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Effect of COVID-19 infection in the third trimester of pregnancy on innate immunity parameters, association with obstetric and perinatal outcomes

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ABSTRACT

Aim. To analyze and compare parameters of innate immunity with obstetric and perinatal outcomes in patients with COVID-19 in the third trimester of pregnancy.

Materials and methods. The study included 2 groups: the main group encompassed patients with mild (subgroup 1, *n* = 31) and moderate (subgroup 2, *n* = 40) COVID-19 during the third trimester of pregnancy; the control group included women who did not have COVID-19 during pregnancy (*n* = 22). By the enzyme-linked immunosorbent assay (ELISA), we determined the level of anti-SARS-CoV-2 immunoglobulin (Ig)M and IgG, tumor necrosis factor alpha (TNFα), interleukin 6 (IL-6), and interferon gamma (IFNγ) in the blood plasma. Complete blood count was performed on the automated hematology analyzer. Expression of CD-14 and HLA-DR antigens in monocytes was analyzed on the flow cytometer. SARS-CoV-2 RNA in placenta samples was detected by the reverse transcription polymerase chain reaction (RT-PCR).

Results. A moderate course of COVID-19 in the third trimester of pregnancy was associated with lower levels of anti-SARS-CoV-2 IgG and IFNγ in the maternal blood and umbilical cord blood, as well as by lower expression of CD-14 and HLA-DR by monocytes compared to mild COVID-19. A mild course of the disease was characterized by an increase in the number of monocytes in the maternal blood. No differences in leukocyte and lymphocyte counts were noted. There were also no differences in birth weight and one-minute Apgar score. At 5 minutes, the Apgar scores for moderate COVID-19 were lower than those for mild infection. The moderate course of COVID-19 increased the risk of preterm birth, neonatal cerebral ischemia, intraventricular hemorrhage, and respiratory distress syndrome. No risk of intrauterine SARS-CoV-2 infection was detected.

Conclusion. The severity of COVID-19 in the third trimester of pregnancy is associated with dysregulation of the innate immunity, which determines the nature of obstetric and perinatal complications.

Keywords: COVID-19, innate immunity, cytokines, obstetric and perinatal outcomes

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at the Far Eastern Research Center for Physiology and Pathology of Respiration (Protocol No. 144 of 09.06.2023).

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Влияние перенесенной в третьем триместре беременности инфекции COVID-19 на показатели врожденного иммунитета, связь с акушерскими и перинатальными исходами

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РЕЗЮМЕ

Цель. Анализ и сопоставление данных врожденного иммунитета с акушерскими и перинатальными исходами при перенесенной в третьем триместре беременности инфекции COVID-19.

Материалы и методы. В исследование включены две группы: основная – с перенесенной в третьем триместре беременности инфекцией COVID-19 легкого (подгруппа 1, *n* = 31) и среднетяжелого течения (подгруппа 2, *n* = 40), контрольная – женщины, не болевшие COVID-19 в течение всей беременности (*n* = 22). В плазме крови иммуноферментным методом определяли уровень анти-SARS-CoV-2 иммуноглобулинов (Ig) классов M и G, содержание цитокинов фактора некроза опухоли альфа (TNFα), интерлейкина (IL) 6 и интерферона гамма (IFNγ). Клинический анализ крови осуществляли на автоматическом гематологическом анализаторе, экспрессию CD14- и HLA-DR-антигенов в моноцитах – на проточном цитометре, РНК SARS-CoV-2 в образцах плаценты – методом обратной транскрипции полимеразной цепной реакции.

Результаты. Среднетяжелое течение COVID-19 в третьем триместре беременности ассоциировалось с более низким уровнем в крови у матери и в крови пуповины новорожденных анти-SARS-CoV-2 IgG, IFNγ, а также экспрессии моноцитами CD14 и HLA-DR по сравнению с легкой формой заболевания. При легкой форме отмечено повышение количества моноцитов в крови матери. Различий в показателях лейкоцитов и лимфоцитов не выявлено. Также отсутствовали различия по массе тела новорожденных и оценке по шкале Апгар на 1-й мин. На 5-й мин показатели при среднетяжелом течении заболевания были ниже, чем при легкой форме инфекции. Среднетяжелое течение COVID-19 увеличивало риск преждевременных родов, развития церебральной ишемии мозга новорожденных, внутрижелудочковых кровоизлияний и синдрома дыхательных расстройств. Риск внутриутробной SARS-CoV-2 инфекции отсутствовал.

