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IMMUNE SYSTEM DISORDERS OF PREGNANT WOMEN WITH CHRONIC PYELONEPHRITIS

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Abstract: This article sanctifies the immune system of pregnant women, its role in maintaining and carrying the fetus, the peculiarities of cellular and humoral immunity of pregnant women with chronic pyelonephritis. Data on the impact of chronic inflammatory process on the immune system of pregnant women are presented.
Keywords: immune system; chronic pyelonephritis; pregnancy,

Introduction

Chronic pyelonephritis in the structure of extragenital pathology in pregnant women occupies a leading place (48–54%) due to the high prevalence [10,14,16], complicated by pregnancy and childbirth. It is one of the triggers of gestosis and bleeding during childbirth, leading to miscarriage and perinatal morbidity and mortality [5.18]. Chronic pyelonephritis triggers a cascade of reactions, primarily immune, at the systemic and local level [18]. In connection with the above, the study of the role of the immune system of pregnant women with chronic pyelonephritis is of great interest.

A recognition of the role of immune mechanisms in the development and maintenance of pregnancy was the discovery made by the results of classical studies by P. Medavar et al. (1953), i.e. about the unique role of the immune tolerance of the mother's organism with respect to the genetic alien fetus [33.35]. For the discoveries of this phenomenon, scientists were recognized with the Nobel Prize in the field of physiology and medicine in 1960. Since the publication of this work, studies are currently underway to study the role of the pregnant immune system.

In pregnant women with CP, the role of the immune system is not only a pathological process occurring in the kidneys, but also takes into account a number of changes in the rebuilding of the pregnant immune system.

Due to a special restructuring in the pregnant woman's immune system, morphological and functional changes occur that ensure the normal development of the fetus in the mother's body. These immune relationships form harmony in the mother-placenta-fetus system. For the normal implementation of the entire program of intrauterine development and timely delivery, immune changes occur in the mother's body aimed at creating a favorable immunological background for embryo implantation, growth and maturation of the placenta [1,20,30,34].

The pregnant woman's immune system functions by implementing immunological tolerance, which is ensured by specific (immune complexes, antigens, blocking antibodies) and non-specific (hormones, glycoproteins and a number of other complexes) mechanisms.

The cellular immunity of the mother is one of the most important mechanisms ensuring the preservation of the fetus. During physiological pregnancy, there is a decrease in the blood absolute and relative number of T-lymphocytes, an increase in the number of T-suppressors and a slight decrease in T-helpers [6]. This explains a number of authors

explaining the presence of non-specific T-cell suppression during physiological pregnancy, which ensures the immunological tolerance of the pregnant woman to the fetus. But according to other researchers, on the contrary, they believe that pregnancy does not cause changes in the state of cellular immunity, which can be interpreted as manifestations of physiological immunodeficiency.

With an uncomplicated pregnancy in the first and second trimesters, the relative and absolute number of lymphocytes decreases, in the third trimester their number is restored and does not significantly differ from the number of lymphocytes of non-pregnant women [24].

The physiological course of pregnancy is maintained due to the activity of T-suppressors, which prevent the strengthening of the immune response. The increase in the number and functional activity of T-suppressors is carried out by increased production of progesterone, chorionic gonadotropin. Already in the early stages of gestation, fetal T-suppressors can penetrate the mother's bloodstream or produce humoral factors that cross the placenta into the mother's body. As a result of this, the mother's immune system develops an immunological reaction of the humoral and cellular type, aimed at alloantigens of the fetus [24].

