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Experience in managing severe and extremely severe COVID-19 in pregnant women

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BACKGROUND: In the context of the COVID-19 pandemic caused by the SARS-CoV-2 virus, viral pneumonia is the leading clinical form of coronavirus infection and a significant cause of maternal mortality.

AIM: The aim of this study was to assess the course of severe and extremely severe forms of COVID-19, its impact on pregnancy and fetus, as well as on maternal mortality.

MATERIALS AND METHODS: In this retrospective study, we evaluated 39 case histories of patients with severe and extremely severe COVID-19, which were divided into two groups. Group 1 included 22 pregnant women with a severe course of coronavirus infection and a favorable outcome. Group 2 comprised 17 pregnant women in whom complications caused by SARS-CoV-2 were fatal.

RESULTS: More than 80% of patients with severe disease course had anaemia in pregnancy. The most significant clinical and anamnestic factors of adverse outcome were gestational diabetes mellitus ($p = 0.02$), preeclampsia ($p = 0.05$), and oligoamnios ($p = 0.01$). Obesity in group 2 was twice more common. The clinical manifestations of the disease in the both study groups were dominated by fever, shortness of breath, weakness and dry cough. In patients with a fatal outcome at the height of the disease, the levels of leukocytosis, urea and lactate dehydrogenase were higher than in those who recovered ($p = 0.05$). Besides, the levels of alanine transferase and aspartate transaminase were twice as high as in pregnant women who recovered later. Patients in the both study groups required oxygen support as respiratory failure progressed. The vast majority of patients with severe and extremely severe forms of coronavirus infection were in the third trimester of pregnancy.

CONCLUSIONS: Women in the third trimester of pregnancy are more susceptible to severe and extremely severe COVID-19 with an unfavorable outcome. Gestational diabetes mellitus, preeclampsia and oligoamnios are significant comorbidities that predispose to severe course and poor outcome in pregnant women and puerperas with COVID-19. The characteristic clinical manifestations of the severe course of coronavirus infection are shortness of breath and fever against a backdrop of significant damage to the lung tissue. A pronounced increase in hepatic enzymes and placental insufficiency is a harbinger of an unfavorable outcome as a manifestation of multiple organ failure.

Keywords: COVID-19; maternal mortality; pregnancy.

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Опыт ведения беременных с тяжелой и крайне тяжелой формами COVID-19

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Обоснование. В условиях пандемии COVID-19, вызванной вирусом SARS-CoV-2, вирусная пневмония является ведущей клинической формой коронавирусной инфекции и весомой причиной материнской смертности.

Цель — оценить характер течения тяжелой и крайне тяжелой форм COVID-19, ее влияние на беременность и плод, а также на материнскую смертность.

Материалы и методы. Произведена ретроспективная оценка 39 историй болезни пациенток с тяжелой и крайне тяжелой формами COVID-19, которые были разделены на две группы. Первая группа включала 22 беременные с тяжелым течением коронавирусной инфекции и благоприятным исходом, вторая — 17 беременных, у которых осложнения, вызванные SARS-CoV-2, привели к летальному исходу.

Результаты. Более чем у 80 % пациенток с тяжелым течением болезни выявлена анемия беременных. Наиболее значимыми клинико-анамнестическими факторами неблагоприятного исхода были гестационный сахарный диабет (p = 0,02), преэклампсия (p = 0,05), маловодие (p = 0,01). Ожирение в группе умерших встречалось в два раза чаще. Среди клинических проявлений болезни в обеих группах преобладали лихорадка, одышка, слабость и сухой кашель. В лабораторных анализах у пациенток с летальным исходом на высоте заболевания уровень лейкоцитоза, мочевины и лактатдегидрогеназы был выше, чем у поправившихся (p = 0,05). В обеих группах наблюдались повышение активности аланинаминотрансферазы и аспартатаминотрансферазы, причем у погибших средний показатель этих трансаминаз был в два раза выше, чем у впоследствии поправившихся беременных. Пациентки в обеих группах нуждались в кислородной поддержке по мере нарастания дыхательной недостаточности. Преобладающее большинство пациентов с тяжелой и крайне тяжелой формами заболевания подверглись коронавирусной инфекции в III триместре беременности.