Заключение. Тяжесть течения COVID-19 в третьем триместре беременности связана с дисрегуляцией врожденного иммунитета, что определяет характер акушерских и перинатальных осложнений.

Ключевые слова: COVID-19, врожденный иммунитет, цитокины, акушерские и перинатальные исходы

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Since March 2019, the world has been affected by the pandemic of novel coronavirus infection (COVID-19), which was listed as a public health emergency of international concern until May 2023 [1]. Viral mutations and new variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are associated with a varying clinical course of the disease (ranging from mild to severe) linked to immune dysregulation [2]. It is reported that pregnant women with COVID-19, particularly those with the Delta variant of the disease, have an increased risk of hospitalization and developing severe disease compared to the general population [3].

According to other studies, pregnant and non-pregnant patients show similar risks of infection and developing severe manifestations of COVID-19 [4]. The role of COVID-19 in the development of placental insufficiency, preterm birth, and stillbirth has also been determined [5]. However, definitive conclusions can only be drawn after the end of the pandemic.

Myeloid cells (monocytes / macrophages) are believed to be directly involved in the pathogenesis of COVID-19. Studies have reported various responses of monocytes to SARS-CoV-2, determining the development of systemic inflammatory response syndrome [6], hyperactivation or a lack of response to type I interferons (IFN-I) in the blood and lung tissues in severe forms of the disease [7]. Authors noted dysregulation of innate immunity and decreased expression of human leukocyte antigen class II (HLA-DR) by monocytes, which is considered as a marker of immunosuppression and severity of COVID-19 [8].

Other studies have shown the differences in phenotypes of peripheral and lung myeloid cells with low expression of HLA-DR, dysfunctional blood monocytes, and hyperactive monocytes / macrophages of the respiratory tract producing proinflammatory cytokines in moderate and severe COVID-19 [9]. However, the effect of pregnancy on the development of innate immunity in mothers and their newborns following COVID-19 remains poorly studied, and research is limited in scope [10].

The aim of this work was to analyze and compare parameters of innate immunity with obstetric and perinatal outcomes in mothers with COVID-19 in the third trimester of pregnancy.

MATERIALS AND METHODS

The study was carried out in accordance with the principles of the Declaration of Helsinki and approved by the Bioethics Committee at the Far Eastern Research Center for Physiology and Pathology of Respiration (Protocol No. 144 of 09.06.2023). All participants signed a written informed consent to participate in the study. The clinical site for the study was the maternity unit of the Blagoveshchensk City Clinical Hospital. Laboratory studies were carried out at the Far Eastern Research Center for Physiology and Pathology of Respiration. From January 2022 to March 2023, 93 women at 35–40 weeks pregnant were examined: 71 women with mild (subgroup 1, $n = 31$) and moderate (subgroup 2, $n = 40$) COVID-19 during the third trimester of pregnancy (main group) and 22 women who did not have COVID-19 during the entire pregnancy (control group). All studies were conducted during the predominant circulation of SARS-CoV-2 Omicron strain.

Inclusion criteria for the main group were: singleton, spontaneous pregnancy; COVID-19 in the third trimester of pregnancy; clinical symptoms of a respiratory disease; CT (computed tomography) signs of viral pneumonia with a typical clinical presentation and relevant epidemiological history. Exclusion criteria were multiple pregnancies; pregnancy resulting from *in vitro* fertilization; exacerbation of chronic noninfectious diseases; presence of chronic nonspecific lung diseases; extrapulmonary foci of infections; specific bronchopulmonary diseases; developmental genital anomalies; detected sexually transmitted infections; progestogen support; immunodeficient conditions; smoking. All study participants were selected as cases and controls and were comparable in age and body mass index (BMI).

