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РЕГУЛЯЦИЯ ДИФФЕРЕНЦИРОВКИ ПЕРИФЕРИЧЕСКИХ В-ЛИМФОЦИТОВ ПРИ ПРИВЫЧНОМ НЕВЫНАШИВАНИИ БЕРЕМЕННОСТИ

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Резюме. Доказана важная роль иммунных нарушений в привычном невынашивании беременности. Уточнение характера дифференцировки В-лимфоцитов и факторов ее регуляции у женщин с угрожающим выкидышем и привычным невынашиванием беременности в анамнезе является актуальной проблемой, поскольку позволит выявить иммунные механизмы патогенеза данной патологии.

Цель: установить особенности дифференцировки В-лимфоцитов и факторов ее регуляции у женщин с привычным невынашиванием беременности в анамнезе и угрожающим самопроизвольным выкидышем на момент обследования.

Были обследованы беременные женщины в возрасте 18-40 лет в сроке гестации 5-12 недель. Основную группу составили 60 беременных женщин с угрожающим самопроизвольным выкидышем на момент обследования и привычным невынашиванием в анамнезе. В качестве контроля обследовано 35 беременных женщин с неосложненным течением беременности. Группу сравнения составили 25 первобеременных женщин с угрожающим самопроизвольным выкидышем на момент обследования. Материалом исследования служила периферическая венозная кровь. Методом проточной цитофлюориметрии определяли субпопуляции В-лимфоцитов $CD19^+$, $CD19^+IgD^+$, $CD20^+IgM^+$, $CD20^+IgG^+$; $CD19^+CD20^-CD38^+$, $CD19^+CD27^-$, $CD19^+CD27^+$. Сывороточный уровень BAFF и APRIL оценивался методом иммуноферментного анализа.

В основной группе зарегистрировано увеличение в периферической крови доли В-клеток, $CD20^+IgM^+$ лимфоцитов и клеток памяти, наряду со снижением уровня наивных клеток и плазмоцитов. В группе сравнения зарегистрировано увеличение доли незрелых IgM^+В-клеток, циркулирующих клеток памяти наряду со снижением наивных В-лимфоцитов. В основной группе наблюдалось выраженное снижение сывороточного уровня BAFF по сравнению с группой контроля и сравнения. Анализ содержания APRIL показал выраженную тенденцию к снижению в группах с угрожающим выкидышем относительно здоровых беременных. Таким образом, угрожающий привычный и спорадический выкидыши были ассоциированы со сдвигом дифференцировки В-лимфоцитов в сторону незрелых форм и недостатком регулирующего влияния BAFF и APRIL, что выражается в нарушении В-клеточного гомеостаза и ослаблении гуморальных эффекторных механизмов на системном уровне.

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Выявленные изменения могут свидетельствовать о едином механизме развития угрожающего самопроизвольного выкидыша, выраженность которого увеличивается при повторной потере беременности. Эти изменения могут приводить к усилению эффекторных цитотоксических механизмов и увеличению провоспалительных цитокинов, что может привести к развитию повреждающих реакций в фетоплацентарном комплексе, отражением чего может являться клиническая картина угрозы прерывания беременности.

Ключевые слова: беременность, угроза прерывания беременности, привычное невынашивание, В-лимфоциты, BAFF, APRIL

REGULATION OF PERIPHERAL B-LYMPHOCYTE DIFFERENTIATION IN RECURRENT MISCARRIAGE

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Abstract. The important role of immune disorders in recurrent miscarriage has been proven. Clarification of the character of B-lymphocyte differentiation and its regulation factors in women with threatened miscarriage and recurrent miscarriage in history is an urgent problem, since it will reveal the immune mechanisms of the pathogenesis of this pathology. Purpose: to establish the features of B-lymphocyte differentiation and factors of its regulation in women with a history of recurrent miscarriage and threatening spontaneous miscarriage at the time of examination.