Заключение. В III триместре беременности более часто отмечается тяжелое и крайне тяжелое течение COVID-19 с неблагоприятным исходом. Значимыми сопутствующими заболеваниями, предрасполагающими к тяжелому течению и неблагоприятному исходу у беременных и родильниц с COVID-19, являются гестационный сахарный диабет, преэклампсия и маловодие. Тяжелое течение коронавирусной инфекции сопровождается одышкой и лихорадкой на фоне значительного поражения легочной ткани. Выраженное повышение активности печеночных ферментов и нарастание плацентарной недостаточности служат предвестниками неблагоприятного исхода как проявления полиорганной недостаточности.

Ключевые слова: COVID-19; материнская смертность; беременность.

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ЭКО•ВЕКТОР

BACKGROUND

The coronavirus disease-2019 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a severe infectious disease that remains a major public health problem worldwide [1].

The World Health Organization, from the pandemic onset to November 2021, registered 260,493,573 million infected people, of them, 5,195,354 million died [2]. According to the report "On the state of sanitary and epidemiological well-being of the population in the Russian Federation in 2020," more than 3159 million cases of coronavirus infection were detected in 85 regions of the country, and the incidence rate was 2152.63 per 100 thousand people of the population.

An analysis of international and Russian literature sources shows that pregnant women more often develop severe COVID-19, as well as pregnancy-associated complications with this disease [3]. Heavily pregnant women, having physiological changes in the body, such as a decreased functional residual volume of the lungs, due to the diaphragmatic elevation and changes in cellular immunity, are known to be more susceptible to viral infections [4].

In SARS and Middle East Respiratory Syndrome (MERS), up to 35% and 41% of pregnant women have artificial lung ventilation (ALV), and the mortality rate reached 18% and 25%, respectively [4–6]. Most pregnant women with confirmed novel coronavirus infection had a mild or asymptomatic disease course. Hospitalization in the intensive care unit was required only in some cases, and ALV was performed only in a few reported cases [4, 5, 7–9].

Viral pneumonia is the major clinical form of coronavirus infection and one of the important causes of maternal mortality. The symptoms of pneumonia in pregnant women do not differ from those in nonpregnant women [10].

To date, Russian and international authors have described cases of maternal death from COVID-19.

The maternal mortality rate in the Far Eastern Federal District and the Siberian Federal District from March 11, 2020, to December 25, 2020, among the patients with confirmed COVID-19, amounted to 0.14% (12 out of all infected pregnant women, women in labor, and puerperas, $n = 8485$) [11].

No other more generalized data and publications on maternal mortality were found in the Russian Federation.

An article published by the Kazakh National Medical University from the pandemic onset to August 2020 presents 41 cases of maternal death (1%, $n = 4057$) [12].

Concurrently, according to the large-scale meta-analysis results of international publications from March 2020 to October 2020, maternal mortality rates amounted to 11.3% (1130 women out of 10,000 cases) [13].

A large systematic review of scientific publications from January 2020 to July 10, 2020, reported 153 maternal deaths among 11,758 infected pregnant women (1.3%) [14].

The course of the coronavirus infection changes as the infection spreads. Neurological, cutaneous, and ocular manifestations have been described in the literature. The extrapulmonary presence of the virus was found in cholangiocytes [15]. Therefore, constantly supplementing the treatment regimens and conducting further research are necessary.

S.P. Botkin Clinical Infectious Diseases Hospital is the largest infectious disease hospital in Russia, which treated 750 female patients diagnosed with COVID-19, including 129 (17.2%) in the intensive care unit due to the severity of the condition, from April 2020 to March 2021.

This study aimed to assess the nature of the COVID-19 course in female patients with severe and extremely severe forms and its impact on pregnancy and the fetus and maternal mortality.

MATERIALS AND METHODS

A total of 39 case histories of female patients with severe and extremely severe forms of COVID-19, who received treatment at the S.P. Botkin Clinical Infectious Diseases Hospital from April 2020 to September 2021, were retrospectively reviewed. Patients were examined and received therapy following the temporary guidelines on "Prevention, diagnostics, and treatment of a new coronavirus infection (COVID-19)" of the Ministry of Health of the Russian Federation and the guidelines on "Organization of medical care for pregnant women, women in labor, puerperas, and newborns with a new coronavirus infection COVID-19," which were in force at that time.