The age in subgroup 1 was 27.0 (25.0; 30.0) years ($p = 0.441$); the age in subgroup 2 was 27.0 (25.0; 30.0) years ($p = 0.465$), which had no significant difference compared to the control group – 28.5 (25.7; 31.0) years. BMI values in subgroup 1 were 24.7 (23.0; 29.1) ($p = 0.691$) and in subgroup 2 – 24.8 (21.7; 29.3) ($p = 0.669$), which also did not differ significantly from the control group – 24.6 (22.1; 25.0). In the main group, no significant differences in age ($p = 0.968$) and BMI ($p = 0.954$) were found.

Blood samples for the studies were taken at the time of hospitalization in the maternity unit by venipuncture into ethylenediaminetetraacetic acid (EDTA) vacuum tubes (China). Umbilical cord blood was collected from the central vein into EDTA vacuum tubes immediately after cord clamping soon after birth. Blood plasma was obtained by centrifugation

(15 min, 1,000 g). All plasma samples were stored at –70 °C until the analysis was started. Placental material was collected immediately after birth and placed in sterile containers. Sample preparation, extraction, and amplification of SARS-CoV-2 RNA were carried out by reverse transcription polymerase chain reaction (RT-PCR) on the DT-96 detection amplifier (DNA-Technology, Russia) using commercial reagent kits (DNA-Technology, Russia) in strict accordance with the manufacturer's instructions. The enzyme-linked immunosorbent assay (ELISA) was used to determine anti-SARS-CoV-2 IgM and IgG in paired plasma samples (SARS-CoV-2-IgM ELISA-BEST Kit, SARS-CoV-2-IgG quantitative-ELISA-BEST Kit, Russia), levels of tumor necrosis factor alpha (TNFα) (TNF alpha-ELISA-BEST Kit, Russia), interleukin 6 (IL-6) (Interleukin-6-ELISA-BEST Kit, Russia), and interferon gamma (IFNγ) (Interferon gamma-ELISA-BEST, Russia).

All studies were performed on the Multiskan FC microplate photometer (USA) in strict accordance with the manufacturer's instructions for commercial reagent kits. Clinical blood test was carried out on the automated hematology analyzer Mindray BC-5150 (Shenzhen Mindray Bio-Medical Electronics Co., Ltd., China). Flow cytometry of peripheral blood mononuclear cells was conducted on the BD FacsCanto II flow cytometer (USA). We used lysed blood (Invitrogen™ eBioscience™ 10X RBC Lysis Buffer, USA) containing FITC-conjugated monoclonal antibodies to surface antigens CD14 (M5E2) (BD Biosciences, USA) and HLA-DR (L243) (BioLegend, USA). The mononuclear cell pellet obtained after two washes in phosphate buffered saline (PBS) (Biolot, Russia) and centrifugation (5 min, 400 g) was resuspended and used to detect monoclonal antibodies.

Statistical analysis and data processing were carried out using the IBM SPSS Statistics version 23.0 software package (USA). The statistical analysis was performed using the Mann – Whitney test for paired comparisons. To compare three or more groups, the Kruskal – Wallis test was used. Quantitative variables were presented as the median (Me) and the interquartile range (Q_{25}; Q_{75}); categorical data were presented as proportions, frequencies, and percentages. The analysis of frequency differences in two independent study groups was conducted using the Fisher's exact test. With absolute frequencies in contingency tables being less than 10, the Yates' correction was used. The correlation analysis was conducted using the Spearman's rank correlation coefficient. Relative risks (RR) were analyzed using fourfold contingency tables with 95% confidence intervals (95% CI). Differences were considered statistically significant at a $p < 0.05$.

RESULTS

All women in the main group at the time of the study had a confirmed diagnosis of COVID-19: 43.7% were diagnosed with mild acute respiratory viral infection (ARVI) (subgroup 1), and 56.3% – with moderate disease with manifestations of pneumonia (subgroup 2) (RR = 1.27; 95% CI 0.96–1.69). The gestational age at the time of the disease in subgroup 1 was 35.0 (33.0; 37.0) weeks, and in subgroup 2 – 34.0 (32.0; 36.0) weeks ($p = 0.181$). The total time from the disease onset to delivery in subgroup 1 and subgroup 2 was 27.0 (18.0; 36.0) days and 32.0 (15.0; 48.0) days, respectively ($p = 0.286$).