Were examined pregnant women aged 18-40 years at a gestation period of 5-12 weeks. The main group consisted of 60 pregnant women with a threatening spontaneous miscarriage at the time of examination and a history of recurrent miscarriage. As a control, 35 pregnant women with uncomplicated pregnancy were examined. The comparison group consisted of 25 primary pregnant women with threatened spontaneous miscarriage at the time of examination. The material for the study was peripheral venous blood. Subpopulations of B-lymphocytes $CD19^+$, $CD19^+$ IgD^+, $CD20^+IgM^+$, $CD20^+IgG^+$ were determined by flow cytometry; $CD19^+CD20^-CD38^+$, $CD19^+CD27^-$, $CD19^+CD27^+$. Serum levels of BAFF and APRIL were assessed by enzyme-linked immunosorbent assay.

In the main group, an increase in the proportion of B-cells, $CD20^+IgM^+$-lymphocytes and memory cells was recorded in the peripheral blood, along with a decrease in the level of naive cells and plasma cells. In the comparison group, an increase in the proportion of immature IgM^+B-cells, circulating memory cells, along with a decrease in naive B-lymphocytes, was registered. in the main group there was a pronounced decrease in the serum BAFF level compared with the control and comparison groups. Analysis of the APRIL content showed a pronounced downward trend in groups with threatened miscarriage relative to healthy pregnant women. Thus, threatening habitual and sporadic miscarriages were associated with a shift in the differentiation of B-lymphocytes towards immature forms and a lack of regulatory influence of BAFF and APRIL, which is reflected in the disruption of B-cell homeostasis and weakening of humoral effector mechanisms at the systemic level. The revealed changes may indicate a single mechanism for the development of a threatening spontaneous miscarriage, the severity of which increases with repeated loss of pregnancy. These changes can lead to an increase in effector cytotoxic mechanisms and an increase in proinflammatory cytokines, which can lead to the development of damaging reactions in the fetoplacental complex, which can be reflected in the clinical picture of the threat of termination of pregnancy.

Keywords: pregnancy, threatened abortion, recurrent miscarriage, B-lymphocytes, BAFF, APRIL

The problem of the etiology and pathogenesis of recurrent miscarriage remains of high priority, despite the attention paid to it. Currently, the attention is attracted by the immune mechanisms of recurrent pregnancy loss. Recurrent miscarriage in 50% cases is associated with pathological changes in various arms of the immune system and an inadequate maternal response to a semi-allogeneic fetus [2]. Pregnancy is a complex multi-stage process that includes fertilization, implantation, placentation and further embryonic development. Such processes are regulated by hormones, cytokines and many other intercellular interactions. The mother-fetus immune relationship is currently viewed as a two-way interplay process. On the one hand, fetal antigens must be presented to the maternal immune system, and on the other hand, the

maternal immune system must recognize them and respond. [1].

B-lymphocytes play an important role during uncomplicated pregnancy as they produce antibodies involved in humoral immune responses. Recently, the autoantibody-producing B-lymphocytes has been studied in complicated pregnancy, such as spontaneous miscarriage, preeclampsia, intrauterine growth retardation, stillbirth and premature birth [10]. Currently, there are sporadic data on changes in B-lymphocyte subpopulations during recurrent miscarriage. According to Baturina et al., Recurrent pregnancy loss was paralleled with decreased primary naive IgD^+CD38^-B-cell number in peripheral blood [3]. In addition, it was evidenced about increased number of $CD19^+CD5^+$-cells with simultaneously decreased $CD19^+$-lymphocytes in women with a history of recurrent miscarriage [4]. These data suggest that the character of B-lymphocyte differentiation changes significantly in recurrent miscarriage.

Differentiation of B-lymphocytes is regulated by various factors. The most significant factors are soluble ligands BAFF (B-cell activation factor) and APRIL (proliferation-inducing ligand) [5]. Elevated serum levels of BAFF and APRIL are associated with autoimmune diseases. The severity of diseases and the level of pathogenic autoantibodies directly depend on the serum level of BAFF and APRIL [13]. An increased level of BAFF and APRIL was observed in patients with autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, diabetes [12], systemic scleroderma, etc. [14].