COVID-19 diagnosis was established based on a positive nasopharyngeal swab test for SARS-CoV-2 polymerase chain reaction, laboratory examination results, clinical manifestations, and specific changes in lung tissue on computed tomography (CT) and chest X-ray.

The inclusion criteria of patients in the group with severe and extremely severe course of COVID-19 following the current methodological recommendations of the Ministry of Health of the Russian Federation were dyspnea with a respiratory rate of >30 breaths per min, oxygen saturation (SpO_2) of 93% or more, oxygenation index (pO_2/FiO_2) of <300 mmHg, 5 points or more on the NEWS scale, respiratory failure, including acute respiratory failure and acute respiratory distress syndrome, which required respiratory support (humidified oxygen, high-flow oxygenation, noninvasive ALV [NALV], and ALV), and changes in the lungs on CT and radiography with a volume of viral damage to the lung tissue of 50% and higher.

The exclusion criteria were the severity of the patient's condition, corresponding to the mild and moderate course of COVID-19 according to the classification presented in the guidelines of the Ministry of Health of the Russian Federation.

The women were distributed into two groups. Group 1 included 22 pregnant women with severe and extremely severe coronavirus infections. The duration of pregnancy in 13.6% of women (3 patients) corresponded to the second trimester of pregnancy and 86.3% (19 patients) to the third trimester. All were discharged from the hospital in satisfactory condition with progressing pregnancy after the end of treatment.

Group 2 included 17 female patients, of whom 2 (11.8%) are in the second trimester and 15 (88.2%) in the third trimester of pregnancy, with complications caused by SARS-CoV-2 leading to the lethal outcome.

Statistical analysis was performed using Excel MS Office and Quick Statistics Calculators, as well as parametric and nonparametric methods of statistics. Quantitative variables were assessed using the descriptive statistical method with the calculation of the arithmetic mean (*M*) and the mean error of the mean (*m*). The student's *t*-test was used to assess the intergroup differences. The significance of frequency differences between the compared groups was determined using the Fisher test (*F*) and chi-square (χ^2) according to the standard formula. The critical significance level (*p*) for testing null hypotheses was taken as *p*-values of <0.05.

RESULTS AND DISCUSSION

The patients did not significantly differ in age and parity, although multiparous were slightly more in group 1 than in group 2 among the analyzed cases.

The clinical characteristics of pregnant women included in this study are presented in Table 1.

Of pregnant women with severe COVID-19 in both groups, >80% had anemia. Our data support the results of a recently published study showing that iron deficiency anemia is a persistent risk factor for severe cases of COVID-19 in pregnant women [16].

Many authors in the medical community consider obesity and diabetes mellitus as predictors of more severe COVID-19 and death [17, 18]. In our study, obesity was registered 2 times more often ($p < 0.05$), and gestational diabetes mellitus was 4 times more common ($p < 0.01$) in pregnant women with an unfavorable outcome than in recovered patients.

No cases of severe preeclampsia were determined in the examined pregnant women; moderate preeclampsia in COVID-19-complicated pregnancy was almost 3 times more often in the group with a poor outcome ($p = 0.02$). Endothelial dysfunction is known as a key link in the pathogenesis of preeclampsia. Concurrently, recent publications