In all women of the main group, SARS-CoV-2 IgM antibodies were absent in both maternal blood and umbilical cord blood (Table 1). However, the amount of IgG antibodies in subgroup 1 was 1.53 times higher than in subgroup 2. Intragroup paired comparisons did not reveal significant differences between the values of IgG antibodies in maternal blood and umbilical cord blood in subgroup 1 ($p = 0.992$) and subgroup 2 ($p = 0.371$). Further paired correlation analysis in the study subgroups revealed a significant association between the levels of IgG antibodies in maternal blood and umbilical cord blood in subgroup 2 ($r = 0.61$, $p = 0.0001$).

Blood test in women of the study groups revealed an increase in the average monocyte count by 1.16 times in subgroup 1 compared to the control group, while no significant differences were found compared to subgroup 2. No differences in leukocyte and lymphocyte counts were identified when comparing the main group and the control group.

The study of the proinflammatory cytokine profile in the blood of women showed that in subgroup 1, the values of TNFα were 1.72 times and 1.22 times lower than in the control group and subgroup 2, respectively. The level of IL-6 in subgroup 1 was 1.55 times and 1.35 times lower than in the control group and subgroup 2, respectively. The values of IFNγ in subgroup 1 were 1.9 times higher than in subgroup 2. In subgroup 2, the level of IFNγ did not change significantly compared to the control group. Significant differences in the levels of IL-6 and IFNγ were found in umbilical cord blood. In subgroup 1, the levels of IL-6 were

1.45 times lower than in subgroup 2 and did not significantly differ from those in the control group. The levels of IFNγ in subgroup 2 were reduced by 1.23 times and 1.11 times compared to subgroup 1 and the control group, respectively. Paired comparison of TNFα, IFNγ, and IL-6 values in maternal and umbilical cord blood revealed differences between the studied subgroups. The levels of TNFα in maternal blood were 2.02 times (p = 0.0001) and 1.8 times (p = 0.0001) lower than in umbilical cord blood. The levels of IFNγ were 1.1 times (p = 0.0001) and 1.67 times (p = 0.0001) higher, and the levels of IL-6 were 2.15 times (p = 0.0001) and 1.91 times (p = 0.0001) higher in subgroups 1 and 2, respectively.

Table 1

Parameters of innate immunity in maternal and umbilical cord blood in the study groups, *Me* (Q_{25}; Q_{75})

Parameter	Main group		Control group	p
	Subgroup 1	Subgroup 2		
Peripheral blood				
Anti-SARS-CoV-2 IgG, BAU / ml	168.0 (104.0; 216.0)	110.0 (56.0; 197.2)	–	p_3 = 0.029
TNFα, pg / ml	30.0 (22.0; 47.9)	42.3 (27.1; 61.8)	51.5 (36.9; 58.5)	p_1 = 0.001; p_2 = 0.485; p_3 = 0.004
IL-6, pg / ml	20.9 (17.7; 29.5)	27.0 (17.9; 64.3)	31.9 (18.4; 49.2)	p_1 = 0.034; p_2 = 0.900; p_3 = 0.042
IFNγ, pg / ml	4.0 (2.8; 5.0)	2.1 (2.0; 2.6)	2.7 (2.0; 6.1)	p_1 = 0.780; p_2 = 0.074; p_3 = 0.0001
Leukocytes, 10^9 / l	8.75 (7.36; 9.82)	8.1 (7.0; 9.3)	8.2 (7.5; 9.6)	p_1 = 0.950; p_2 = 0.498; p_3 = 0.582
Lymphocytes, 10^9 / l	21.5 (15.0; 25.2)	16.4 (3.4; 21.6)	18.5 (15.9; 20.5)	p_1 = 0.279; p_2 = 0.260; p_3 = 0.164
Monocytes, 10^9 / l	7.34 (6.1; 8.7)	6.7 (5.1; 8.2)	6.5 (4.6; 7.2)	p_1 = 0.044; p_2 = 0.480; p_3 = 0.194
CD14, %	78.9 (73.5; 83.4)	55.1 (49.8; 63.3)	94.5 (92.8 ;97.8)	p_{1_3} = 0.0001
HLA-DR, %	78.3 (74.0; 83.2)	52.9 (48.5; 60.7)	95.2 (92.8; 98.4)	p_{1_3} = 0.0001
Umbilical cord blood				
Anti-SARS-CoV-2 IgG, BAU / ml	142.0 (102.0; 240.0)	109.0 (25.3; 194.0)	–	p_3 = 0.037
TNFα, pg / ml	60.5 (58.6; 81.3)	76.0 (65.2; 89.5)	85.1 (74.8; 90.0)	p_1 = 0.006; p_2 = 0.236; p_3 = 0.064
IL-6, pg / ml	9.7 (7.6; 11.0)	14.1 (10.9; 23.6)	7.9 (4.8; 35.0)	p_1 = 0.657; p_2 = 0.358; p_3 = 0.0001
IFNγ, pg / ml	4.3 (3.3; 5.7)	3.5 (2.6; 4.0)	3.9 (3.1; 5.7)	p_1 = 0.619; p_2 = 0.007; p_3 < 0.0001
CD14, %	77.7 (74.5; 82.7)	55.6 (50.7; 59.7)	96.4 (92.6; 98.2)	p_{1_3} = 0.0001
HLA-DR, %	78.6 (73.2; 83.1)	58.6 (50.9; 66.1)	95.4 (93.8; 96.7)	p_{1_3} = 0.0001

