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Features of the diagnosis of immune disorders in women with reproductive losses.

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Abstract. To determine the criteria for diagnosing disorders of the immune mechanism in women with complicated pregnancy, a comprehensive clinical and clinical laboratory examination of 70 patients with habitual miscarriage, threatened miscarriage, and undeveloped pregnancy was conducted. The indicators of general clinical blood tests, cellular and humoral immunity, interleukin and progesterone levels, and other biochemical parameters were evaluated. In women with complicated early pregnancy, against the background of a decrease in progesterone content in blood serum, the criteria for the threat of termination of pregnancy are a unidirectional increase in the number of helper-inductor activity of CD4+, cytotoxic lymphocytes CD8+, cytotoxic killer cells and a shift in the cytokine balance towards the production of proinflammatory cytokines IL-2, IL-6, which is combined with an increase in expression IL-4.

Keywords: reproductive losses, impaired immune status, indicators of cellular, humoral immunity and interleukins.

Introduction. In the structure of reproductive losses, undeveloped pregnancy occupies one of the leading places, despite numerous studies in this area [2, 9]. The frequency of miscarriage varies from 10% to 25% of all pregnancies. About 20% of miscarriage is a habitual miscarriage [8]. To date, there is no consensus on the etiology and pathogenesis of this pregnancy complication. The main difficulties associated with the study of the problem of miscarriage are due to the polyethologicity of this pathology. In recent years, an increasing amount of data has been accumulating on the association of various forms of miscarriage with impaired immune status [10, 11]. However, the immune mechanisms of reproduction have not been fully disclosed. Reproductive pregnancy losses (spontaneous miscarriage, undeveloped pregnancy, antenatal fetal death) are still an urgent problem of modern obstetrics and perinatology.

The purpose of the study was to determine the indicators of cellular, humoral immunity and interleukins in peripheral blood to identify pathogenetic mechanisms of miscarriage.

Materials and methods.

In order to determine the role of immune mechanisms in the genesis of miscarriage in the first trimester, we conducted a comprehensive clinical and clinical laboratory examination of 70 patients with habitual miscarriage, threatened miscarriage, and undeveloped pregnancy. To clarify the criteria for diagnosing disorders of the immune mechanism in women with complicated pregnancy, a group

of women with the exception of hereditary thrombophilia, antiphospholipid syndrome (AFS), infectious and inflammatory pathology (inflammatory diseases of the genitals, extragenital pathology of an infectious nature) was selected in the number of 44 patients (main group). The comparison group consisted of 37 pregnant women with uncomplicated pregnancy in the first trimester without acute and chronic gynecological and extragenital pathology.

The main group included 24 (54.5%) women with a threatening spontaneous miscarriage, 5 (11.4%) with an undeveloped pregnancy, 15 (34.1%) with a history of habitual miscarriage. The average age of patients in the main group and the comparison group was 29.7±0.63 and 29.24±0.79 years, respectively, and the average gestation period was 9.02±0.36 and 12.04±0.07 weeks. 72.7% of the women were pregnant again.

Laboratory tests were performed according to standard methods. The indicators of general clinical blood tests, cellular and humoral immunity, interleukin and progesterone levels, and other biochemical parameters were evaluated.

The cellular link of the immune system was studied by flow cytofluorometry. The population and subpopulation composition of lymphocytes was determined using monoclonal antibodies with double and triple labels.

Results and Discussion.

It is generally accepted that the assessment of the body's condition is primarily carried out based on the results of a general clinical blood test. A study of the general blood test in pregnant women of the main group in relation to the comparison group showed that women with complicated pregnancy had changes in three populations of leukocyte cells. The characteristic clinical signs were: relative and absolute neutrophilosis towards an increase in segmented cells, monocytosis and lymphocytopenia.

Vascular neutrophils represent a powerful antibacterial system of the body, carrying out phagocytosis. The shift of neutrophils towards an increase in segmented cells may reflect the primary insufficiency of granulocytopoiesis. According to the analysis, significant differences in the parameters of the leukocyte formula were obtained between the main group and the comparison group.

Peripheral blood monocytes and the organ- and tissue-specific macrophages formed from them form a macrophage system (or a system of mononuclear phagocytes). The main functions of this system are phagocytic reaction, secretion of biologically active substances, participation in the immune response, regulation of hematopoiesis, lipid metabolism, and hemostasis. Monocytes, along with T-lymphocytes, are active participants in effector reactions of cellular immunity [4, 5]. The number of monocytes in the peripheral blood largely depends on the activity of the functioning of T-lymphocytes.

Consequently, segmented neutrophils and monocytes are sensitive cells to changes in the state of the body and may indicate autoimmune disorders in the body of pregnant women and the early stage of the threat of miscarriage and, possibly, are a trigger for miscarriage.

Lymphocytes (non-phagocytic leukocytes) carry out highly specific immune responses to maintain the constancy of antigenic homeostasis and autoimmune response. An increase or decrease in the number of lymphocytes in the leukocyte formula is associated with a change in the number of neutrophils in the peripheral blood. The decrease in the number of lymphocytes in pregnant women of the main group is a reflection of the restructuring of the immunological reactivity of the body.

The leading role in combining many mechanisms in the formation of immunosuppression and regulation of their activity is currently claimed by subpopulations of T lymphocytes (4+25+), called regulatory cells [11], which are able to control tolerance to their own antigens and regulate autoimmunity. Physiological pregnancy proceeds with a balance of both T-helper cells and the number of regulatory cells. The decidual tissue is dominated by immunocompetent cells with the CD3 phenotype" CD16+, CD56+, which produce cytokines and do not respond to paternal antigens. They control trophoblast invasion and protect the fetus from infections and maternal antibodies. Their number correlates with the number of peripheral NCS [10, 11].