Table 1. Clinical characteristics of the groups of examined pregnant women

Indicator	Group 1 *n* = 22	Group 2 *n* = 17	χ^2 *p*
Age, years	33.0 ± 1.93	31.2 ± 2.68	>0.5
Duration of the disease at the time of admission, days	6.7 ± 1.7	8.2 ± 1.87	>0.5
Body mass index, kg/m^2	27.0 ± 2.9	32.0 ± 3.7	0.087
Obstetric and gynecological history (*n*) %			
Multiparous	(17) 77.3	(10) 58.8	0.63 0.4
Abortion	(5) 22.7	(4) 23.5	0.15 >0.5
Inflammatory diseases of the genital tract	(6) 27.3	(3) 17.6	0.17 >0.5
Spontaneous miscarriage	(5) 22.7	(7) 41.2	0.89 0.3
Scar on the uterus after a cesarean section	(4) 18.2	(3) 17.6	0.22 >0.5
Oligohydramnios	(1) **4.5**	(7) **41.2**	7.89 **<0.01**
Polyhydramnios	0	5.9	0.03 >0.5
Preeclampsia	(4) **18.2**	(9) **52.9**	5.21 **0.03**
Gestational diabetes mellitus	(3) **13.6**	(10) **58.8**	8.81 **<0.01**
Extragenital diseases			
Obesity	(6) **27.3**	(10) **58.8**	3.95 **<0.05**
Anemia	(18) 81.8	(15) 88.2	0 >0.5
Arterial hypertension	(4) 18.2	(4) 23.5	0 >0.5
Bronchial asthma	4.5	0	0.03 >0.5
Urinary tract infections	(7) 31.8	(5) 29.4	0.05 >0.5
Varicose disease	(3) 13.6	(2) 11.8	0.16 >0.5
Chronic herpes infection	(4) 18.2	0	3.41 0.06
Cardiomyopathy	(4) 18.2	(4) 23.5	0 >0.5

on the pathogenesis of a new coronavirus infection provide data on direct endothelial infection and its immune-mediated damage, which can result in widespread endothelial dysfunction [19]. Endothelial damage contributes to the development of preeclampsia in severe COVID-19. However, pre-existing endothelial dysfunction in patients, as a cause of preeclampsia, can aggravate the disease severity. Further studies are required to identify the relationship between endothelial damage and the severity of COVID-19 in pregnant women.

Of deceased pregnant women, >40% had oligohydramnios, while it was noted only in 1 patient among the recovered patients ($p < 0.01$). Oligohydramnios, as a rule, serves as a marker of placental insufficiency; a possible consequence of the spread of infection to the fetal membranes, with damage to the amniotic epithelium as the main producer of amniotic fluid [20]. Our study evaluated the results of the histological examination of the placenta only in the group with a poor outcome since the recovered patients were discharged pregnant and subsequently had safe delivery in various hospitals in the city (the data are presented below). Placental insufficiency was histologically confirmed in all patients in the group with a poor outcome, while it was compensated in two cases and subcompensated in another two cases (23.5%). Accordingly, 76.5% of pregnant women in this group had placental insufficiency with acute decompensation. Concurrently, histological examination revealed that all pregnant women with oligohydramnios had decompensated placental insufficiency (100%), with the presence of DNA-RNA-viral choriodeciduitis in all cases, and purulent-focal chorioamnionitis in 4 out of 7 (57.1%) patients. Decompensated placental insufficiency associated with DNA-RNA-viral choriodeciduitis was recorded only in half of the cases with a normal amount of amniotic fluid or polyhydramnios, while "the onset of ascending amniotic infection" was histologically noted only in two cases. The data obtained concluded that oligohydramnios in pregnant women with COVID-19 is an unfavorable sign, indicating the development of chorioamnionitis.

Fever, dyspnea, weakness, and dry cough prevailed among the clinical manifestations in patients. Fever was detected in all patients; pyretic or febrile fever was diagnosed with the same incidence in both groups. No statistical differences were found in the clinical disease manifestations in patients from groups 1 and 2. The main clinical manifestations of COVID-19 in the examined pregnant women are presented in Table 2.

Laboratory parameters of patients at the time of admission and the height of the disease are summarized in Table 3.

According to laboratory examinations, patients in both groups had a high level of C-reactive protein. Attention is drawn to the increased level of procalcitonin, which indicates the infectious process generalization and the probable overlay of a bacterial infection. Table 3 demonstrates that as respiratory failure increased, the activity of lactate dehydrogenase increased, and the index of this marker of tissue destruction increased to critical values in the group with a lethal outcome. Additionally, all patients with severe COVID-19 at the height of the disease had significantly increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities. Thus, ALT activity increased from 43.5 ± 26.2 U to 194.7 ± 29.2 U ($p = 0.001$) in group 1 and from 46.5 ± 20.7 U to 288.1 ± 106.6 U ($p = 0.04$) in group 2. AST activity increased even more significantly, and it was almost 3 times higher in pregnant women with a lethal outcome at the height of the disease than in recovered patients ($p = 0.04$). Concurrently, ALT and AST values were higher than 1000 U ($\chi^2 = 5.26$; $p = 0.02$) in 5 cases of pregnant women in group 2, whereas such high values of transaminases were not detected in the group with a favorable outcome.

