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CHANGES IN CELLULAR AND HUMORAL IMMUNITY IN PREGNANT WOMEN INFECTED WITH COVID-19

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ABSTRACT

According to the literature, pregnant women are more susceptible to coronavirus infection due to changes in their bodies, especially in the respiratory and immune systems. **The aim of this study** was to examine the cellular and humoral factors of adaptive immunity in pregnant women infected with COVID-19. Eighty-five pregnant women at 33-37 weeks of gestation with confirmed COVID-19 diagnosis **were examined**. They were divided into two groups based on the severity of COVID-19: 56 women with moderate severity and 29 women with severe disease. The number of cells with phenotypes CD3, CD4, CD8, CD16 in peripheral blood, and levels of IgA, IgG, and IgM in serum were studied using the ELISA method. It was found that pregnant women with COVID-19 show a severity-dependent imbalance in the studied parameters of cellular and humoral immunity.

KEYWORDS. COVID-19, pregnant women, cellular and humoral immunity.

INTRODACTION

COVID-19 can have negative consequences for pregnant women and their newborns.[1-5] According to statistics, pregnant women, people over 60 years old, and those with severe comorbid conditions (broncho-pulmonary, cardiovascular, autoimmune diseases).[3-4] are most vulnerable to this virus. Limited publications on the impact of COVID-19 on the gestational period, fetus, and newborn suggest that pregnant women are less tolerant to respiratory pathogens and therefore may be more susceptible to COVID-19.[5] However, leading countries have developed various protocols for managing and treating pregnant women with COVID-19.[5,6,7]

As of January 12, 2021, data published in the Cochrane Library and presented at the XV International Congress on Reproductive Medicine (January 19-21, 2021), showed the following perinatal outcomes worldwide: a total of 43,107 cases, including 8,414 cases in the third trimester, with pneumonia developing in 3,758 cases, 1,673 patients admitted to intensive care units, 733 maternal deaths, 16,749 women gave birth (6,331 by cesarean section). A total of 16,394 children were born, with neonatal pneumonia noted in 47 cases, fetal distress in 102 cases, neonatal intensive care unit admission in 1,621 cases, stillbirth in 124 cases, and neonatal death in 97 cases.

High susceptibility to respiratory infections and severe pneumonia in pregnant women is associated with immunosuppression and other physiological changes during pregnancy, necessitating intensive care and mechanical ventilation in severe cases.[7]

Pneumonia most commonly develops in the third trimester, when cell-mediated immunity is at its most altered state, leading to rapid respiratory failure and secondary bacterial complications. The most frequent complications of COVID-19 include ARDS, DIC syndrome, renal failure, secondary bacterial pneumonia, and sepsis. According to D.I. Sheveleva (2020), COVID-19 infection is more common in first-time mothers in the first (61.6%) and third (70.6%) trimesters of pregnancy and in repeat mothers in the second (62.5%) trimester with a complicated obstetric history (58.3%) and comorbid conditions (41.5%).

Study Objective. To study the cellular and humoral adaptive immunity parameters in pregnant women infected with COVID-19.

MATERIALS AND METHODS

To study the clinical and immunological features of the gestational process, 85 pregnant women at 33-37 weeks of gestation with a confirmed diagnosis of COVID-19 were observed. They were divided into two groups based on the severity of COVID-19: 56 women with moderate severity and 29 women with severe disease. Immunological studies included the analysis of lymphocytes with phenotypes CD3, CD4, CD8, CD20 in peripheral blood using monoclonal antibodies (Sorbent Ltd., Moscow, Russia) and levels of IgG, IgA, IgM in serum by ELISA using the "Vector Best" test system (RF). The control group included 20 women with physiologically normal pregnancies. Data were statistically processed using the Student's t-test with a standard statistical software package for Windows 2000.

