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FETAL CYTOKINES IN PREGNANT WOMEN WHO HAVE COVID-19 IN THE SECOND TRIMESTER OF GESTATION

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Abstract:

Of the 387 pregnant women who had COVID-19 and were admitted to the hospital, 23.8% were ill in the first trimester, 49.9% of pregnant women in the second trimester, and the remaining 26.3% of pregnant women in the third trimester. In terms of severity, 51.4% of women had a mild form, 43.2% had a moderate form and 5.4% had a severe form of the disease. The most common extragenital diseases were anemia of pregnant women (58.9%), heart disease in the form of chronic myocarditis (22.7%) and obesity (21.1%). Of the obstetric outcomes in pregnant women with a history of COVID-19, the most common were premature birth, which amounted to 13.7%, and a high incidence of severe preeclampsia, which amounted to 18.3%. The incidence of premature birth in pregnant women with severe COVID-19 at 22-28 weeks was significantly more than 8 times higher than in pregnant women with mild COVID-19.

Keywords: cytokines, fetus, pregnant women, COVID-19, obesity.

Currently, the whole world is gripped by a pandemic that poses a global threat to humanity. One of the most controversial and unstudied aspects of the COVID-19 problem remains the epidemiology and course of the new coronavirus infection in pregnant women. During COVID-19, patients are faced with a cytokine storm - a powerful inflammatory reaction of the body, which is a pathological factor that causes the development of thrombosis, vascular inflammation and other problems for vital organs "...In connection with the epidemic, the World Health Organization (WHO) declared an emergency a health situation of international importance, and the risks at the global level are assessed as very high..." [1,2,3,4,5,6,7,8,9,10].

All over the world, information has been accumulated on the manifestations of the infectious process in pregnant women when infected with SARS-CoV-2, the new pandemic coronavirus that causes COVID-19. The relevance and need to study these problems is quite obvious, since the study of the pathogenetic mechanisms of the development of various complications during pregnancy and the postpartum period will help clarify the impact of COVID-19 on the course of pregnancy and the postpartum period. Therefore, a method for studying neurological disorders in the postpartum period in women who have had coronavirus infection is needed. Pregnant women with COVID-19, compared with pregnant women without COVID-19, are more likely to give birth prematurely and have an increased risk of maternal mortality and intensive care unit admission. Their babies are more likely to be admitted to a neonatal unit [2,11,12,13,14,15,16].

Our country is implementing comprehensive large-scale programs for the early detection, high-quality diagnosis and treatment of neurological diseases in pregnant and postpartum women, in particular, one of the main tasks of modern healthcare is "... carrying out comprehensive measures to radically improve the quality and expand the range of high-tech specialized care for patients with immune diseases systems..." [1,17,18,19,20].

The resolution assumes the active introduction into the system of specialized medical care of the achievements of modern research activities in all areas of medicine.

The current COVID-19 pandemic is a serious public health problem, particularly affecting vulnerable populations. Pregnant women and newborns represent a high-risk group during outbreaks of infectious diseases complicating respiratory tract pathologies and neurological pathologies.

Many works discuss the features of the course of infection in pregnant women and the organization of medical care, including obstetric care for pregnant women, women in labor and postpartum women with this disease, indications for hospitalization, possibilities and indications for etiotropic therapy. [2,21,22,23].

In Uzbekistan, the pathogenetic mechanisms of the development of complications of pregnancy and childbirth after various viral infections, including after COVID-19, are being studied from the point of view of domestic authors (Abdullaeva L.M. et al., 2019)

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Most scientists in our country are working to study the infectious process in pregnant women who have had SARS (Severe acute respiratory syndrome)-CoV-2 (Severe Acute Respiratory Syndrome, Coronavirus-2) as well as the impact of the COVID-19 pandemic on the course of pregnancy and the postpartum period.

Compared with pregnant women without COVID-19, women with the disease had increased odds of maternal death (OR=2.85, (1.08-7.52)) and need for intensive care unit admission (OR=18.58) , (7.53-45.82)) and preterm birth (OR=1.47, (1.14-1.91)). The odds of NICU admission (OR=4.89, (1.87-12.81)) were higher in infants born to mothers with COVID-19 compared to infants without COVID-19.

Currently, the issues of innate immunity of the fetus in pregnant women who have had COVID-19 on their perinatal outcomes have not been addressed, which is aimed at improving the quality of life of pregnant women with COVID-19 and preventing complications of pregnancy and childbirth in such women. In the literature available to us, there is information about some studies in this area, most often descriptive, but there is no information about the state of the fetal immune system, their immunoglobulin and cytokine profile of those who have had COVID-19, although it is obvious that the study of the adaptive mechanisms of the fetal immune system is necessary during pregnancy. background of COVID-19.

OBJECTIVE: to study the main 4 cytokines of the fetal immune system IL-1β, IL-18, IL-4 and IL-6 in pregnant women who had COVID-19 in the second trimester of gestation.