Currently, only sporadic data on the level of BAFF in recurrent pregnancy loss are available. The BAFF level was significantly reduced in patients with repeated spontaneous decidual and trophoblast abortion compared with healthy pregnant women [8]. Serum BAFF was reduced in pregnant women with fetal growth retardation [6]. Currently, no literature data on the APRIL level during pregnancy are found.

The aim of our study was to establish the characteristics of B-lymphocyte differentiation and factors of its regulation in women with former recurrent miscarriage and threatened termination of pregnancy at the time of examination.

Materials and methods

The study was carried out at the V. Gorodkov Ivanovo Research Institute of Maternity and Childhood of Ministry of Health of Russia in the years 2018-2020. Pregnant women aged 18-40 years were examined at the gestation period of 5-12 weeks. The main group consisted of 60 women with threatened spontaneous miscarriage upon examination and former recurrent miscarriage. The control group consisted of 35 women with uncomplicated course of pregnancy. The comparison group included 25 pregnant women with threatened sporadic miscarriage upon examination. The inclusion criteria for the study were: spontaneous singleton uterine viable pregnancy confirmed by ultrasound and signs of threatened miscarriage. The exclusion criteria were: a miscarriage in progress, structural changes in the karyotypes of spouses established at the pregravid stage, anomalies in development of the reproductive system, anembryonia, pregnancy with the help of assisted reproductive technologies, autoimmune diseases, endocrine dysfunctions, acute and exacerbated inflammatory chronic diseases, allergic reaction upon examination, cancer processes. Peripheral blood samples were used in the study.

Using a flow cytometer FACSCanto II (BD Biosciences, USA), we determined percentage of $CD19^+$B-cells, expression of immunoglobulins $CD19^+IgD^+$, $CD20^+IgM^+$, $CD20^+IgG^+$; level of plasma cells ($CD19^+CD20^-CD38^+$) and naive cells ($CD19^+CD27^-$); memory cells $CD19^+CD27^+$. We determined the percentage of subpopulations in the pool of $CD19^+$ or $CD20^+$-lymphocyte gate cells. We used the following monoclonal antibodies: anti-CD19 conjugated with PE (Beckman Coulter, France), anti-CD19 conjugated with APC (Beckman Coulter, France), anti-CD20 conjugated with FITC (Beckman Coulter, France), anti-CD27 and CD38 conjugated with PE (Beckman Coulter, USA) and anti-IgD conjugated with FITC (Beckman Coulter, USA), anti-IgM conjugated with PE (eBioscience, USA), anti-IgG conjugated with PE-Cy7 (Becton, Dickinson and Company, USA). There were analyzed at least 10,000 cells in each sample by using the BDFACS Diva Software (Becton Dickinson, USA). The level of serum BAFF and APRIL was measured by ELISA (eBioscience, Austria).

Statistical data processing was carried out using licensed software packages, e.g., Microsoft Office 2010, Statistica for Windows 13.0. The data are presented as mean (M) and standard error of the mean (m). Statistical significance between differences was assessed by the Student's test, because the data followed the criteria of normal distribution. Differences were considered statistically significant at $p < 0.05$.

Results and discussion

While assessing the count of peripheral B-lymphocytes, it was found that women with threatened recurrent miscarriage had it significantly increased among $CD19^+$-cell subset compared to remaining pregnant women (Table 1) ($p < 0.05$ in all cases). Assessing the level of IgM- and IgG-positive $CD20^+$B-lymphocytes in the peripheral blood in main group found increased percentage of $CD20^+IgM^+$-lymphocytes compared to the control group ($p < 0.05$) that tended to increase while compared to pregnant

TABLE 1. CHARACTERISTICS OF THE CONTENT OF CD19⁺B-LYMPHOCYTES, IgM⁺ AND IgG⁺ CELLS IN THE POOL OF CD20⁺ LYMPHOCYTES, NAIVE B-CELLS, PLASMA CELLS, MEMORY B-CELLS IN THE POOL OF CD19⁺ PERIPHERAL BLOOD LYMPHOCYTES IN WOMEN WITH TREATENED SPONTANEOUS ABORTION AND RECURRENT MISCARRIAGE IN HISTORY