Previous studies have shown that SARS-CoV and MERS-CoV cause liver damage [21]. With COVID-19, abnormalities in the functional state of the liver were also revealed, which were associated with the progression and severity of the infectious process [22]. This was expressed in increased activity of ALT and AST, and the total bilirubin levels. The literature reports that liver damage is rather common in critically ill patients with COVID-19 who have been hospitalized for a long time [23]. Nevertheless, drawing unequivocal conclusions at this stage is premature since a pronounced increase in the activity of hepatic transaminases may be associated with both the direct effect of SARS-CoV-2 on the liver and its drug damage. More than a tenfold increase in the activity of liver transaminases indicates the development of multiple organ failure in patients. The mechanisms of liver damage by SARS-CoV-2 are still poorly understood; however, possible

Table 2. Clinical manifestations of COVID-19 in the examined pregnant women

Clinical manifestations	Group 1 ($n = 22$) %	Group 2 ($n = 17$) %	χ^2 p
Dry cough	(19) 86.4	(11) 64.7	0.94 0.3
Dyspnea	(20) 90.9	(17) 100	0.03 0.85
Anosmia	(6) 27.3	(5) 29.4	0.06 0.8
Weakness	(21) 95.5	(17) 100	0
Sore throat	(2) 9.1	(4) 23.5	0.86 0.35
Nasal congestion	(6) 27.3	(7) 41.2	0.37 0.6
Rhinorrhea	(3) 13.6	(4) 23.5	0.2 0.7
Joint pain	0	(1) 5.9	0.03 0.85
Fever	(22) 100	(17) 100	0
pyretic	(8) 36.4	(8) 47.0	0.12 0.75
febrile	(14) 63.7	(9) 52.9	0.11 0.75

Table 3. Laboratory parameters of patients at the time of admission and the height of the disease

Indicator	Group 1 at admission	Group 2 at admission	p_{1-2}	Group 1 at the height of the disease	Group 2 at the height of the disease	p_{1-2}
Hemoglobin, g/l	104.4 ± 9.8	102.7 ± 10.8	0.9	99.8 ± 9.0	98.2 ± 10.1	0.9
Leukocytes, 10^9/L	7.9 ± 1.8	9.3 ± 1.9	0.12	10.2 ± 2.1	19.4 ± 3.8	**0.05**
Platelets, 10^9/L	179.0 ± 25.9	192.2 ± 39.2	0.75	233.0 ± 39.2	181.6 ± 39.3	0.08
Neutrophils, %	82 ± 6.4	76.7 ± 11.2	0.54	66.9 ± 5.1	85.7 ± 8.1	0.09
Lymphocytes, *n*	1.8 ± 1.8	1.75 ± 1.7	0.86	1.7 ± 1.8	2.1 ± 1.7	0.58
ALT, U/l	43.5 ± 26.2	46.5 ± 20.7	0.58	194.7 ± 29.2	288.1 ± 106.6	0.51
AST, U/l	60.8 ± 36.0	63.1 ± 29.1	0.45	**170.7** ± 26.9	**483.5** ± 141.7	**0.04**
Bilirubin, μmol/l	10.1 ± 2.5	12.6 ± 6.5	0.84	11.7 ± 3.2	13.3 ± 5.0	0.9
Creatinine, μmol/l	45.3 ± 4.8	59.0 ± 22.0	0.66	41.2 ± 3.0	90.1 ± 36.3	0.06
Total protein, g/l	59.5 ± 3.8	57.3 ± 5.0	0.58	56.3 ± 3.5	53.1 ± 5.0	0.68
Urea, mmol/l	3.3 ± 1.7	3.2 ± 1.7	0.88	3.7 ± 1.0	8.0 ± 1.8	**0.05**
Glucose, mmol/l	6.2 ± 1.4	5.7 ± 1.3	0.21	7.1 ± 1.5	8.3 ± 2.5	0.95
CRP, mg/l	69.5 ± 17.0	99.7 ± 40.2	0.24	97.8 ± 23.3	129.9 ± 48.7	0.58
LDH, U/l	189.6 ± 50.6	416.5 ± 107.3	0.19	**367.8** ± 110.1	**960.0** ± 261.0	**0.05**
PCT, ng/ml	1.6 ± 2.0	1.2 ± 1.8	0.99	10.5 ± 13.2	3.3 ± 3.3	0.43
D-dimer, μg/ml	2.0 ± 1.8	2.7 ± 1.8	0.62	**2.2** ± 1.2	**6.2** ± 1.5	**0.05**