Note. Here and in Table 2–4: p_1 – statistical significance of differences between subgroup 1 and the control group; p_2 – statistical significance of differences between subgroup 2 and the control group; p_3 – statistical significance of differences between subgroup 1 and subgroup 2.

Significant paired correlations in subgroup 1 were found between the levels of TNFα (r = 0.78, p = 0.0001), IL-6 (r = 0.72, p = 0.0001), and IFNγ (r = 0.84, p = 0.0001) in maternal blood and umbilical cord blood. In subgroup 2, a correlation was found between the levels of IFNγ in maternal blood and umbilical cord blood (r = 0.60, p = 0.0001). Investigating the antigen composition of monocytes in maternal blood revealed that in subgroup 1, the expression of CD14 was 1.2 times lower than in the control group and 1.43 times higher than in subgroup 2. In subgroup 2, the number of monocytes expressing CD14 was 1.71 times smaller than in the control group. The analysis of HLA-DR expression in subgroup 1 revealed a decrease by 1.21 times compared to the control group and an increase by 1.48 times compared to subgroup 2. In subgroup 2, the HLA-DR values were 1.8 times lower than in the control group. In subgroup 1, a decrease in the circulation of CD14 by 1.24 times was noted in umbilical cord blood compared to the control group and an increase by 1.4 times compared to subgroup 2. In subgroup 2, monocytes were characterized by lower levels of CD14 (by 1.73 times) compared to the control group.

The analysis of HLA-DR expression in umbilical cord blood monocytes in subgroup 1 showed a decrease by 1.21 times compared to the control group and an increase by 1.34 times compared to subgroup 2. In subgroup 2, the HLA-DR values were 1.63 times lower compared to the control group. In paired comparisons of the average CD14 and HLA-DR values in maternal blood monocytes and umbilical cord blood, no significant differences were found for subgroup 1 (p = 0.576 and p = 0.468, respectively) and for subgroup 2 (p = 0.968 and p = 0.05, respectively). Significant paired correlations in subgroup 1 were found between the parameters of maternal blood and umbilical cord blood for CD14 (r = 0.63, p = 0.0001) and HLA-DR (r = 0.48, p = 0.007).

It is worth noting that in the studied subgroups, none of the placental samples showed the presence of SARS-CoV-2, indicating the absence of a risk of its vertical transmission to the fetus.