The humoral factors of the immune response are also of great importance in the physiological course of pregnancy. Serum levels of various classes of immunoglobulins, which reflect the functional state of B-lymphocytes and humoral immunity, are heterogeneous. Immunological tolerance during pregnancy is provided by the content of mainly immunoglobulins of three classes (IgA, IgM, IgG) during a physiologically ongoing pregnancy, which does not differ from the level of a healthy woman outside pregnancy. According to other authors, during physiological pregnancy in the first trimester, a significant increase in the content of all three classes of immunoglobulins is noted, in the second trimester, the level of immunoglobulins decreases markedly and gradually increases in the third trimester, not reaching normal values, which may be explained by a decrease in humoral immunity in pregnant women. Activation of the natural (non-specific, innate) immunity link allows you to compensate for the suppression of the specific link of the mother's immune response during pregnancy. This allows you to create a unique balance between the specific and nonspecific immunity of the mother, in which not the lymphocyte, but the monocyte becomes the central cell of the mother's immune adaptation. This indicates that during pregnancy, despite physiological immunosuppression, the functional activity of T and B lymphocytes does not change and does not affect the general resistance of the body of a healthy pregnant woman [8].

Researchers are attracted by the study of the role of the above immunological mechanisms in the pathogenesis of pyelonephritis [21,30,31]. The state of immunity and nonspecific resistance of the body, along with microbial aggression against the background of functional and mechanical disorders of urodynamics, contributes to the development of pyelonephritis as well as the result of "failure" of the mechanisms of regulation and self-regulation of adaptive value, which is an important factor supporting the hemostasis of the body.

It should be noted that in medicine there is a distinction between immune and inflammatory processes. The immune processes include reactions, in which the leading role is played by leukocytes, which are triggered by a specific antigen. Along with this, immune responses can also occur in places where there is no lymphoid tissue, and the local immune response develops into inflammation, which greatly enhances the immune response. It follows from this that immunity and inflammation are two sides of the same process, i.e. inflammation is an inducer of the immune response and the main tool for assessing the reactivity of an organism. On the role of the immune factor in the pathogenesis of gestational pyelonephritis, it should be noted that the participation of immune mechanisms in this

nosology is recognized by most authors, however, the specificity of the immune shifts arising from this disease remains controversial. The heterogeneity of changes in the immune system revealed during gestational pyelonephritis is noteworthy and, often, the lack of a clear correlation with the clinical picture of the disease, which, apparently, can be explained by various methodological approaches, insufficient consideration of the phase of the disease, complications, etc. [4] .

The literature data on the study of the state of the T-system of lymphocytes in pyelonephritis of pregnant women are diverse. Many authors pointed to a decrease in the number of T and B lymphocytes, noting the imbalance of subpopulations of T lymphocytes with a decrease in the number of T-helpers against the background of an increase in T-suppressor cells. Along with this, the erased clinical picture and relapsing course of the disease, as well as frequent purulent complications of the disease, are associated with severe T-cell suppression [27,28].

In studies, it is noted that in the blood serum of pregnant women suffering from a urinary tract infection, an increase in the content of class M, A, G immunoglobins is determined, while similar studies on the study of the immune status note a decrease in the level of basic immunoglobulins or even the absence of changes in their content. An increase in serum IgM was detected in women with acute pyelonephritis in pregnant women, in cases of exacerbation of chronic pyelonephritis, IgG and IgA levels were reduced, IgM did not change, which is associated with secondary immunodeficiency in pregnant women and a long-term infection process [17].

It is known that the level of basic immunoglobulins is closely related to the hormonal status of a pregnant woman. So, in acute and chronic pyelonephritis, estrogens have an inhibitory effect on the synthesis of IgM and IgG, while progesterone stimulates. With the development of pyelonephritis, inhibition of common factors of nonspecific resistance is considered as a factor accompanying the development of a purulent process.

An assessment of the state of immunity cannot be considered without the participation of the cytokine network in diseases accompanied by secondary immune deficiency [7,12,25].

Cytokines are also considered a factory of immune mediators. Cytokines are low molecular weight proteins produced by predominantly activated cells of the immune system that regulate numerous intercellular interactions. The peripheral blood of healthy donors contains less than 0.01% of the cells that synthesize and secrete cytokines [11].