Note. ALT — alanine aminotransferase; AST — aspartate aminotransferase; CRP — C-reactive protein; LDH — lactate dehydrogenase; PCT — procalcitonin test.

Table 4. Indicators of the transfer of group 1 patients to artificial lung ventilation

Patient	Day of illness when transfer to ALV	Duration of ALV	Degree of lung damage	RF, degree	p_aO_2/FiO_2
1	11	1	CT3	III	71
2	5	6	CT3	III	116.4
3	13	1	CT2	III	116

Note. ALV — artificial lung ventilation; RF — respiratory failure; CT — computed tomography; CT3 — the prevalence of lesion according to CT of 50%–75% of the lung volume; CT2 — the prevalence of lesion of 25%–50% of the lung volume.

causes include virus-induced effects, systemic inflammation (cytokine storm), and hypoxia associated with respiratory failure due to pneumonia. One of the main functions of the liver is detoxification, thus the toxic effect of drugs on the liver cannot be excluded.

Patients in both groups required oxygen support as respiratory failure progressed, from insufflation of humidified oxygen through a mask to ALV.

All women in group 2 were on ALV (100%) due to third-degree respiratory failure; whereas, 3 (23%) patients in group 1 were on ALV, of them 1 had lung damage CT2 (25%–50%) after ALV was transferred to NALV for 4 days.

The disease duration of pregnant women in group 1 upon hospital admission was 6.7 ± 1.7 days, and 8.0 ± 1.6 days when transferred to ALV. Ten (45%) pregnant women were transferred to high-flow oxygenation on days 10.5 ± 1.1 of illness, with the average high-flow oxygenation duration of 4.8 ± 1.46 days. Two (9%) pregnant women were transferred to NALV on days 8.6 ± 6.7, with the average duration of NALV use of 2.3 ± 1.72 days. The remaining 7 (31.8%) female patients had sufficiently high saturation rates on humidified oxygen supplementation through a face mask, and they did not require active respiratory support. The criterion for starting respiratory support for pregnant women was a combination of factors, such as an increased respiratory failure, a decreased SpO_2, and an oxygenation index. The method of respiratory support was determined based on the combination of these parameters (Table 4).

In group 2, 17 lethal outcome cases were registered due to complications in the extremely severe course of COVID-19.

Table 5. Indicators of the transfer of patients of group 2 to artificial lung ventilation

Patient	Day of illness when transfer to ALV	Duration of ALV, days	ECMO/duration, days	Degree of lung damage according to CT	RF, degree	p_aO_2/FiO_2
1	8	11		CT3	III	51
2	10	2		CT3	III	48.9
3	12	7		CT2	III	49
4	8	7		CT4	III	37.4
5	15	21	7	CT4	III	70.1
6	11	1		CT3	III	210
7	10	8		Rg4	III	54
8	15	8		Rg4	III	44
9	30	1		Rg4	III	70
10	17	6		Rg4	III	71
11	10	11		Rg4	III	71
12	15	7		Rg4	III	54
13	25	21	19	CT4	III	53
14	18	1		CT4	III	93
15	9	7		Rg4	III	121
16	25	1		Rg4	III	39
17	32	1		Rg4	III	55

Note. CT — computed tomography; Rg — radiography; ALV — artificial lung ventilation; RF — respiratory failure; ECMO — extracorporeal membrane oxygenation. *CT4, Rg4 — critical volume with the lesion prevalence of >75% of the lung volume.