RESULTS AND DISCUSSION

Analysis of anamnesis showed that COVID-19 infection in pregnant women primarily affects the upper and lower respiratory tracts. Among 13.4% of pregnant women, upper respiratory tract infection was observed, while 49% were diagnosed with bilateral viral pneumonia. The main indications for hospitalizing pregnant women with confirmed COVID-19 were various obstetric pathologies. The most common obstetric complication was oligohydramnios in pregnancies over 30 weeks (21.3%). Other frequent diagnoses included premature detachment of a normally located placenta (1.3%), polyhydramnios (0.9%), and antenatal fetal death (0.5%). Preeclampsia was diagnosed in 5 pregnant women, with 4 cases being mild and 1 case severe, leading to premature termination of pregnancy.

Pregnant women with COVID-19 often had comorbid somatic conditions. The most common was iron-deficiency anemia (68.6%), with the majority of cases being chronic anemia that developed before the current pregnancy (64%). Pregnant women with chronic respiratory diseases, obesity (7.5%), and urinary tract infections (2.98%) were more likely to contract COVID-19.

The clinical course of COVID-19 in pregnant women was particularly severe in the third trimester (Table 1). Despite continuous monitoring by gynecologists and intensivists, with periodic consultations by virologists from the Institute of Virology, Ministry of Health of the Republic of Uzbekistan, nearly half of the infected pregnant women showed symptoms of respiratory failure (48.7%), such as dyspnea, increased respiratory rate over 22 per minute, decreased oxygen saturation (SpO2 below 95%), and elevated body temperature (38˚-39˚) lasting 3-4 days.

SARS-CoV-2 leads to significant disruptions in the coagulation system. Despite the use of antiplatelets and injectable anticoagulants, 7 (10.4%) pregnant women in the third trimester developed thrombotic complications.

Table 1: Complications from COVID-19 in pregnant women in the third trimester of gestation.

Complications	Pregnant Women with COVID-19 (n=85, abs/%)
Respiratory failure	40/47,05
Cardiovascular failure	3/3,53
Thromboembolic complications	2/2,35
Maternal mortality	1/1,18
Perinatal mortality: Antenatal. Intranatal, Postnatal.	10/11,76 3/3,53 2/2,35 3/3,53

In the absence of pregnancy, inflammation caused by the virus attracts T-cells (mainly Th-1 CD4+), which can clear infected cells and prevent further viral spread and replication. The virus is then blocked by neutralizing antibodies, and macrophages clear neutralized viruses and apoptotic cells through phagocytosis. During pregnancy, there is a shift in the population of CD4+ T-cells (with a predominance of Th-2), which may alter the clearance of infected cells during the immune response to viral infections.[2]

Immunological Study Results: Pregnant women with COVID-19 exhibited suppressed cellular immunity (Table 2). As shown in Table 2, immunosuppression manifested as general lymphopenia, a 1.7-fold decrease in absolute T-lymphocyte count ($P<0.01$). Relative values analysis showed a significant decrease in CD3-cell levels ($P<0.01$), as well as a reduction in the relative number of T-helpers (CD4+) ($P<0.05$) and T-suppressors ($P<0.01$).

Table 2: Indicators of the cellular immune response in examined pregnant women.

Immune Indicators	Women with physiological pregnancy (n=20)	Pregnant Women with Moderate COVID-19 (n=56)	Pregnant Women with Severe COVID-19 (n=29)
Leukocytes, abs.	8,1 ± 0,2	11,5 ± 0,3*	12,5 ± 0,3*
Lymphocytes, %	24,2 ± 1,2	19,3 ± 1,0*	16,9 ± 1,0*
Lymphocytes, abs.	2,19 ± 0,012	2,2 ± 0,073*	2,11 ± 0,051*
CD3+, %	51,4 ± 1,5	47,3 ± 1,1*	45,3 ± 1,2*
CD3+, abs.	1,13 ± 0,05	1,04 ± 0,04*	0,95 ± 0,037*
CD4+, %	32,5 ± 1,16	28,5 ± 1,1*	26,5 ± 1,2*
CD4+, abs.	0,77 ± 0,045	0,63 ± 0,034*	0,56 ± 0,031*
CD8+, %	29,5 ± 1,3	25,4 ± 1,1*	23,2 ± 1,0*
CD8+, abs.	0,64 ± 0,045	0,56 ± 0,03*	0,49 ± 0,023*