There are more than 90 molecules of the class of cytokines: more than 15 interleukins, tumor necrosis factor, lymphotoxin, interferons, etc. Depending on the functions performed, cytokines can be divided into several main groups: pro-inflammatory, anti-inflammatory, cytotoxic, stimulating antibody formation involved in allergic reactions, regulating cell proliferation and differentiation.

Acting on all parts of the immune system, cytokines regulate normal immunopoiesis, act as the main mediator of the immune response and, moreover, in very low doses [11].

With their help, immune mechanisms are implemented aimed at eliminating any genetic invasion (infectious agent), damaged structures and restoring the constancy of the internal environment. The stimulating or inhibitory effect of cytokines is carried out by binding to receptors on the cell surface, as a result of which the signal enters the nucleus, and the corresponding genes are expressed, which leads to the production of new proteins.

In diseases of the urinary tract, cytokines act as inducers and regulators of local and local, as well as general and systemic reactions. Cytokines of systemic action include, first of all, interleukins (IL) -1β, IL-4, IL-6, IL-12, tumor necrosis factor and interferons [7].

In addition to the immune system, the action of cytokines extends to other body

systems: the nervous, endocrine, hematopoietic and vascular. Cytokines control the growth, differentiation, and functional activity of cells of various tissue belonging [7,12,29].

Interleukin-1 (IL-1) is considered one of the main inflammatory mediators. Acting as a local inflammatory mediator, IL-1 promotes the release of histamine, plasminogen, a platelet and leukotriene activation factor from inflammatory infiltrate cells and stimulates the formation of free oxygen radicals. Interleukin-1 mediates inflammatory reactions: fever, weight loss, leukocytosis, increased vascular permeability, induces the formation of acute-phase inflammatory proteins [3,7,12].

IL-1 has a biological role in the activation of local defense reactions. In the focus of inflammation, IL-1β increases the decreased functional activity of leukocytes, antimicrobial properties of neutrophils. Activation of neutrophils leads to the stimulation of degranulation, the induction of the synthesis and secretion of lysosomal enzymes, leukotrienes, bactericidal factors with the formation of an autocrine cell regulation pathway. Pro-inflammatory cytokines are mutual inductors: IL-1β enhances its own production, as well as the production of IL-6, IL-8, TNF-α. TNF-α, in turn, induces the synthesis of IL-1, IL-6, IL-8 [7,12,25].

The wide range of biological activity of IL-1 indicates that IL-1 is the main mediator of the development of local inflammatory response and acute phase response at the body level. In patients with purulent-destructive diseases of the lungs, skin, subcutaneous tissue and with sepsis in the blood plasma, an increase in the level of IL-1β was noted. The content of IL-1β correlates with the prevalence, as well as with the severity of the inflammatory process, i.e. IL-1β acts as a synergist for chronic infections [3,12].

It is known that IFN-γ is the main mediator of cellular immunity. A high level of IFN-γ helps maintain the inflammatory process in the lesion, increase the cytotoxic activity of cells that infiltrate the affected tissue. Together with the tumor necrosis factor-α, IFN-γ provides immune surveillance aimed at eliminating foreign substrates from the body, causing a synergistic pronounced effect of cytolysis, destruction of infected, defective cells.

For many inflammatory diseases, including pyelonephritis, an important role belongs to the imbalance of cytokines with pro-inflammatory and anti-inflammatory regulatory effects. The pro-inflammatory group of interleukins is: IL-1, IL-2, IL-6, IL-8, IL-12, IL-15, IL-18, tumor necrosis factor-α, IFN-γ. The group of anti-inflammatory interleukins includes: IL-4, IL-10, IL-11, endogenous IL-1 receptor antagonists, transforming growth factor [8].

