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CYTOKINES AND ITS MAIN ROLE IN BACTERIAL VAGINOSIS IN PREGNANT WOMEN

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Abstract
Cytokines are a universal regulatory system of mediators that control the processes of proliferation and differentiation of cellular elements in the hematopoietic, immune and other homeostatic systems of the body. Violation of regulatory mechanisms is a condition for the development of pathological conditions and diseases, and in these cases, cytokines play the role of pathogenetic factors. Cytokines produced by T-helpers type 1 (Th1) are the most important inducers of the cellular immune response, hematopoiesis and reparative processes. Cytokines produced by T-helpers type 2 (Th2) promote the activation of B-cells and the production of antibodies, i.e. they activate the humoral immune response. Th2 cytokines participate in the development of allergic reactions and have an anti-inflammatory effect. Deficiency of Th1 cytokines in combination with high level of Th2 cytokines is a sign of immunosuppression and anergy of immune response. In some cases, the criterion of dysregulation of the immune system is precisely the imbalance of cytokines of opposing pools, and not the level of hypercytokinemia of a single mediator. To determine the imbalance, it is important to evaluate the ratio of interferon γ (IFNγ)/interleukin-10 (IL-10) – the leading cytokines in their groups.

Keywords: Cytokines, interleukins, pregnancy, bacterial vaginosis, cervical canal, immune system.

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Purpose of the study. Determination of the amount of proinflammatory and anti-inflammatory cytokines in the cervical canal discharge as indicators of the state of local immunity in pregnant women with bacterial vaginosis.

Material and methods. The study included 35 pregnant women who came to the clinic in the early stages of gestation. The main group consisted of 22 pregnant women who had a verified diagnosis of BV, the comparison group consisted of 13 pregnant women with normal vaginal microbiocenosis. The level of cytokines in the cervical canal discharge was determined in the first trimester of pregnancy before BV treatment, then repeated after treatment at 22–23 and 33–34 weeks of gestation. At the same time, the content of cytokines in the cervical canal discharge was also determined in patients of the control group.

Thus, a comparison of the endocervical level of proinflammatory cytokines IL-1b, IL-6, IL-8 in pregnant and non-pregnant patients with BV and the same somatic status in both groups showed that the level of cytokines in pregnant women was significantly higher than in non-pregnant women, which may be associated with the immune compromise of pregnancy.

The prevalence of dysbiotic changes in the vaginal microflora and the persistence of microorganisms in the cervical canal in pregnant women with habitual miscarriage lead to a significant excess of proinflammatory cytokines TNF-α, IFN-γ, IL-6 over regulatory IL-4, IL-10, in contrast to healthy pregnant women.

In a Swedish population of pregnant women with premature rupture of membranes at less than 34 weeks, intrauterine microflora and cytokines IL-6 and IL-8 were studied during amniocentesis. Bacterial flora in the amniotic fluid was detected in 25% of pregnant women. Concentration of IL-6 in the amniotic fluid over 0.80 ng/ml was associated with intrauterine infection and a high risk of premature birth in the next 7 days, and an increase in the concentration of IL-8 indicated birth before 34 weeks.

The obtained data are consistent with other similar studies indicating that low concentrations of proinflammatory cytokines IL-1α, IL-1b, IL-6, IL-8 in cervical discharge at 22–34 weeks of gestation, especially the level of IL-8, represent a high risk of early infectious disease of newborns. Among other markers of

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premature birth, the study of IL-6 content in vaginal discharge will allow identifying pregnant women with a high risk of neonatal infection and predicting the onset of labor before 34 weeks of gestation. According to some data, the levels of IL-1b, IL-6 in vaginal discharge were significantly higher in pregnant women with BV.

Another study concerning the frequency of detection of 7 proinflammatory cytokines and polymorphism of the Toll-like receptor gene in pregnant women with and without BV at a gestation period of less than 30 weeks showed that polymorphism at the isolated loci of IL-1b, IL-6, IL-8 is associated with a change in the severity of BV during pregnancy.

