases of severe dysbiosis were identified. The differences between the relative values in both groups were statistically significant when comparing the groups by the number of cases of grade I dysbiosis ($\chi^2 = 12$; $df = 1$; $p < 0.001$) and grade III ($\chi^2 = 10.3$; $df = 1$; $p = 0.01$).

When studying the qualitative and quantitative composition of the intestinal microflora in patients of the main group, a statistically significant decrease in the number of representatives of intestinal normal flora (*Lactobacillus* spp., *Bifidobacterium* spp.) compared to the control group was noted, as well as a statistically significant high concentration of OM. Microbiological disorders of the intestinal flora in the control group were characterized mainly by a decrease in the intensity of the colon colonization with normal flora relative to the reference values.

Blood test analysis by gas chromatography-mass spectrometry revealed that the average level of endotoxin in the blood serum in pregnant women of the main group was 0.57 ± 0.02 nmol/ml and was classified as "increased." The level of lipopolysaccharides in the blood

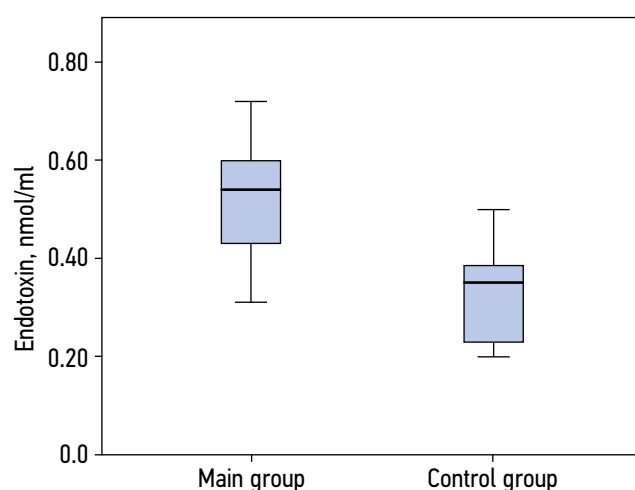


Fig. 2. Average level of endotoxemia of pregnant women in the compared groups

Table 1. Indicators of the cytokine profile in pregnant women of the main and control groups

Indicator	Main group (n = 30)	Control group (n = 20)	Statistical significance (Mann-Whitney test)
IL-1 β , pg/ml	4.9 \pm 1.6	1.8 \pm 0.2	$U = 86$; $Z = -3.6$; $p < 0.001^*$
IL-6, pg/ml	4.8 \pm 1.5	2.1 \pm 0.2	$U = 148$; $Z = -2.5$; $p = 0.012^*$
IL-10, pg/ml	18.04 \pm 4.5	30.3 \pm 4.4	$U = 180$; $Z = -1.7$; $p = 0.08$

Table 2. Relationships between indicators of endotoxin and interleukins in women of the groups under study

Attribute pairs		Spearman's rank correlation coefficient	Statistical significance, p
Endotoxin	IL-1	0.51	0.025*
Endotoxin	IL-6	0.55	0.017*
Endotoxin	IL-10	-0.3	0.17
IL-1	IL-6	0.92	<0.001*
IL-6	IL-10	0.2	0.2
IL-1	IL-10	0.05	0.8

*Statistically significant differences.

serum of pregnant women in the control group was 0.34 ± 0.02 nmol/ml and was characterized as "low" (Fig. 2). Intergroup differences were statistically significant ($U = 51.5$; $Z = -4.7$; $p < 0.001$).

There was a direct strong correlation ($r = 0.8$; $p < 0.001$) between the grade of intestinal dysbiosis and the level of endotoxemia, which is associated with pronounced disorders of the intestinal microbiocenosis due to a significantly larger number of microorganisms with a high pathogenic potential.

Analysis of the level of cytokines in the blood serum (Table 1) showed changes in the cytokine balance in the main group, characterized by a statistically significant increase in the concentration of proinflammatory cytokines (IL-1 β , 4.9 ± 1.6 pg/ml; IL-6, 4.8 ± 1.5 pg/ml) in presence of lower indicators of anti-inflammatory IL-10 (18.04 ± 4.5 pg/ml) compared with the control group (1.8 ± 0.2 ; 2.1 ± 0.2 ; 30.3 ± 4.4 pg/ml, respectively).

Based on a comparative analysis of the ratios of pro- and anti-inflammatory cytokines, a shift in the balance toward the production of anti-inflammatory cytokines in female patients of both groups was noted, which has a favorable prognostic value for the outcome of pregnancy. The ratio of IL-10 to IL-1 β in the female patients of the main group averaged 7.7 ± 2.0 and that of IL-10 to IL-6 was 5.9 ± 1.7 , and in patients of the control group, these were 10.75 ± 2.7 and 9.9 ± 2.5 , respectively.

Evaluation of the correlation between the indicators of endotoxin and cytokines in the blood serum of the women examined revealed a statistically significant, medium-strength positive association with proinflammatory cytokines and a weak negative association with anti-inflammatory IL-10 (Table 2).