According to the results of several studies, changes in the production of many cytokines in inflammatory diseases of the urinary tract, including pyelonephritis, were revealed. So it was found that acute pyelonephritis is associated with a T-immune response, and therefore with excessive synthesis of pro-inflammatory mediators, such as IL-1, IL-2, IL-6, IL-8 and a slight change in the content of tumor necrosis factor-α. As an early diagnostic criterion for acute pyelonephritis, it is proposed to use the content of IL-6 in various biological media. In studies, it was found that asymptomatic bacteriuria is accompanied by an increase in the level of IL-6 in the urine, and the development of acute pyelonephritis is accompanied by an increase in the content of IL-6 in the blood and urine. So in the experiment, by introducing E. coli rats into the bladder, local production of IL-6 and IL-8, identified immunochemically, as well as destruction of the renal parenchyma, accompanied by severe leukocyte infiltration, were recorded. These results indicate the participation of pro-inflammatory cytokines in the immunopathogenesis of pyelonephritis at the earliest stages of its development [8].

In the works devoted to the study of the participation of cytokines in the development of chronic pyelonephritis, changes in the cytokine status were detected [4], and quantitative characteristics of some factors (IL-6, IL-8) associated with inflammation in patients with chronic pyelonephritis in remission and exacerbation were obtained [4.9].

The synthesis profile of cytokines is under genetic and hormonal control. Corticosteroids are powerful modulators of the immune response that affect all its stages and components. They have a direct hormonal effect on energy metabolism, migration, functional activity of immunocompetent cells, and the synthesis of cytokines. Corticosteroid drugs reduce the activation and proliferation of T-lymphocytes, inhibit the production of macrophages and T-helpers of type 1 IL-1, IL-2, IL-8, tumor necrosis factor-a, IFNu, regulate the production of T-helpers of type 2 IL-4, IL-10, IL-13, however, do not significantly affect the functional properties of cytokines. The immunosuppressive effect of corticosteroids is largely associated with inhibition of the synthesis of cytokines, prostaglandins, leukotrienes, bradykinin, platelet activating factor, histamine, and neutral proteases. Since corticosteroids mainly inhibit the activation of type 1 T-helper cells and the synthesis of the corresponding cytokines, the intensity of phagocytosis, cellular and, to a lesser extent, humoral immune reactions is reduced [8].

Corticosteroids, along with immunosuppressive, have a powerful anti-inflammatory effect, characterized by suppression of all phases of inflammation, mainly due to the stabilization of lysosomal membranes, suppression of fibroblast proliferation. It should be emphasized that endogenous glucocorticoids protect the body from the negative effects of large amounts of cytokines produced by various pathogenic agents, primarily infectious and toxic.

Against the background of hormonal changes occurring in women during pregnancy, changes in the cytokine balance in gestational pyelonephritis undoubtedly have a number of features [36].

In the physiological course of pregnancy, the participation of cytokines is unquestionable. In physiological course of pregnancy there is a shift towards relative increase of T-helpers of type 2 and cytokines produced by them (IL-4, IL-5, IL-10) against the background of decrease of T-helpers of type 1 producing IFN-, IL-2, tumor necrosis factor-α. At normal course of pregnancy dynamic equilibrium of these cytokine profiles with temporary predominance of one or another depending on gestation period is observed [32].

The study of hormones of the reproductive system in the regulation of immune status attracts the attention of the researchers. The immunomodulatory functions of estrogens have been studied to the fullest extent. Estrogen receptors were found in various immunocompetent cells, including CD4 and CDs cells, macrophages. Estrogens have a modulating effect on the production of cytokines: they inhibit the activity of T-helpers of type 1 and, accordingly, reduce the synthesis of pro-inflammatory cytokines (IL-1r, IL-6, IL-8, IL-12, tumor necrosis factor-α, IFN-γ) and stimulate the production of T-helpers of type 2 anti-inflammatory cytokines (IL-10, IL-4).