Indicator, % (M±m)	Control group (n = 35)	Main group (n = 60)	Comparison group (n = 25)
CD19⁺B-cells	4.6±0.4	6.00±0.47 $p_1 = 0.02$	5.21±1.00
Immature B-cells CD20⁺IgM⁺	30.0±4.0	40.43±3.24 $p_1 = 0.05$	36.77±4.73
Mature B-cells CD20⁺IgG⁺	8.0±1.9	5.05±0.98	6.01±1.14
Plasmacytes CD19⁺CD38⁺CD20⁻	3.1±0.5	1.96±0.25 $p_1 = 0.03$	6.90±1.75 $p_2 = 0.05$ $p_3 = 0.01$
B memory cells CD19⁺IgD⁺	33.9±2.3	50.06±4.28 $p_1 = 0.01$	43.98±3.02 $p_2 = 0.02$

Note. p_1 is the level of statistical significance of the differences between the main and control groups; p_2 is the level of statistical significance of the differences between the comparison group and the control group; p_3 is the level of statistical significance of differences between the main group and the comparison group.

TABLE 2. CHARACTERISTICS OF THE FACTORS REGULATING THE DIFFERENTIATION OF B-LYMPHOCYTES IN WOMEN WITH THREATENING SPONTANEOUS MISCARRIAGE AND RECURRENT MISCARRIAGE IN HISTORY

Indicator, % (M±m)	Control group (n = 35)	Main group (n = 60)	Comparison group (n = 25)
BAFF	1.5±0.1	1.30 ±0.05 $p_1 = 0.03$	1.90±0.21 $p_2 = 0.01$
APRIL	1.2±0.8	0.34±0.06	0.31±0.43

Note. p_1 is the level of statistical significance of the differences between the main and control groups; p_2 is the level of statistical significance of the differences between the comparison group and the control group.

women with threatened sporadic miscarriage. The number of CD20⁺IgG⁺B-lymphocytes was reduced in groups with threatened recurrent and sporadic miscarriage compared with healthy pregnant women ($p < 0.05$).

Analyzing differentiation features of peripheral B-lymphocytes showed that the number of naive CD19⁺CD27⁻B-lymphocytes in the main group and the comparison group was lower than in the control group. The number of plasma cells CD19⁺CD20⁻CD38⁺-cells in the main group was significantly lower than in remaining subjects ($p < 0.05$ in all cases). In the peripheral blood of patients of the main group and the comparison group, the number of CD19⁺CD27⁺B-memory cells was higher than in those lacking threatened termination of pregnancy.

Evaluation of the factors regulating B-lymphocyte differentiation showed a significant decrease in the serum BAFF level in the study group compared to other pregnant women (Table 2). The difference in serum BAFF concentration in comparison vs. control group was statistically significant. Analysis of the serum APRIL level showed that in the main group it prominently tended to decrease in pregnant women with threatened termination of pregnancy compared with healthy pregnant women.

According to the literature, physiological pregnancy is accompanied by hormone-mediated B-cell lymphopenia and increased level of circulating BAFF, which is necessary for differentiation of immature transitional B-cells into naive mature B-cells [10]. Here, we estimated the number of circulating B-lymphocytes and subset composition, as well as serum concentration of factors regulating B-cell differentiation. The data obtained showed that women with threatened habitual miscarriage were characterized by pronounced changes in B-lymphocyte subset composition. According to our data, threatened recurrent miscarriage was associated with B-cell lymphocytosis, increased percentage of immature CD20⁺IgM⁺ and memory B-cells, along with decreased count of naive and plasma cells.