The disease duration in patients upon hospital admission was 8.2 ± 1.87 days and 10.0 ± 1.84 days upon the intensive care unit transfer. All 17 patients stayed in the intensive care unit with varying amounts of lung tissue damage on CT and respiratory failure of the third degree, which required transfer to ALV in all cases. The disease duration, when transferred to ALV, was 16.0 ± 3.4. The patients received ALV for 7.6 ± 3.0 days. Two patients on ALV with CT4 lung damage (>75%) (patient 5, Table 5) underwent venovenous extracorporeal membrane oxygenation for 7 and 19 days, respectively, according to vital indications (Table 5).

In group 1, all women were discharged in a satisfactory condition with a progressive pregnancy after recovery with recommendations for follow-up by a local therapist, pulmonologist, and obstetrician-gynecologist at the primary healthcare facility.

Women who are discharged from the hospital with a progressive pregnancy were monitored; and at the time of writing the article, 18 have childbirth, with vaginal delivery in 12 cases and cesarean section in 6. The indications for operative delivery include reasons not related to COVID-19, namely exacerbation of genital herpes in case 1, foot presentation of the fetus in a pregnant woman with a uterine scar after a previous cesarean section in case 2, premature discharge of amniotic fluid (rupture to delivery interval of 23 h) and lack of biological readiness of the soft birth canal in case 3, a uterine scar after conservative myomectomy in case 4, a clinically narrow pelvis in case 5, and *vasa previa* in case 6. The satisfactory condition of all children was registered. No perinatal mortality occurred. One woman remained pregnant at the time of writing, and the other 4 could not be contacted.

In group 2, all women had delivered in St. Petersburg S.P. Botkin Clinical Infectious Diseases Hospital, 14 (82.4%) by cesarean section and 3 (17.6%) through vaginal delivery. Of the three women who spontaneously gave birth, 1 delivered at term and two delivered prematurely. Additionally, the labor was induced due to antenatal fetal death in one case. A total of 5 patients (29.4%) had delivered at full-term pregnancy, and the labor was preterm in 12 (70.6%) cases. An operative delivery was performed at full term due to the failure of the uterine scar after cesarean section in one (7%) case. In the vast majority of cases (93%), emergency cesarean section indications were placental insufficiency (according to Doppler data) in combination with an increased respiratory failure in the mother and the absence of ALV effect. Fifteen (88%) female patients had delivered in the third trimester of pregnancy and 2 (12%) in the second trimester. Fifteen live babies were born, 4 of them were in satisfactory condition, including 3 full term

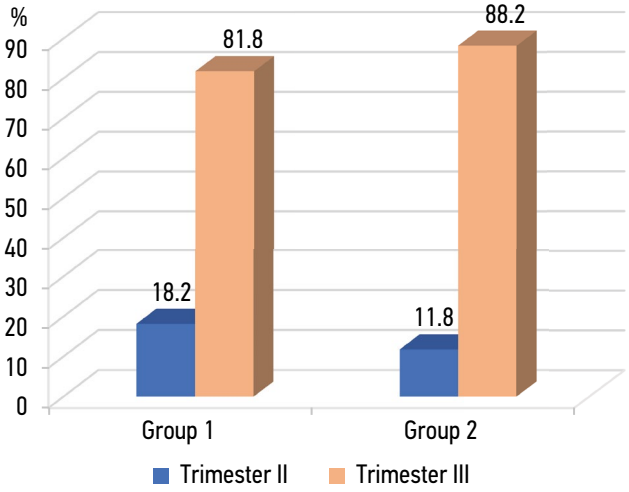

Figure. Distribution of pregnant women with severe COVID-19 by trimesters

and 1 premature baby born at week 32/33 of gestation. In the remaining 11 children, a varying degree of severe general condition was registered, which was associated with prematurity and with decreased compensatory capabilities of the fetus in the presence of placental insufficiency. Additionally, 2 cases of antenatal fetal death occurred. Thus, progressive placental insufficiency was noted in 15 out of 17 dead patients (in 88%). Perinatal mortality in this group was 1.18%.

The newborns were isolated and examined for COVID-19, all children had a negative nasopharynx swab test result, and they were transferred to children's city hospitals with further discharge according to indications.