Progesterone significantly blocks and suppresses the activation and proliferation of cytotoxic T-helpers of type 1, the activity of natural killers, as well as the production of IFN-γ, IL-2, tumor necrosis factor-α, in this regard, this hormone is considered a natural immunosuppressant.

In the literature there is a lot of data on the relationship of the development of purulent infection with severe disorders in the immune system. It is of interest to study the role of cytokine-mediated mechanisms of the formation of immune deficiency in chronic infections [17].

As a result of tissue infection, a complex and multicomponent sequence of reactions is developed in the body aimed at preventing further tissue destruction, isolating or destroying the pathogen, activating reparative processes, and restoring the initial homeostasis. The initiation and main stages of the development of the inflammatory response are controlled mainly by proinflammatory cytokines, which are produced by macrophages, neutrophils and T cells in response to stimulation by bacterial antigens. Pro-inflammatory

cytokines play a protective role, as they ensure the recruitment of effector cells (neutrophils, macrophages) into the foci of infection, stimulate their phagocytic, bactericidal activity and induces the launch of an antigen-specific immune response, which together contributes to the elimination of the pathogen.

The protective role of pro-inflammatory cytokines is manifested when these mediators work locally, in the focus of inflammation, but their systemic production does not mean the high efficiency of anti-infection immunity. On the contrary, excessive and generalized production of proinflammatory cytokines leads to the development of bacterial toxic shock and organ dysfunctions. An increase in the concentration of pro- and anti-inflammatory cytokines (tumor necrosis factor-α, IL-1, IL-6, IL-10, IL-8, soluble antagonists of interleukin-1a receptors) in purulent-septic diseases has been confirmed in numerous studies [13,27]. Many anti-inflammatory cytokines (IL-10, IL-4, IL-13) also have immunosuppressive properties, which gave researchers reason to believe that a more pronounced systemic reaction subsequently initiates deeper immunosuppression.

Changes in immunity indicators are more pronounced in pregnant women with gestational pyelonephritis, first detected during pregnancy, than in pregnant women suffering from chronic pyelonephritis, exacerbated during pregnancy. The following parameters have diagnostic value in determining the clinical variant of pyelonephritis: the content of the C3 component of complement, the C1 inhibitor, lactoferrin and the functional reserve of neutrophils [18,21].

In the works of N.V. Belyaeva, an important role of the immune system is noted both in the development of pregnancy and during the course of primary chronic pyelonephritis [2].

The emergence of immune deficiency in primary chronic pyelonephritis contributes to the prolonged persistence of microorganisms in the kidneys [15].

Significant changes in immunity indicators were observed among pregnant women with primary chronic pyelonephritis compared with healthy pregnant women. Without exacerbating the disease, the changes are manifested by a significant increase in the level of IgG, circulating immune complexes, spontaneous HCT activity of neutrophils and a decrease in the HCT test induced by zymosan, which indicates a decrease in the functional reserves of the immune system and the need for its correction. With an exacerbation of the inflammatory process in the kidneys, the content of CD8 + lymphocytes, the reserves of the functional activity of neutrophils are significantly reduced, and the level of IgA, IgM, circulating immune complexes significantly increases, which is associated with a long and persistent course of exacerbation of the disease [26].

Currently, studies are being conducted on the role of cytokines in the regulation of the immune system in patients with pyelonephritis. It seems that the study of the relationship between the content of cytokines in CP with a change in immunological status indicators is relevant, and will further improve the prevention and treatment of this disease. The level of IL-8 in serum in patients with CP in the phase of active inflammation was significantly higher than in patients with CP in the phase of persistent remission and did not differ from the level of IL-8 in the blood serum of patients with CP in remission with a frequent exacerbation of the inflammatory process in throughout the year. High values of serum IL-8 in patients with CP in the active phase of inflammation, indicates the continuation of a sluggish inflammatory process. Such patients need additional monitoring and treatment. The results of the correlation analysis showed that serum IL-8 has the maximum number of connections with other indicators. The highest degree of correlation is observed between IL-8 serum and CD3 + CD8 +. This result confirms the high diagnostic significance of serum IL-8 in predicting frequent exacerbations in accordance with the established threshold value. The author considers the change in the level of IL-8 in serum to be the most significant

immunological factor in predicting the activation of chronic pyelonephritis [22].