CD20⁺IgM⁺B-cells are characterized as immature, short-lived B-lymphocytes that undergo antigen-independent positive selection leading to elimination of cells exerting high affinity to autoantigens. This

B-cell subpopulation is characterized by long-term inactivation after contacting cognate antigen and reduced potential for further clonal proliferation and differentiation. In addition, immature B-cells exhibit reduced affinity to antigens, immature phenotype and lowered expression of receptors for major regulatory ligands [11].

Similar changes in B-lymphocyte differentiation were observed among women at risk of terminated first pregnancy. We observed increased percentage of immature IgM^+-cells, circulating memory cells and decreased naive B-lymphocytes. We assume that the data obtained may suggest a single mechanism for developing threatened miscarriage. Moreover, the magnitude of skewed B-lymphocyte differentiation progress along with recurrent loss of pregnancy.

BAFF and APRIL signal through the three receptors: BAFF specific receptor (BAFF-R), L-TACI (transmembrane activator-1 and calcium modulator and cyclophilin ligand interacting with CD267) and BCMA (B-cell maturation antigen, CD269). The BAFF-BCMA interaction plays an important role in the survival of plasma cells. The BAFF-BAFFR interaction leads to activation of the NFB- B pathway and the transcription of the anti-apoptotic factor Bcl-2. This promotes the survival of marginal, follicular zones, as well as IL-10-producing B-lymphocytes [9]. Signaling through TACI and BCMA is important for survival of APRIL-induced IgA^+Breg [5].

BAFF plays a critical role in the homeostasis of the entire B-lymphocyte pool under physiological conditions, contributing to survival and maturation of B-cells. It is known that increased activation of B-cells leads to excessive generation of plasma cells and potentiation of humoral reactions, which can lead to the development of autoimmune processes [11]. In addition, the BAFF / BAFF-R interaction activates the PI3K-Akt signaling pathway as well as increases viability and activation of T-lymphocytes, which are involved in recurrent miscarriage [9]. Thus, BAFF is involved in maintaining B-cell homeostasis and is an essential factor in the pathogenesis of recurrent miscarriage.

It has been shown that exposure to BAFF and APRIL in vitro and in vivo enhances the expression of the immunosuppressive cytokine IL-10 by regulatory B-cells via the TACI receptor [5]. Deficiency in IL-10 production by B-lymphocytes interferes with full proliferation, survival and differentiation of Breg. This disrupts the maturation of plasma cells – the main antibody producers. Plasmocytes are a source of blocking aIgG antibodies. These asymmetric antibodies bind other Igs as well as monocytes and macrophages at the mother-fetus border [7]. Consequently, aIgG deficiency leads to weakened protective mechanisms of the semi-allogenic fetus against cellular cytotoxicity and phagocytosis of the maternal immune system.

APRIL acts later in B-cell differentiation and modulates function and survival of B-cells after contact with antigen being involved in generation and survival of bone marrow long-lived plasma cells [13]. In addition, APRIL promotes the differentiation of naive human B-cells into IL-10-producing IgA^+B-cells. These APRIL-induced IgA^+B-cells exhibit the Breg phenotype and inhibit effector T-cells and macrophages via IL-10 and PD-L1 [5].

The decrease in serum BAFF concentration recorded by us in women with threatened habitual miscarriage may indicate both accelerated ligand binding to the receptor and impaired homeostasis of both B- and T-cell immunity. A decrease in the serum APRIL level among women with threatened pregnancy loss (both in primary pregnant women and group of recurrent miscarriage) may point at lowered survival of mature high-effector B-lymphocytes, as well as Breg. These changes can lead to enhanced cytotoxic effects and cytokine profile skewed to pro-inflammatory response against fetal antigens, which can lead to developing reactions damaging placenta and the fetus being reflected in the clinical picture of the threatened termination of pregnancy.

Thus, threatened recurrent miscarriageis is associated with disturbed regulatory effect of BAFF and APRIL on B-lymphocyte differentiation. These changes at systemic level are manifested by increased number of immature subsets and deficiency in highly efficient cells. The changes revealed in B-cell homeostasis and compromised regulation of humoral effector mechanisms lead to insufficient execution of the maternal immune tolerance to semi-allogeneic fetus.

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