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Differentiated Approach to Assessing the Immune Status in Pregnant and Lactating Women

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Relevance. For a long time, the problem of premature birth (PR) has occupied one of the leading places in modern obstetrics, and its medical and socio-economic significance is undeniable [1]. PR is the leading cause of neonatal morbidity and mortality of newborns. Thus, premature infants account for 60-70% of early neonatal and 65-75% of infant mortality. In addition, one should not forget about the high cost of nursing premature babies, the high frequency of childhood disability, as well as the possibility of developing long-term adverse consequences of under sharing [2.3].

Despite the progress in the provision of medical care, the frequency of premature births in recent years has not tended to decrease, and in some countries there is even an increase in this indicator. According to WHO, 15 million babies are born prematurely every year (before the full 37 weeks of pregnancy). Preterm birth rates vary from 5 to 18% in different countries of the world, in the Russian Federation this figure is 6-15% in different regions. According to the classification, premature birth is divided into spontaneous (70-80% of all premature births) and induced (20-30%), which are associated with the health of the pregnant woman and / or fetus. Spontaneous labor can begin both with the development of regular labor with a whole fetal bladder (true premature labor, they account for about 40-50% of cases), and with premature rupture of the fetal membranes in the absence of regular labor (about 50%) [7. 8].

Most researchers in the pathogenesis of premature birth tend to believe that two main trends are directly realized in the mechanism of their development: the predominance of non-inflammatory and infectious causes. According to the literature, about 40 % of premature births are caused by infectious factors [5. 6. 7. 9]. The leading pathogenetic mechanism in the realization of premature birth of infectious genesis includes the development of a nonspecific systemic inflammatory response of the body to infectious agents. In systemic inflammatory response syndrome (SERS), local tissue damage in the area of inoculation of infectious pathogenic agents causes a combination of systemic reactions. This is associated with the dysfunction of innate and acquired immunity and is manifested by a violation of the ratio of pro and anti-inflammatory cytokines. Currently, the role of cytokines in the realization of premature birth is being actively studied [10].

In this test system, after isolation of the total pool of DNA and RNA, a reverse transcription reaction was performed to obtain complementary DNA from the m-RNA matrix, which was further amplified by PCR. After the amplification stage, the mRNA expression level of innate immunity genes (IL1B, IL10, IL18, TNFa, TLR4, GATA3, CD68, B2M) was programmatically calculated according to the indicator cycle indicator. Based on an integral assessment of the obtained levels of gene expression, a conclusion was made about the presence or absence of a local inflammatory reaction by the value of the inflammation index (IV). The IV value of more than 60% was assessed as inflammation, with IV less than 50% – the absence of an inflammatory reaction, the range of 50-60% – "cannot be excluded" (gray zone) [11.13.15].

Currently, 8 antigenic serotypes of the Herpesviridae family are known: herpes simplex viruses of the 1st and 2nd types (HSV-1 and HSV-2); Herpesvirus varicellae – the causative agent of chickenpox and herpes zoster; cytomegalovirus (CMV); Epstein–Barr virus (EBV); GV types 6– 8. All GW are capable of lifelong persistence in the human body and have pronounced immunosuppressive and oncogenic effects.

There are two stages in the life cycle of GW:

1. lytic, characterized by active replication of viral DNA;
2. latent, in which the virus in the body is preserved in the form of subviral structures.

These stages in the process of vital activity of GW repeatedly cyclically replace each other, the mechanisms of latency and activation of GW are insufficiently studied, however, it is known that the above transitions are carried out under the control of the immune system. Innate immunity plays an important role in the course of GVI [16]. The system of innate immunity is the first line of defense of the body during primary infection of GVI, reactivation of chronic and latent forms of GVI. The regulation of the immune response (IO) is carried out by the production of pro- and anti-inflammatory cytokines, primary infection of GW and/or reactivation of latent and chronic GW cause the development of early cytokine reactions underlying natural IO [19]. Early cytokine reactions include the synthesis of pro-inflammatory cytokines, which include interleukins (IL) -1, -6 and -12, tumor necrosis factors (TNF)-α and -β, interferons (IFN)-α, -β, -γ, etc.

The development of IO fully suppresses the reproduction of viruses and prevents their dissemination, however, during pregnancy, due to physiological immunosuppression, sensitivity to non-embryonic antigens decreases, which leads to the activation of chronic viral infection. Primary infection with HBV or activation of long-lasting persistent latent HBV in the body of a pregnant woman leads to the realization of IO by stimulating type 1 T-helper cells (Th1), resulting in a disturbed balance between pro- and anti-inflammatory cytokines, while increasing the risk of termination of pregnancy. With insufficient IO, GW can have a direct embryotoxic effect on the fetus [17.18].

