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# Clinical course of novel COVID-19 infection in pregnant women

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**ABSTRACT**

**Objectives:** Evaluation of clinical course of COVID-19 during pregnancy and maternal and perinatal outcomes of this pregnancy.

**Methods:** 66 women with polymerase chain reaction (PCR) – confirmed SARS-CoV-2 and their 42 neonates were included in the prospective observational study. Demographic, epidemiological, clinical, laboratory and instrumental data of pregnancy, delivery, postpartum period, including pharmacotherapy and neonatal outcomes were analyzed.

**Results:** 15 (22.7%) women were asymptomatic, 25 (38%) had mild disease, while moderate and severe forms were detected in 20 (30.2%) and 6 (9.1%) cases, respectively. Additional oxygenation was required in 6 (9%) cases: 4 (6%) received CPAP therapy and 2 (3%) – mechanical ventilation. Main clinical symptoms were cough (51.5%), anosmia (34.9%), and hyperthermia (33.3%). Laboratory changes included increased levels of lactate dehydrogenase (LDH), creatinine, D-dimer, and C-reactive protein (CRP), anemia, and leukopenia. All pregnant women received low molecular weight heparin and interferon alfa-2b according to the National clinical recommendations. Antimicrobial drugs included Amoxicillin/Clavulanic acid (46%) and macrolides (28%) or carbapenems in severe cases of disease. Spontaneous abortion was reported in 6.1% of cases. Eight preterm (19%) and 34 term deliveries (81%) occurred. The mean weight of neonates was (3283 ± 477) g, 1- and 5-min Apgar score was (7.8 ± 0.6) and (8.7 ± 0.5), respectively. No cases of neonatal COVID-19 infection were reported.

**Conclusions:** Mostly, the manifestations of COVID-19 were mild. However, 9% of cases were severe, and could contribute to preterm delivery or maternal morbidity. Main predictors of severe COVID-19 course in pregnant women were a decrease in the levels of erythrocytes and lymphocytes and increase in the levels of alanine aminotransferase and CRP. Elimination of the virus in pregnant women required more time due to altered immunity. No evidence of vertical transmission during pregnancy and delivery was found. However, the possibility of this cannot be excluded.

## Introduction

Pregnancy is characterized by altered immunity with predisposition to respiratory viral infections [1]. In previous years, infection caused by the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) in pregnant women led to an increased rate of admissions to an intensive care unit. The reported rate of lethal outcomes from SARS-CoV was up to 25% [2,3].

In course of pregnancy transverse diameter of the thorax increases, diaphragm is displaced upwards; this decreases maternal tolerance to hypoxia [4]. Moreover, alteration of the lung capacity and vasodilation may

lead to swelling of the mucous membrane and increase in secretion within upper respiratory tract that contributes to development of respiratory failure [5].

Possibility of transplacental transmission of SARS-CoV-2, which may lead to negative neonatal outcomes remains unclear [6,7].

Considering controversial data about the course of COVID-19 in pregnant women and neonates [8–11], evaluation of clinical manifestations, maternal and perinatal outcomes in pregnant women with COVID-19 were the main goals of this research.

## Materials and methods

Research was carried out at the National Medical Research Center for Obstetrics, Gynecology and Perinatology, Ministry of Healthcare of Russian Federation. From the onset of pandemic all women admitted to the Center for treatment and/or labor were tested on COVID-19. 66 women with PCR – confirmed SARS-CoV-2 and their 42 neonates were included in the prospective observational study. COVID-19 testing was performed in women admitted to the hospital (due to the threatening miscarriage and preterm labor, for preinduction, etc.). When a woman appeared to be PCR positive she was admitted to a special medical unit for treatment of COVID-19 positive patients. Nasopharyngeal swabs were collected from all pregnant women and neonates and then were tested using reverse transcriptase real-time PCR. The same method was used for the virus detection in vaginal discharge in women during labor, amniotic fluid, placenta, and colostrum

All women underwent the following tests: blood test, urine test, CRP, coagulogram, biochemical blood test, and computed tomography (CT) in cases where moderate or severe forms of COVID-19 were suspected.