Conclusions

Based on the presented literature sources, changes in the cellular and humoral immunity during physiological and pathological pregnancy are diverse, and the addition of a bacterial infection to physiological pregnancy leads to a significant imbalance in the woman's immune system.

Thus, in view of the significant changes that are observed in the immune system in chronic pyelonephritis of pregnant women, the study of cellular and humoral immunity will help to reveal new aspects of the pathogenesis of gestational pyelonephritis, since they are assigned a decisive role in the processes of activation, proliferation and differentiation of immunocytes. This approach allows us to conclude about the prognostic value of immunological parameters in gestational pyelonephritis.

References

[1] Aylamazyan E.K. - ed. Obstetrics: national leadership. / E.K. Aylamazyan, V.I. Kulakov, V.E. Radzinsky, G.M. Savelyeva. - M .: GEOTAR - Media - 2009 - 1200 s.

[2] Belyaeva, N.V. Clinical and immunological features of pregnancy at 18–20 and 21–22 weeks and the period after its termination in women of various age groups / N.V. Belyaeva, I.K. Bogatova, N.Yu.Sotnikova // Reproductive health of children and adolescents. - 2009. - No. 1. - S. 75–80.2.

[3] Vanko L.V., Matveeva N.K., Lomova N.A. Functional activity of granulocytes in pregnant women with high infectious risk and their newborns. Obstetrics and gynecology. 2012; 7: 14-20. [Van'ko LV, Matveeva NK, Lomova NA. The functional activity of granulocytes at pregnant women with high infectious risk and their newborns. Akusherstvo i gynekologiya. 2012; 7: 14-20. (In Russ.)].

[4] Ermishina V.I., Kazeko I.I., Berdichevsky V. B. Clinical, biochemical and immunological parameters in the diagnosis and treatment of chronic pyelonephritis against intercurrent diseases. Urology. 2014; 5: 1-4. [Ermishina VI, Kazeko II, Berdichevskii VB. Clinical and biochemical and immunological parameters in the diagnostics and treatment of chronic pyelonephritis on the background of intercurrent diseases. Urologiya. 2014; 5: 1-4. (In Russ.)

[5] Iremashvili V.V. Urinary tract infections: a modern view of the problem. Russian medical journal. 2007; 15 (29): 2231–6 .;

[6] Kazimirko N.K. and other Immunology of physiological pregnancy. Young Scientist. 2014; 3 (6): 132–7./Kazimirko N.K. i dr. Immunologiia fiziologicheskoi beremennosti. Molodoi uchenyi. 2014; 3 (6): 132–7. [in Russian].

[7] Ketlinsky S.A. Cytokines. SPb .: Tome. 2008; 552. [Ketlinsky SA. Tsitokiny. [Cytokines]. SPb .: Foliant. 2008; 552. (In Russ.)].

[8] Clinical, microbiological and immunological aspects of the formation of the serous form of acute gestational pyelonephritis. Training manual. P.V. Glybochko, I.V. Mikhailov, V.M. Popkov, A.N. Ponukalin, B.I. Blumberg, M.L. Chekhonatskaya. Saratov LLC Sarvet-plus, 2006.

[9] Kozinova O.V., Shekhtman M.M. Anomalies in the structure of the kidneys and hydronephrosis in pregnant women. Gynecology. 2010; 12: 1: 43-46. [Kozinova OV, Shechtman MM. Anomalies of renal structure and hydronephrosis at pregnant. Ginekologiya. 2010; 12: 1: 43-46. (In Russ.)].