The increase in the prevalence of chronic hepatitis virus (HCV) B and C led to an increase in this pathology among people of young, re -productive age, including pregnant women. Women of fertile age with CVH, if indicated, should be given antiviral therapy before the planned pregnancy [2]. However, due to the predominantly latent course, CVH B and C, as a rule, are first detected during pregnancy. Standard antiviral therapy of HCV B and C is contraindicated during pregnancy. At the same time, there is a real risk of vertical transmission of hepatitis B and C viruses during pregnancy and childbirth. The main way to prevent viral hepatitis B in young children is vaccination. Despite the immunization of children against hepatitis B, vertical transmission of the hepatitis B virus still occurs. The dependence of the risk of vertical transmission of hepatitis B and C viruses on the viral load of the mother has been established. With HCV B and C, an increase in viral load is noted in the third trimester of pregnancy [20.22.24].

Based on the results obtained, the following conclusions were made. GVI potentiates a high risk of gestational complications and perinatal losses. When studying the cytokine status of pregnant women with active and latent course of GVI, significant violations of the cytokine regulation of IO were found. Activation of latent forms of HVI during pregnancy is a trigger factor for switching immune stimulation from Th2 to Th1, while the implementation of IO is carried out mainly at the local level. The development of systemic IO is a consequence of the disruption of compensatory and adaptive mechanisms and poses a great threat to the development of undeveloped pregnancy, perinatal loss syndrome, intrauterine infection in the fetus. The cause of a systemic inflammatory reaction may be autoimmune diseases, immunosuppression due to prolonged persistence of GW and many other factors. Therefore, the study of the cytokine status during pregnancy, as well as at the stages of pre-pregnancy preparation, will help identify risk groups for gestational complications and will determine the need for immunocorrective therapy. The administration of immunomodulatory drugs during pregnancy in most cases is the only way to treat viral infections due to the impossibility of etiotropic therapy [21.23.25.27].

Substitution therapy with IFN-containing drugs in pregnant women with GVI is justified, given the direct antiviral effect of IFN alpha-2 and a pronounced deficiency of IFN, which forms with prolonged persistence of viruses in the body, as well as during gestation. Currently, a fairly large number of works are devoted to the search for the causes and the possibility of forecasting PR [1. 6. 10. 17]. However, despite the obvious progress in understanding the causes and methods of prevention of PR, many issues remain not fully clarified. Thus, the risk factors for the development of PR most researchers include: premature birth, late miscarriages, medical abortions in the anamnesis, nicotine addiction, low socio-economic standard of living, stressful situation, cervical conization, induced pregnancy, cervical-vaginal infection, urinary tract infection, severe extragenital pathology [19.21.24.26].

Our research has confirmed the data of the world literature. It should be noted that in addition to well-known factors, we noted a large percentage of high BMI in women with PR compared to the control group ($p= 0.009$). Thus, the risk factors for PR in this study were: indications of a history of premature birth, two or more intrauterine interventions, smoking, impaired fat metabolism, acute and chronic infections. In recent years, the development of the PR mechanism has been associated with a violation of the balance of pro- and anti-inflammatory substances. However, there is no single view on this process. Thus, in the variant of PR that began with PRPO, a high index of inflammation is more likely ($p <0.01$). According to domestic and foreign authors, the most common pathogenetic mechanism of the development of PRPO is infection of the lower pole of the fetal bladder [8.12.16]. When pathogenic agents enter the body, the first line of immunological protection, represented by elements of innate immunity, comes into operation.

The primary inflammatory response to pathogens is mediated by specific Toll–like receptors (TLRs), activation of which occurs when interacting with the cell wall of microorganisms. The result of this interaction is an increase in the synthesis of pro-inflammatory cytokines, chemokines and prostoglandins. It is known that an increase in cytokine synthesis in the cervix is the cause of leukocyte infiltration and opening of the cervix. The increased activity of proteases in this case can lead to destabilization of the fetal membranes and their premature rupture [16]. The involvement of TLRs in the development of preterm labor has been confirmed by many studies [14]. Thus, Tyutyunnik V.L. et al. [17] in their study showed a significant decrease in the expression of the TLR-4 gene in a group of women with premature birth, however, this pattern was revealed in the presence of dysbiotic disorders of the vaginal microflora in these patients.

According to other authors [13. 15], in preterm labor, there is an increase in the expression of the TLR-4 and TLR-2 genes immediately before childbirth both in the mucous membrane of the cervical canal and in placental tissue. The increased expression of TLRs leads to the release of pro-inflammatory cytokines that enter the bloodstream, including the fetal bloodstream, and contribute to the premature activation of corticotropin-releasing hormone and the placental-adrenal endocrine cascade.

In our study, we did not obtain significant differences between the groups of premature and timely delivery in terms of the expression of most genes of innate immunity ($p>0.05$). As is known, cytokines normally regulate the onset of labor during the development of physiological pregnancy. The onset of labor is preceded by infiltration of the placenta and surrounding maternal tissues by various cytokines, even in the absence of infection. The result of this activation is the synthesis of pro-inflammatory cytokines IL-1, IL-6, IL-8, TNF and prostaglandins that stimulate uterine contraction [17].