For clinical variants of diseases caused by opportunistic infections, it is desirable to rely on immunological factors that could be objective markers in assessing the effectiveness of treatment. Since cytokines are key factors in the phases of induction and development of the immune response, as well as evasion from it, then the quantitative determination of their content in the secretory components of the reproductive tract is of great importance. The aim of this study was to determine proinflammatory and anti-inflammatory cytokines in cervical canal discharge as indicators of local immunity in pregnant women with BV. □ □ □

The state of the vaginal microbiocenosis was assessed based on microscopy of vaginal smears stained by Gram and a cultural study of vaginal contents for facultative anaerobic bacteria, yeast-like fungi, genital mycoplasmas and lactobacilli. The degree of microbial contamination was determined by sector seeding of vaginal discharge on 5% blood agar, Sabouraud medium and MRS. Species identification of microorganisms was carried out by generally accepted methods.

Microbiological diagnostics of BV by microscopy of vaginal smears was based on the following criteria: presence of key cells; absence of pronounced leukocyte reaction; massive microbial contamination with a predominance of morphotypes of obligate anaerobic bacteria (bacteroides, mobiluncus, fusobacteria, leptotrichia) and gardnerella; absence or detection of single gram-positive rods of the lactobacilli morphotype in the field of vision. The content of proinflammatory

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(TNF-α, IFN-γ, IL-1α, IL-2, IL-6, IL-8) and anti-inflammatory cytokines (IL-4, IL-10) in the cervical canal mucus was determined using enzyme immunoassay. The quantitative content of cytokines in cervical mucus was normalized by recalculation to the total protein in the samples. Protein in the samples was determined by a colorimetric method using bicinchoninic acid (Sigma, USA).

Research Results:

There were significant differences in the cytokine content in the cervical canal discharge in the first trimester in pregnant women with BV and in pregnant women with normal vaginal microbiocenosis: the levels of both pro- and anti-inflammatory cytokines in the main group were 2 times or more higher than similar indicators in the comparison group. Analysis of changes in the cytokine content in cervical mucus in a group of patients with normomicrobiocenosis of the vagina showed that in the first trimester of pregnancy, almost all studied cytokines are quantitatively characterized by minimal values. Furthermore, in the absence of reliable differences, different trends are found in the change in the content of the studied cytokines in subsequent trimesters (with the exception of IL-10, the level of which significantly increases in the third trimester compared to the content in the first trimester). However, despite this, it is obvious that in normomicrocinosis of the vagina, local immune reactions tend to maintain a certain constant concentration of secreted cytokines throughout the entire pregnancy. This is somewhat different from the picture described by a number of researchers regarding the content of these cytokines in the blood of women during physiological pregnancy, including those not complicated by BV. According to the observations of these authors, in the blood of women during physiological pregnancy, signs of an inflammatory reaction with an increase in the content of a number of cytokines are observed. Probably, this difference is explained by the adequate functioning of the histohematic barrier and, as a consequence, the creation of the most favorable conditions for the developing pregnancy. When examining women in the second and third trimesters of pregnancy, there was no reliable difference in the cytokine content between the groups. The exceptions were IL-6 and IL-2. It should be noted that after BV treatment, the vaginal