Note: *Values are significant compared to the control group (P<0.05 - 0.001)

Persistent T-cell immunity deficiency contributes to prolonged virus persistence and creates a risk of chronic infection.[2] The imbalance between the infectious agent and the body's defense mechanisms can result in either suppression or activation of immune responses. Changes in immune status can lead to infection activation. It is suggested that prolonged asymptomatic infection triggers immunity to microbial epitopes, which are also present in humans (Neuer A., 1999). The late stages of pregnancy are at risk because the fetoplacental system experiences significant stress due to the large release of serotonin induced by the infection, as well as the direct toxic effects of the virus on the mother's immune system.[6]

The study of the total pool of B-lymphocytes revealed a significant increase in their relative number (p<0.05), with the highest values observed in women with severe COVID-19 (P<0.05). Immunoglobulins are known to play a crucial role as mediators in the cascade development of the immune response and can partially determine the effectiveness of the final effector responses of cellular immunity in the inactivation and elimination of bacterial and viral antigens.[7] The data presented in Table 3 show that women with COVID-19 exhibit dysimmunoglobulinemia of the G class, while the levels of IgA and IgM were significantly increased (P<0.05), with more profound changes observed in severe COVID-19 cases.

Table 3: Parameters of B-cell immunity in examined pregnant women.

Immune parameters	Women with physiological pregnancy (n=20)	Pregnant women with moderate COVID-19 (n=56)	Pregnant women with severe COVID-19 (n=29)
CD20+, %	23,8 ± 1,4	27,8 ± 1,2	30,8 ± 1,3*
CD20+, abs	0,53 ± 0,05	0,61 ± 0,03*	0,65 ± 0,031*
IgG, g/l	12,4 ± 0,45	9,32 ± 0,3*	7,53 ± 0,25*
IgA, g/l	2,1 ± 0,013	2,6 ± 0,015*	2,88 ± 0,012*
IgM, g/l	1,5 ± 0,02	2,14 ± 0,012*	2,64 ± 0,02*

Note: *Values are significant compared to the control group of women with physiological pregnancy (P<0.05 - 0.001).

Increased levels of IgA and IgM are associated with the synthesis of incomplete immunoglobulins by B-lymphocytes, according to several authors.[4,5] The IgG molecule consists of three fragments: two identical antigen-binding fragments (Fab) and one crystallizing fragment (Fc). The Fab fragment binds to the antigen's determinant group using its active center. The intensity of this interaction is determined by the affinity of the antibodies, which can be either high or low. Low-affinity antibodies do not effectively bind to the antigen, making them less effective in eliminating it from the body. The existence of a non-utilized antigen-antibody complex, in which the virus remains virulent, maintains infection in the body for a long time.[2,3]

There is concern that the coronavirus infection affecting the mother can cross the fetoplacental barrier, causing similar immune protective changes in the developing fetus as seen in the mother. It is known that the transplacental transfer of maternal immunoglobulins to the fetus is a crucial factor for its protection during the gestational period. Significant disruptions occur in the metabolism of the fetoplacental barrier during coronavirus infection. Firstly, the synthesis of major placental hormones—estriol, estradiol, dehydroepiandrosterone, and progesterone—is sharply suppressed, reducing the level of T-suppressors to 7-5.3% in the third trimester of pregnancy.[5,6]

Physiological changes in the immune, cardiovascular, and respiratory systems during pregnancy suggest that pregnant women are particularly vulnerable to pathogenic infectious agents and severe infections. This vulnerability can lead to higher morbidity and mortality rates for both mother and fetus. Pregnant women with pneumonia are more likely to experience preterm births,

deliver low birth weight infants, and have higher rates of cesarean sections. Additionally, pregnancy increases the risk of developing hypertension and gestational diabetes, which are recognized risk factors for severe acute respiratory syndrome caused by coronaviruses, including SARS-CoV-2.

CONCLUSIONS

In pregnant women beyond 32 weeks of gestation, coronavirus infection has a damaging effect on the immune system parameters depending on the severity of the disease. The more severe the disease, the more pronounced the changes in the immune system, and the more frequent the obstetric pathology.

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