Thus, it turns out that the ratio TLR4 / GATA3 and IV determine the beginning of PR. If the process of inflammation prevails over anti-inflammatory substances, a cascade of reactions develops, leading to CVD and, as a consequence, to PRPO. In the case of true PR, apparently, other mechanisms of activation of the "mother-placenta-fetus" system are involved. Their study continues. Women have SLE more often than men. Sex differences in the frequency and severity of autoimmune diseases are explained by the influence of female sex hormones on the immune system. Estrogens and prolactin play a particularly important role in this, having a significant modulating effect on the immune

response [4]. During pregnancy, high progesterone levels can reduce the activity of the disease by inhibiting Th1- and Th17-cytokines and inducing anti-inflammatory cytokines [5].

Since SLE occurs mainly in women of reproductive age (90% of women aged 13-30 years), relevant issues related to the development of this pathology during pregnancy, the effect of pregnancy on the activity and prognosis of SLE, as well as the effect of SLE on the course of the gestational process and childbirth, pregnancy outcomes, on the development of the fetus and newborn [6. 7].

The frequency of SLE exacerbations during pregnancy varies from 46 to 70%. An important point is the degree of activity of the disease at the time of conception. Women with active SLE at the time of conception, with lupus nephritis or with antiphospholipid syndrome (AFS) have the highest risk of developing pregnancy complications [8]. It is known that the lowest frequency of exacerbation of SLE during gestation will be if conception occurred against the background of prolonged remission (at least 6 months). In addition, the higher the degree of SLE activity at the time of conception, the higher the percentage of disease activation during the gestational process [9].

Exacerbation of SLE during pregnancy is not always easily recognized, therefore it is recommended to conduct monitoring, including monthly laboratory tests, ultrasound examination and cardiotocography of the fetus in mothers with SS-A (Ro) or SS-B (La) antibodies. There is an opinion that in the absence of signs or symptoms of active SLE, specific therapy during pregnancy is not required. Exacerbation of SLE during pregnancy is usually treated with hydroxychloroquine, low-dose prednisone, pulse intravenous administration of methylprednisolone and azathioprine. The use of high doses of prednisone and cyclophosphamide is associated with significant pregnancy complications and poor obstetric outcome [10]. A history of nephritis or activation of SLE within 6 months before conception predicts a bad outcome for the fetus. Pregnancy is recommended to be postponed until a 6-month remission is achieved [11].

Recently, due to the improvement of clinical outcomes, pregnancy in women with SLE has become more commonplace. In most cases, a live baby is born, but pregnancy remains a high-risk factor. Although epidemiological data indicate an improvement in the prognosis of pregnancy in these women, there remains an increased risk of pregnancy complications such as miscarriage, stillbirth, preeclampsia and fetal growth retardation [12]. Maternal and fetal morbidity and mortality are increased compared to the general population. Apparently, deviations in the immune adaptation to pregnancy contribute to this. The predictors of a poor outcome are activation of SLE in the mother, involvement of the kidneys, the presence of specific autoantibodies and organ damage. Therapeutic effects are limited during pregnancy, as it is necessary to weigh the benefits for the mother and the risk for the fetus. It is necessary to prevent miscarriage and premature birth, as well as cardiac blockade in the fetus [13].

The immunopathological mechanisms inherent in SLE, disorders of estrogen metabolism, coagulopathy, thrombocytopathy, various visceritis lead to a high incidence of spontaneous abortions, stillbirths, myocarditis, preeclampsia, and renal failure in pregnant women. The frequency of premature birth, labor anomalies, bleeding during childbirth and the early postpartum period is high. According to I. Iozza et al., the frequency of complications in pregnant women with SLE is 50-60%, the frequency of pregnancy losses increases by 4.8 times, and the frequency of premature birth – by 6.8 times. The most serious complications occur in 10% of cases. Maternal mortality is 2-3% [14]. In addition, there is a high incidence of complications of the early neonatal period, such as hypotrophy, neonatal lupus. Perinatal mortality is high. Mothers with SLE have an increased risk of cesarean section, postpartum bleeding, and hemotransfusion. They are more likely to have premature babies, children with low weight and with congenital heart block [12].

The data available in the literature do not fully characterize the condition of pregnant women with this multisystem autoimmune disease, the peculiarities of the course of pregnancy and the dependence of clinical manifestations of the disease and pregnancy complications on the activity of various components of the immune system. To date, many issues concerning the optimal management of pregnancy in women suffering from SLE, including the treatment of the underlying disease, remain debatable.

It is known that SLE, being a multisystem autoimmune disease, is characterized by the presence of hyperactive immune cells, dysregulated activation of T-lymphocytes, polyclonal activation of B-lymphocytes producing autoreactive antibodies to many nuclear and cytoplasmic antigens, and the formation of immune complexes that cause damage to tissues and organs. The changes in the ratios of immunocompetent cells found in our study do not have pronounced signs of hyperactivation of the immune system in the pregnant women we examined, which may be explained by the state of pregnancy and the effects of immunosuppressants they receive – cytostatics and glucocorticosteroids [2.15.19.23.27].

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