[10] Kravchenko, E.N. Infectious and inflammatory diseases of the kidneys in pregnant women. Diagnosis and treatment / E.N. Kravchenko, I.A. Gordeeva, D.V. Kubarev // Obstetrics and gynecology. - 2013. - No. 4. - S. 29-32 .;

[11] Krechetova L.V., Nikolaeva M.A., Vanko L.V. In vitro production of cytokines by

peripheral blood mononuclear cells during alloimmunization in patients with a common miscarriage. Obstetrics and gynecology. 2014; 4: 51-56. [Krechetova LV, Nikolaeva MA, Van'ko LV. Vitro cytokine production by mononuclear peripheral blood cells during alloimmunization in patients with habitual miscarriage. Akusherstvo i gynekologiya. 2014; 4: 51-56. (In Russ.).

[12] Levkovich M.A. Modern ideas about the role of cytokines in the genesis of the physiological and pathological course of pregnancy. Russian Bulletin of the Obstetrician-Gynecologist. 2008; 3: 37-40. [Levkovich MA. Modern views of the cytokines role in the genesis of physiological and pathological course of pregnancy. Rossiiskii vestnik akushera-gynekologa. 2008; 3: 37-40. (In Russ.)

[13] Litvinov V.A., Cherepakhina N.E., Sanaev A.A. Chronic pyelonephritis: Features of immunopathogenesis and principles of clinical immunodiagnosis // Doctor. - 2008. – № 1.– C. 12-17.

[14] Logutova, L.S. Extragenital pathology and pregnancy. Practical Guide / L.S. Logutova. - M .: Litterra, 2012 .-- 544 p .;

[15] Makarov, I.O. Evaluation of the effectiveness of cefexime (suprax) in uncomplicated gestational pyelonephritis / I.O. Makarov, E.I. Borovkova, T.R. Shemanaeva // Ros. Vestn. obstetrician-gynecologist. - 2011. - No. 1. - S. 67–72.

[16] Minasyan, A.M. Pregnancy against the background of chronic pyelonephritis (review) / A.M. Minasyan, M.V. Dubrovskaya // Saratov Journal of Medical Scientific Research. - 2012. - No. 4. - S. 920-925;

[17] Nikulicheva VI, Safuanova G.Sh., Karpina N.S., Lekhmus T.Yu., Vagapova DR, Alonova SV. Immuno-inflammatory markers of chronic pyelonephritis. Bulletin of the VSSC SB RAMS, 2014, No. 1 (95). 46-49 pp.

[18] Petrov S.V., Seregin S.P., Kuzmin A.A. et al. The study of cytokine status in the treatment of serous pyelonephritis during pregnancy for decision-making systems // Bulletin of the South-West State University. - 2012; 2 (43): 56–60.

[19] Petrov S.V., Seregin S.P., Novikov A.V., Agarkov N.M. Analysis of multimodal changes in immunity parameters depending on the clinical variant of uncomplicated pyelonephritis during pregnancy to predict it. Immunopathology and clinical immunology 2014. Pages 77-79.

[20] Poletaev, A.B. Immunopathology of pregnancy and child health / A.B. Poletaev, F. Aliyev, L.I. Maltseva // Russian Medical Journal. - 2010. - No. 4. - S. 162-167.

[21] Seregin S.P., Petrov S.V., Kholimenko I.M. Prediction of the course of various forms of pyelonephritis in pregnant women according to changes in the parameters of innate immunity. Obstetrics and gynecology. 2018; 1: 48-52.

[22] Serezhenkov A.V. Evaluation of the effectiveness of immunotherapy in the complex treatment of chronic pyelonephritis in the active phase of inflammation. Diss. for the degree of candidate of medical sciences 2016.137 p.

[23] Serov V.N. Gestational pyelonephritis: diagnosis, prevention, treatment / V.N. Serov, V.L. Tyutyunnik // RMZh.– 2008.– T. 16, No. 1. - P. 10–13.