RESEARCH METHODS: studies were conducted at the Republican Perinatal Center in 2022 on 40 fetal umbilical cord blood serum taken by transabdominal cordocentesis from pregnant women who had COVID-19 in the second trimester. There were 3 groups. Group I (control) pregnant women with physiological pregnancy and without obstetric and somatic diseases (n=10). Group II: pregnant women who had moderate COVID-19 (n=15). Group III: pregnant women who had severe COVID-19 in the second trimester of their gestation (n=15). Immunological studies of cytokine levels were carried out by enzyme immunoassay using commercial test systems "Human", (Germany) at the Institute of Human Immunology and Genomics.

At the first stage of the study, anamnesis was collected to study the outcomes of previous pregnancies, somatic, obstetric and gynecological history data, coronavirus infection, and a study of the characteristics of the course of this disease, that is, in what form she was ill. All pregnant women were consulted by a therapist. An obstetric examination and a set of laboratory research methods were also carried out - general blood and urine analysis, maternal blood group and Rh, blood biochemistry and coagulogram. These analyzes were repeated throughout pregnancy for the purpose of dynamic monitoring.

At the second stage of the study, pregnant women with a history of coronavirus infection underwent instrumental and functional studies such as Doppler ultrasound of the fetus to determine prognostic criteria for fetal development. Also, after the patient's informed written consent, some pregnant women in the second and third trimester underwent transabdominal cordocentesis to collect blood from the fetal umbilical cord vein. At this stage, the timing of the onset of the disease was also taken into account, that is, in which trimester the pregnant woman was ill during the actual pregnancy.

At stage III, a laboratory immunological study was carried out. The study material was fetal blood serum taken by transabdominal cordocentesis from pregnant women who had COVID-19. Determination of the level of main immunoglobulins and cytokines in biological fluids was carried out by enzyme immunoassay using commercial test systems "Human", Germany 2020. The test systems are based on the sandwich method of enzyme-linked immunosorbent assay using horseradish peroxidase as an indicator enzyme. The kits are intended for the quantitative determination of human cytokines in peripheral blood serum and biological fluids. The optical density in each well was measured using an automatic microplate photometer at a wavelength of 450 nm using an enzyme-linked immunosorbent assay on a Stat-Fax analyzer (USA).

RESULTS: Age characteristics data show that women of the compared groups were predominantly in the age range of 20-34 years (80.9%), characterized as active reproductive age. There were a minimum number of young women of only 2 (0.51%), while there were significantly more women of late reproductive age, amounting to 72 (18.6%).

An analysis of the parity of women who had coronavirus infection revealed that the main proportion was 134 women (34.6%) with their first pregnancy, 99 women (25.5%) each had a second and third pregnancy

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equally, 44 (11.3%) had a pregnancy 4th, in 11 (2.9%) women – 5th.

Of the somatic pathologies that were common in pregnant women who had COVID-19, there was anemia in 228 cases (58.9%), heart disease in the form of chronic myocarditis in 88 cases (22.7%) and obesity in 82 cases (21.1%).

We conducted a Doppler study of blood flow in the uterine artery, spiral arteries of the myometrium, umbilical cord artery and middle cerebral artery in 20 women with a physiological pregnancy and in 80 women who had COVID-19 in various forms. The following angle-independent blood flow indicators were determined: pulsatility index (PI), systole-diastolic ratio (S/D) and resistance index (IR) in the indicated vessels. The assessment of blood flow in the vessels was carried out according to the recommendations of the International Fetal Medicine Foundation (FMF). In connection with the above, the study of changes in the adaptive humoral mechanisms of the fetus at these times has important diagnostic and prognostic significance.

The content of IL-1β and IL-18 in fetuses with severe COVID-19 was significantly increased by 9 and 11 times, while the same indicators in fetuses with moderate COVID-19 were increased by 4 and 3.4 times. IL-1β levels in the control group were 5.81 ± 1.47 pg/ml, and IL-18 values were 12.5 ± 1.83 pg/ml. Increased values of fetal proinflammatory multifunctional IL-1β in the second trimester indicate the first protective response of the fetal immune system to maternal pathogenic factors

The levels of IL-4 and IL-6 in fetuses with severe COVID-19 were significantly increased by 4 and 2.6 times compared to the control group, while these indicators were increased in fetuses with moderate COVID-19 2.1 and 1.7 times. IL-4 values in the control group were 6.21 ± 1.33 pg/ml, and IL-6 values were 7.32 ± 1.39 pg/ml. Overproduction of anti-inflammatory IL-4 by fetal mast cells is most likely an allergic reaction to a foreign antigen. An excess of the most important mediator of the acute phase of inflammation, IL-6, in the fetus can cause tissue damage due to its autoimmune reaction.

CONCLUSION: The level of pro-inflammatory and anti-inflammatory mediators of inflammation in fetuses from mothers with a history of COVID-19 significantly exceeds those of fetuses from healthy mothers who have not had COVID-19 during pregnancy. These indicators are significantly high in those fetuses whose mothers suffered severe COVID-19 during their gestation.

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