Table 2 presents pregnancy outcomes in the studied groups. Full-term births occurred in all women in subgroup 1 and in 87.5% of women in subgroup 2. The gestational age at the time of delivery in subgroup 1 was 39.0 (38.0; 40.0) weeks and did not have significant differences from the control group – 39.0 (38.0; 40.0) weeks (p = 0.756); however, it was significantly higher than in subgroup 2 – 38.0 (37.0; 39.0) weeks (p = 0.034). The differences between subgroup 2 and the control group were also statistically significant (p = 0.027). Preterm births (PB) (O60.1) occurred in 12.5% of women in subgroup 2. Natural childbirth delivery (NCD) took place in 93.55% of women in subgroup 1 and in 87.5% of women in subgroup 2, while cesarean delivery (CD) – in 6.45% and 12.5% of women, respectively. Indications for elective CD were: mismatch between the pelvic size and the fetal head size, uterine scar after CD, incompetent cervix, breech presentation of the fetus with anticipated weight of more than 3,600 grams, and placenta previa. Premature rupture of membranes (PROM) (O42) occurred in 12.9% of women in subgroup 1, which was significantly less often than in subgroup 2 – 27.5%. The study showed that moderate severity of COVID-19 increased the risk of PROM (RR = 2.13 (95% CI 1.17–3.87)) compared to subgroup 1.

The average birth weight of newborns did not significantly differ between the subgroups and compared to the control group. The condition of the newborns was assessed by the Apgar score at 1 and 5 minutes (Table 3).

Table 2

Pregnancy outcomes in women of the study groups

Parameter	Main group				Control group		p
	Subgroup 1		Subgroup 2				
	abs.	%	abs.	%	abs.	%	
NBD	29	93.55	35	87.5	21	95.45	$p_1 = 0.552$; $p_2 = 0.049$; $p_3 = 0.158$
CD	2	6.45	5	12.5	1	4.54	$p_1 = 0.746$; $p_2 = 0.069$; $p_3 = 0.595$
PB	–	–	5	12.5	–	–	
PROM	4	12.9	11	27.5	2	9.1	$p_1 = 0.498$; $p_2 = 0.002$; $p_3 = 0.022$

Table 3

Birth weight and Apgar score in newborns delivered by mothers of the study groups, *Me* (Q_{25}; Q_{75})

Parameter	Main group		Control group	p
	Subgroup 1	Subgroup 2		
Birth weight, g	3,300.0 (3,190.0; 3,550.0)	3,295.0 (2,817.0; 3,737.0)	3,200.0 (3,040.0; 4,000.0)	$p_1 = 0.550$; $p_2 = 0.768$; $p_3 = 0.503$
Apgar score:				
– at 1 minute;	8.0 (8.0; 9.0)	8.0 (8.0; 9.0)	8.0 (8.0; 9.0)	$p_1 = 0.735$; $p_2 = 0.628$; $p_3 = 0.806$
– at 5 minutes	9.0 (9.0; 10.0)	9.0 (8.0; 9.0)	9.0 (9.0; 10.0)	$p_1 = 0.798$; $p_2 = 0.007$; $p_3 = 0.003$

No significant differences in the Apgar scores at 1 minute were found either between subgroups 1 and 2 or between the control group and the study subgroups. However, a decrease in the Apgar score at 5 minutes was determined in newborns delivered by mothers in subgroup 2 compared to those delivered by mothers in subgroup 1 and the control group. Cerebral ischemia (CI) (P91.0) was diagnosed in 6.45% of newborns in subgroup 1 and in 21.9% of babies in subgroup 2 (Table 4). Newborns of mothers in subgroup 2 had a higher risk of CI, RR = 3.83 (95% CI 1.63–9.01) compared to those delivered by mothers in subgroup 1. Respiratory distress syndrome (RDS) and intraventricular hemorrhages (IVH) were diagnosed only in newborns delivered by mothers in subgroup 2.

Table 4

Incidence in newborns delivered by mothers of the study groups, persons

Parameter	Main group				Control group, 22		p
	Subgroup 1, 31		Subgroup 2, 40				
	abs.	%	abs.	%	abs.	%	
CI	2	6.45	9	22.5	–	–	0.003
IVH	–	–	5	12.5	–	–	
RDS	–	–	7	17.5	–	–	

Note. Statistical difference between the parameters of subgroup 1and subgroup 2 – p.