[24] Smirnova T.L., Portnova E.V., Sergeeva V.E. Immunity and pregnancy. West.Chuvash University. 2009; 2: 79–85./Smirnova T.L., Portnova E.V., Sergeeva V.E. Immunitet i beremennost.Vestn.Chuvashskogo universiteta. 2009; 2: 79–85. [In Russian].

[25] Sukhikh G.T., Vanko L.V. Immune factors in the etiology and pathogenesis of pregnancy complications. Obstetrics and gynecology. 2012; 1: 128-136. [Sukhikh GT, Van'ko LV. Immune factors in the etiology and pathogenesis of complications of pregnancy. Akusherstvo i ginekologiya. 2012; 1: 128-136. (In Russ.).

[26] Talaev A. M., Sotnikova N. Yu., Talaeva E. M. Features of the immune status in pregnant women with chronic pyelonephritis. Bulletin of the Ivanovo Medical Academy. T. 17, No. 4, 2012, 51-54 pp.

[27] Trizno N.N., Gallimzyanov H.M., Miroshnikov V.M., Suchkova V.M. The modern model of immunopathogenesis of a chronic relapsing infectious disease: chronic pyelonephritis and intracranial infectious and inflammatory processes // Astrakhan Medical Journal. – 2011. – №1. – P.12–18.

[28] Cherepakhina N.E. The modern concept of immunopathogenesis of chronic and chronically recurrent diseases of an infectious nature as the foundation for the development of a modern immunodiagnostics protocol: Dis .... Cand. honey. Sciences: 14.00.36. –M., 2009. - 149 p.

[29] Howren MB, Lamkin DM, Suis J. Associations of depression with Creative protein, IL-1, and IL-6: a metaanalysis. Psychosom Med. 2009;71:171-186.

[30] owicki B, Sledzinska A, Samet A, Nowicki S. Pathogenesis of gestational urinary tract infection: urinary obstruction versus immune adaptation and microbial virulence. BJOG 2011; 118: 109–112.

[31] oto E., Romero R., Vaisbuch E., Erez O., Mazaki-Tovi Sh., J.P. Kusanovic, Z. Dong, T. Chaiworapongsa, L. Yeo, P. Mittal & S.S. Hassan. Fragment Bb: evidence for activation of the alternative pathway of the complement system in pregnant women with acute pyelonephritis. The Journal of Maternal-Fetal and Neonatal Medicine, October, 2010; 23(10): 1085–1090.

[32] Southcombe J.H., Redman C.WG, IL [Sargent,, and I Granne. Interleukin-1 family cytokines and their regulatory proteins in normal pregnancy and pre-eclampsia.Clin Exp Immunol. 2015 Sep; 181(3): 480–490.Published online 2015 Jun 29.doi: 10.1111/cei.12608.

[33] Steinborn A et al. Pregnancy-associated diseases are characterized by the composition of the systemic regulatory T-cell (Treg) pool with distinct subsets of Tregs. Clin Exp Immunol 2012; 167 (1): 84–98.

[34] Sulagna Dutta. Defining pregnancy phases with cytokine shift. Sulagna Dutta and Pallav Sengupta. Journal of Pregnancy and Reproduction J Pregnancy Reprod, 2017 doi: 10.15761/JPR.1000124 Volume 1(4): 1-3 ISSN: 2515-1665.

[35] Warning JC, McCracken SA, Morris JM. A balancing act: mechanisms by which the fetus avoids rejection by the maternal immune system. Reproduction 2011; 141: 715–24.

[36] Ysabel C. Casart, Katiuska Tarrazzi &María I. Camejo. Serum levels of interleukin-6, interleukin-1β and human chorionic gonadotropin in pre-eclamptic and normal pregnancy. Gynecological Endocrinology. Received 28 Aug 2006, Accepted 07 Mar 2007, Published online: 07 Jul 2009. Pages 300-303.