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microflora in pregnant women of the main group, according to the microbiological examination data, corresponded to the indicators in healthy pregnant women. A significant decrease in the level of a number of cytokines in pregnant women of the main group during pregnancy dynamics, with the exception of the levels of TNF-α and IL-8, may also be associated with the absence of pronounced inflammation of the vaginal mucosa in BV, which could result in a change in the active synthesis of adhesive molecules and killer activity of phagocytic cells mediated by these cytokines. It is also known that there is an antagonistic interaction between TNF-α and IL-6 [1]. An increase in TNF-α production in the first trimester leads to an increase in IL-6 production. However, consistently elevated concentrations of IL-6 in the second and third trimesters of pregnancy cause a decrease in TNF-α secretion and, as a consequence, suppression of leukocyte migration into the tissue. A detailed analysis of the dynamics of cytokines by trimesters in the main group of pregnant women showed that the change in the content of IFN-γ, IL-1α, IL-8 and IL-10 has the following trend: increased content in the first trimester, decreased in the second trimester (after treatment) and again an increase in content in cervical mucus in the third trimester of pregnancy. Moreover, it is noted that with a reliable decrease in their concentration after treatment, the average values of the content of IFN-γ, IL-8, IL-10, as well as IL-1α in the second trimester of pregnancy remain elevated compared to similar indicators in the group of pregnant women with normomicrobiocenosis of the vagina. The absence of reliable differences between the groups in the content of these cytokines gives grounds to assume that the changes caused by pathogenic microorganisms, as well as those that occurred due to the shift of microecological niches in the genital tract of pregnant women, while not being critical for pregnancy, create a higher background proinflammatory level. It should be noted that the average values of the content of these cytokines in the third trimester of pregnancy in the main group are as close as possible to the values in the comparison group. Also noteworthy is the high level of IL-1α in cervical mucus. It is known that IL-1α is a transmembrane protein, in its free form it is inside the cell and is secreted in various pathological conditions. Its detection in biological fluids of the body indicates activation of the

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macrophage link of immunity. The level of the secretory form of IL-1α in pregnant women of the main and control groups revealed in this study indicates antigenic stimulation by bacterial products.

The levels of IL-6, IFN-γ, and IL-2 decreased especially actively with increasing pregnancy term in patients with BV. At the same time, a reliable increase in the concentration of the anti-inflammatory cytokine IL-10 in healthy pregnant women in the late stages of gestation is noteworthy, which may be due to a change in the state of the body's immune system before childbirth. The dynamics of IL-10 is shown in the figure. An important property of IL-10 is the suppression of immune cell activity, which leads to the completion of the inflammatory reaction, elimination of the pathogen and restoration of the structure of damaged tissue. The high content of IL-10 in BV in the first trimester of pregnancy is probably associated with the implementation of the regulatory function against the background of active production of proinflammatory cytokines.

The results obtained in determining IL-2 and IL-4 in cervical mucus in BV indicate a reliable decrease in the content of both cytokines after treatment with the preservation of minimal concentrations by labor. It is difficult to talk about reliable differences between the groups and the dynamics of IL-2 and IL-4 in the normomicrocenosis of the vagina due to the small number of studies of these cytokines in this group of pregnant women.

Thus, the analysis of the obtained results showed that the content of pro- and anti-inflammatory cytokines in the discharge of the cervical canal in pregnant women with BV is significantly higher than in the comparison group at the stage preceding drug treatment. The loss of vaginal function observed in this pathology is manifested in the activation of local immunity with the secretion of molecules that have an autocrine, paracrine and endocrine effect. The detection of these molecules in cervical mucus does not mean that they are active in it. They probably act indirectly on the cells of the immune system and the receptor apparatus of the cells that form the mucous membrane of the vagina and endocervix. When the protective barrier, which is lactobacilli, is eliminated, conditions are created for the unbalanced production of cytokines and, as a consequence, for the formation of a microenvironment in which the final products

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of cellular metabolism change, which affects the quality and composition of the secreted mucus. Taking this into account, the remodeling of the cervix that occurs during pregnancy and before childbirth may have particular features in pregnant women with BV. Dysbiotic disorders in the vagina lead to a decrease in the functional reserve of cells and, as a result, to a change in their metabolic activity. In turn, a change in protein synthesis by endocervical cells leads to a variation in the ratio of soluble and insoluble collagen fractions in tissues and, ultimately, to a change (deterioration) in the biomechanical properties of the cervix.

Qualitative and quantitative changes in cytokine levels reflect the degree of activation of immunocompetent cells in any pathological process. The results obtained in this study reflect a certain autonomy of immune reactions in the lower parts of the female genital tract.

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