DISCUSSION

Studies have shown that COVID-19 can alter innate immunity in pregnant women not only during the acute phase of the disease but also after recovery. Our results showed that COVID-19 infection in the third trimester of pregnancy induced a sustained antibody and cytokine response at the time of delivery and caused a significant decrease in transplacental transfer of IgG antibodies with a more pronounced negative proinflammatory effect of TNFα and IL-6 and a reduced proinflammatory effect of IFNγ in moderate infection, which is in line with the available data [11].

Mild infection was associated with higher levels of IgG antibodies and reduced levels of TNFα and IL-6 in maternal blood and umbilical cord blood. In moderate infection, reduced IFNγ levels were also noted, apparently due to increased circulation of IL-6 and insufficient production of antiviral antibodies [12]. Maternal levels of IgG antibodies and proinflammatory cytokines were correlated with values in umbilical cord blood; the strength of the correlation was determined by the severity of COVID-19 in the third trimester of pregnancy.

We also detected no significant differences in lymphocyte and leukocyte count in maternal blood regardless of the severity of COVID-19 amidst the variability of the proinflammatory cytokine profile, indicating their dysfunction. Nevertheless, the predominance of the inflammatory cytokine profile in the blood of mothers with past COVID-19 should be considered in the context of significant fluctuations in parameters during full-term and preterm labor [13]. The study of the monocyte response to COVID-19 in the third trimester showed an increase in their count in maternal blood in mild COVID-19 compared to moderate disease. The percentage of classical CD14 monocytes and monocytes expressing HLA-DR in maternal blood and umbilical cord blood was reduced according to the severity of COVID-19 infection, determining complex immune dysregulation and forming temporary immunosuppression [14]. The decrease in the HLA-DR expression on cell membranes of CD14 monocytes was likely linked to the inhibitory effect of IL-6 [15]. Maternal levels of CD14 and HLA-DR were correlated with the ones in the umbilical cord blood. Regarding obstetric and perinatal outcomes, moderate COVID-19 in the third trimester increased the risk of preterm births, which is consistent with the data of systematic reviews and meta-analyses [16].

However, according to some reports, Omicron variant infection of pregnant women did not increase the risk of preterm birth compared to the Delta variant [17], though these findings require confirmation. PROM in moderate COVID-19 occurred 2.13 times more frequently than in mild infection, potentially increasing the risk of neonatal infection and associated complications. However, no SARS-CoV-2 nucleic acid was detected in any of the placental samples obtained from women with COVID-19 in the third trimester of pregnancy, which is consistent with the available data [18].

In assessing the condition of newborns, no differences in body weight and 1-minute Apgar score were found, although 5-minute scores in moderate infection were lower than in mild forms of the disease, which is consistent with research data and possibly indicates lower adaptive capacity of the newborn [19]. The risk of CI in newborns delivered by mothers with moderate COVID-19 increased by 3.83 times compared to mild infection. In 12.5% of newborns, IVH was diagnosed, and 17.5% of babies had RDS.

Therefore, the dysregulation of innate immunity in maternal blood and umbilical cord blood established in the study, the extent of which was associated with the severity of COVID-19 in the third trimester of pregnancy, contributes significantly to the development of obstetric complications and associated disorders in newborns, altering their individual adaptive response to infection.

CONCLUSION

We showed that the severity of COVID-19 in the third trimester of pregnancy was associated with the complexity of immune dysregulation characterized by reduced levels of SARS-CoV-2 IgG antibodies and proinflammatory IFNγ in maternal and umbilical cord blood, as well as with the decreased expression of CD14 and HLA-DR by monocytes. This may indicate the development of temporary immunosuppression. Parameters of innate immunity and cytokine response in the maternal blood were correlated with the ones in the umbilical cord blood. Moderate severity of COVID-19 increased the risk of preterm births, neonatal cerebral ischemia, intraventricular hemorrhage, and respiratory distress syndrome. No risk of vertical SARS-CoV-2 transmission to the fetus was detected.

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Andrievskaya I.A. – conception and design, drafting of the manuscript, final approval of the manuscript. Lyazgiyan K.S. – analysis and interpretation of the data, statistical processing of the research results. Zhukovets I.V. – drafting and editing of the article. Ustinov E.M. – collection and processing of the material, carrying out of studies.

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