The positive correlation between pro- and anti-inflammatory interleukins is noteworthy. According to Levkovich, in the pathological course of the gestational period, the levels of immunosuppressive interleukins increases in response to an increase in the level of the proinflammatory mediator in order to suppress its synthesis [15]. In contrast, a decrease in the level of interleukins produced by Th2 in presence of excessive production of proinflammatory cytokines is an unfavorable prognostic sign for further development of pregnancy, which indicates profound disturbances in the implantation and placentation processes [16].

DISCUSSION

Several scientific studies are focused on the possible causes of the gestational period complications. After the relationship between the course of pregnancy and changes in the immune system was studied and proved, various works were aimed at considering this aspect.

Chistyakova et al. revealed that an increase in the level of proinflammatory cytokines (IL-6, IL-8) with a decrease in the level of anti-inflammatory cytokines (IL-4 and IL-10) may be a criterion for early threatened miscarriage [17].

The same findings were obtained by Kravchenko and Mishutina; that is, with threatened miscarriage, the blood serum levels of IL-1 β , IL-6, IL-8, IL-2, and interferons INF- α and INF- γ increased to varying degrees compared with similar values during physiological pregnancy [12].

Our study confirms the above data, and a statistically significant increase in the concentration of proinflammatory cytokines (IL-1 β and IL-6) was observed in pregnant women with lower values of anti-inflammatory cytokines (IL-10) and

threatened spontaneous miscarriage compared to women with a normal pregnancy.

Several scientific works demonstrate that endotoxin can be an inducer of a systemic inflammatory response and, accordingly, an activator of proinflammatory cytokines in pregnant women.

Bondarenko et al. proved that the pathological course of the gestational process can be caused, to a certain extent, by endotoxin-induced activation of the monocytic-macrophage system cells, and the change in the cytokine status was characterized by a disturbance of the ratio of opposition pools toward an increase in proinflammatory cytokines. Furthermore, it was revealed that the level of endotoxin correlated positively with both proinflammatory and anti-inflammatory cytokines [18].

According to Enikeev, an increase in the concentration of lipopolysaccharides in the systemic circulation is a determining factor in the pathological course of pregnancy. The author explains the cause of systemic endotoxemia by an increase in intra-abdominal pressure, which leads to venous stasis and increased edema of the gastrointestinal tract, which possibly leads to ischemic damage to the intestinal mucosa. The correlations between the indicators of endotoxemia and cytokines indicate the participation of lipopolysaccharides in the pathogenesis of the gestational period complications with the involvement of inflammatory mediators [19].

Subkhankulova assessed the level of endotoxin in pregnant women suffering from constipation, and its increased level of 1.53 ± 0.1 EU/ml (by more than two times compared with that of healthy pregnant women of 0.65 ± 0.005 EU/ml, $p < 0.05$) was caused by intestinal dysbiosis and was associated with a complicated course of the gestational period [20].

According to the results of our study, the average level of endotoxemia in pregnant women with threatened spontaneous miscarriage was significantly higher (0.57 ± 0.02 nmol/ml) compared with that in women with a normal pregnancy (0.34 ± 0.02 nmol/ml, $p < 0.001$). Moreover, there was a direct strong correlation between the level of endotoxemia and grade of intestinal dysbiosis ($r = 0.8$;

$p < 0.001$), as well as with the level of proinflammatory interleukins ($r = 0.5$; $p < 0.05$). Based on the data obtained, it can be concluded that endotoxemia as a result of a disorder of the intestinal microflora in pregnant women, which activates the immune system by a proinflammatory type, can be considered as a trigger factor in the pathogenesis of miscarriage.

CONCLUSIONS

1. Intestinal dysbiosis was diagnosed in 100% of the pregnant women examined, while women with a complicated gestational period showed the most pronounced dysbiotic changes in the intestinal microflora. Grade I intestinal dysbiosis was diagnosed in 30% of patients with threatening spontaneous miscarriage, grade II in 46% of patients, and grade III in 24%, while in the control group, dysbiotic changes corresponded mainly to grade I (67.6%) and grade II (32.4%), and there were no cases of severe dysbiosis. The differences between the relative values in both groups were statistically significant ($p < 0.05$).
2. The average level of endotoxemia in pregnant women of the main group was statistically significantly ($p < 0.001$) higher (0.54 ± 0.02 nmol/ml) compared with that of the control group (0.35 ± 0.02 nmol/ml). A direct strong correlation was revealed ($r = 0.8$; $p < 0.001$) between the grade of intestinal dysbiosis and the level of endotoxemia, which is caused by pronounced disorders in the composition of the intestinal microbiocenosis due to a significantly larger number of microorganisms with a high pathogenic potential.
3. A statistically significant increase in the concentration of proinflammatory cytokines (IL-1 β and IL-6) was found in pregnant women with lower values of anti-inflammatory cytokines (IL-10) and with threatened spontaneous abortion compared with women with normal pregnancies. A direct correlation of medium strength ($r = 0.5$; $p < 0.05$) was established between the level of endotoxin and the concentration of proinflammatory interleukins in the blood serum.

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