Since the beginning of pregnancy, a large number of cells of natural immunity accumulate in the placenta. In the literature [5-8], there are different opinions about the quantitative changes in the main subpopulations of lymphocytes during pregnancy. Some authors find an increase in the relative content of CD4+ and CD8+ cells and a decrease in the total number of lymphocytes [4]. Others have noted an increase in the number of natural killer cells (NKC) or cytotoxic cells (CC). On the one hand, an increase in NK in the mother's blood has a positive effect on pregnancy, but a significant increase in their peripheral blood contributes to a violation of the gestational process.

In the conducted studies and comparative characteristics of the cellular link of immunity, it was found that pregnant women of the main group have a statistically significant increase in the number of T-helper cells (4+), an increase in the number of cytotoxic CD8+ and natural killer cells (56+).

Due to an increase in the number of T-helper cells (4+) and cytotoxic CD8+ cells, the immunoreactive index (IRI) in women of the main group did not differ from its value in healthy pregnant women.

Thus, with early miscarriage, there is a change in the population composition of T-lymphocytes. The absolute number of T-lymphocytes and their main varieties (CD8) reflect the overall picture of changes in the immune system in the mother's body during pregnancy.

An increased number of cytotoxic CD8+ and CD56+ NK lymphocytes in the mother probably contributes to damage to the fetal egg and the progression of its rejection. For the normal development of pregnancy, an immunological balance of T-helper cells and the number of cells with cytotoxic activity of CD8+ T-lymphocytes and ECCS is necessary.

When determining the indicators of the humoral link of immunity in peripheral blood, there were no significant differences among the main classes of

immunoglobulins 1dA, 1dM). There was a tendency to increase the content of 1dM, the concentration of which was increased in 13 (29.5%) women of the main group.

The formation of the body's immune system depends on the biological activity of the so-called cytokine messengers (CC). They play a significant role in many physiological metabolic and pathological processes. CC act at the earliest stages of development in key metabolic processes, participate in the innate and adaptive immune response, acute inflammatory process, and support chronic inflammation. The formation of cellular immunity, primarily of various subpopulations of T cells, depends on the function of cytokines. In turn, by the feedback mechanism, activated T cells (CD8+) contribute to increased synthesis of CC, including by monocytes and macrophages [6]. We conducted a study of the cytokine spectrum (Il-2, Il-4, Il-6) in women of the main group and the comparison group. In the main group of pregnant women, the level of cytokines significantly exceeded those of the control group. Consequently, changes in cytokines and cellular profile at the periphery may be accompanied by significant local changes in the mother-placenta-fetus system. Various subpopulations of trophoblast cells produce cytokines: IL-1, IL-4, IL-6, etc. They have a para- and autocrine effect on the functional activity of the trophoblast and their interaction with cells of the microenvironment. This interaction underlies the control of placental development and maintenance of immunological tolerance in the mother-placenta-fetus system [1].

It is known that the key function of IL-2 is to enhance and maintain the cytotoxic activity of subpopulations of T-lymphocytes No.8+, CD56+). The absolute number of cytotoxic T-lymphocyte population in pregnant women of the main group was significantly increased in comparison with the indicator in the control group. One of the functions of IL-4 is the differentiation and maturation of CD4+ T lymphocytes, activation of the endothelium, and expression of adhesion molecules. An increase in the number of T-helpers in pregnant women with reproductive losses is probably associated with an increase in the level of IL-4 in peripheral blood, which are also produced by trophoblast, fetal endothelial cells, and T lymphocytes.

The acute phase response of the body to tissue damage by any agents is due to an increase in IL-6 in the blood, which is produced by monocytes, fibroblasts, T and B cells of lymphoid tissue. The source of IL-6 is cytotrophoblast, endometrium, decidual and placental macrophages, decidual CD8+ T cells. In turn, proliferation, differentiation and cytotoxicity of T cells are associated with IL-6.

The level of C-reactive protein (CRP) in the women of the main group was increased and amounted to 4.14±0.41 mg/l, in the comparison group - (3.06±0.34), $p<0.05$. The level of CRP correlated with pro-inflammatory IL-6, the correlation coefficient of average strength was 0.30. The results obtained may indicate the course of a subacute inflammatory process in women with habitual miscarriage, threatened miscarriage, and undeveloped pregnancy.

Analyzing the results of the main parameters of a biochemical blood test, it was revealed that liver dysfunction prevails in women of the main group, as evidenced by an increase in the activity of aspartate and aminotransferase ($p<0.05$), alkaline

phosphatase ($p<0.05$), as well as an increase in total bilirubin in blood serum ($p<0.05$).

For a more in-depth characterization of the immune mechanism of miscarriage, we have attempted to evaluate the complex of relationships between cellular, humoral immunity, interleukin and progesterone levels in peripheral blood.

Conclusion.

In women with complicated early pregnancy, against the background of a decrease in progesterone content in blood serum, the criteria for the threat of termination of pregnancy are a unidirectional increase in the number of helper-inductor activity of CD4+, cytotoxic lymphocytes CD8+, cytotoxic killer cells and a shift in the cytokine balance towards the production of proinflammatory cytokines IL-2, IL-6, which is combined with an increase in expression IL-4. An increased amount of CD56+ NK in the mother probably indicates fetal damage and the progression of its rejection. Evaluation of cytokine production along with T-lymphocyte subpopulations makes it possible to clarify the physiological and pathogenetic mechanisms determining embryo protection, contributes to understanding the key immune mechanisms of disorders in women with complicated early pregnancy.

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