Among patients with severe and extremely severe forms of COVID-19, women in the third trimester of pregnancy predominated (Figure). The maternal mortality monitoring in the region during the period under review revealed no cases of lethal outcomes for women due to COVID-19 in the first trimester of pregnancy. Our data are consistent with recent findings by UK authors that pregnant women are not more likely to be infected with COVID-19 than other healthy adults, but are at increased risk of severe COVID-19, especially in the third trimester of pregnancy [24].

The treatment of groups 1 and 2 was performed according to the methodological recommendations of the Ministry of Health of the Russian Federation and is changed following the appearance of new ones. The range of drugs and examination possibilities significantly expanded after delivery. However, there is currently no specific therapy despite the active treatment of COVID-19. We continue to gain experience as the epidemic process progresses.

All patients who stayed in the intensive care unit of our hospital were provided with a telemedicine consultation with the V.I. Kulakov Center for Obstetrics, Gynecology, and Perinatology.

CONCLUSION

The clinical manifestations registered in pregnant women with severe COVID-19 in this study did not significantly differ from those already described in the literature. According to many authors, the main symptoms characteristic of COVID-19 are fever, cough, and dyspnea [25]. Dyspnea has been described in all cases of severe and extremely severe coronavirus infection, and the fact that the majority of women hospitalized with COVID-19 during pregnancy were in the late second or third trimester [24].

In our case, the vast majority of women with severe and extremely severe COVID-19 were in the third trimester of pregnancy. This is probably due to physiological changes that occur in the body during pregnancy, such as reduced functional lung volume, diaphragmatic elevation, and changes in cellular immunity, which make pregnant women more susceptible to viral infections.

Risk factors are expected to be similar to those in the general population, with a significant proportion of women with severe COVID-19 having an elevated body mass index or comorbidities, such as pulmonary, cardiac diseases, or diabetes mellitus [26]. Currently, clinical data are still accumulated, but assuming that the risk of more severe clinical manifestations of coronavirus infection in pregnant women with these comorbidities will be higher is logical. Most pregnant women with severe COVID-19 in our study were anemic. Obesity was twice as common with a poor outcome, and pregnancy was significantly more often complicated by gestational diabetes mellitus, preeclampsia, and oligohydramnios. In the vast majority of cases in this group, emergency delivery was performed due to an increased placental insufficiency associated with pulmonary insufficiency.

With poor outcomes, more pronounced changes in the liver were noted, that is, liver failure often ranks first in the range of manifestations of multiple organ failure in critically ill patients. Thus, hepatic dysfunction may serve as a predictor of condition deterioration in patients with COVID-19 and an indicator of their probable admission to the intensive care unit.

Our study revealed a >75% prevalence of lung tissue damage of lung volume (CT4) in 13 (76.4%) cases in the group with a poor outcome. Comparison with the data of other authors is not possible due to inadequate publications with information on the extent of lung tissue damage.

CONCLUSIONS

Conclusions about the aspects of the course of COVID-19 in pregnant women, women in labor, and puerperas can only be made after the end of the pandemic, but we can conclude the following based on our results:

1) women in the third trimester of pregnancy are more susceptible to extremely severe COVID-19 with a poor outcome;
2) early initiation of respiratory support may promote recovery;
3) anemia is a significant concomitant disease in pregnant women with severe and extremely severe COVID-19. Pregnancy is more often complicated by gestational diabetes mellitus, preeclampsia, oligohydramnios, and obesity in patients with poor outcomes;
4) the most characteristic clinical manifestations of a severe course of COVID-19 are dyspnea and fever;
5) a pronounced increased activity of liver enzymes and increased placental insufficiency serve as a harbinger of poor outcomes as a manifestation of multiple organ failure.

ADDITIONAL INFORMATION

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Author contributions. *A.I. Gareeva* created the concept and design of the study, collected and processed the material, performed statistical data processing, and wrote the text. *E.V. Mozgovaya* analyzed the data obtained, discussed and edited the text. *M.A. Belopolskaya* discussed and edited the text. *A.S. Kovalchuk* collected and processed the material. *A.N. Kucheryavenko* created the concept and design of the study, discussed and edited the text.

All authors made a significant contribution to the study and the article preparation, as well as read and approved the final version before its publication.

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