In this study, CO-RADS system and RSNA consensus were used to interpret the laboratory changes [12]. Moreover, during the pandemic, a simplified semi-quantitative evaluation system of affected lung tissue volume was introduced in Russian Federation, which scored the degree of lung tissue damage by a scale of CT-0 to CT-4. CT-0 was scored when no lung tissue was affected (0%). CT-1 (mild) category was attributed to $<=$ 25% of lung tissue damage; CT-2 (moderate), CT-3 (severe) and CT-4 (critical) were scored when 25–50%, 50–75%, and $>=$ 75% of lung tissue were affected, respectively. Introduction of this system allowed to standardize and accelerate interpretation of

data as well as to convert it into an understandable format for the clinicians [13].

Patients were either asymptomatic or had clinical manifestations of various degree. By the severity of symptoms and results of tests they were categorized into mild, moderate or severe form of COVID-19. Mild form of COVID-19 was characterized by the fever with body temperature below 38.5 °C, cough, fatigue, sore throat and absence of clinical signs of moderate and severe disease. Moderate form was determined as fever 38.5 °C and higher, respiratory rate more than 22 per minute, shortness of breath during physical activity, pneumonia confirmed by CT scan, oxygen saturation more than 95%. The disease was considered severe with respiratory rate more than 30 per minute, oxygen saturation 94% and lower, $PaO_2/FiO_2$ 300 mm. hg and lower, progression of lung damage (increase of damaged tissue by 50% or more in a 24–48 h), decreased consciousness, unstable hemodynamics. arterial blood lactate more than 2 mmol/l, qSOFA more than 2.

Women were tested for SARS-CoV-2 infection once each week. Virus elimination was assumed when two negative PCR tests performed within a 24-h interval. Diagnostics, clinical management and treatment of pregnant women with COVID-19 were carried out according to National clinical recommendations "Organisation of Medical Care for Pregnant Women, Women in Labour, Postpartum Women and Neonates with a Novel Coronavirus Infection COVID-19" [14]. Data were collected from April 2020 to June 2020.

The assessment of demographic, epidemiological, clinical, laboratory and instrumental parameters of pregnancy, birth and postpartum period as well as pharmacotherapy and neonatal outcomes was performed. The research was IRB approved. All women have signed an informed consent.

## Statistical analysis

The statistical analysis was performed with "GraphPad Prism 6" (GraphPad Software, San Diego, CA). D'Agostino–Pearson omnibus test was used to assess normality of distribution. Parametric data were presented as mean value ± standard deviation. Nonparametric data were presented as median (interquartile range). Qualitative data were presented as absolute value (n) and %. T-test (for parametric data), Mann–Whitney U test (for nonparametric data) and Fisher's exact test (for qualitative data) were used for value comparison. The two-sided $p<.05$ was considered to indicate statistical significance.

**Table 1.** Clinical symptoms of novel coronavirus infection in pregnant women.

| Clinical manifestations | $N = 66$ | % |
|---|---|---|
| Hyperthermia (>38) | 22 | 33.3 |
| Pharyngitis | 8 | 12.1 |
| Loss of smell | 23 | 34.9 |
| Shortness of breath | 11 | 16.7 |
| Cough | 34 | 51.5 |
| Fatigue | 11 | 16.7 |

**Table 2.** The forms of novel coronavirus infection in pregnant women.

| Clinical form | $N = 66$ | % |
|---|---|---|
| Asymptomatic | 15 | 22.7 |
| Mild | 25 | 38 |
| Moderate | 20 | 30.2 |
| Severe | 6 | 9.1 |

**Table 3.** Main laboratory data of pregnant women with novel coronavirus infection.

| Parameter, units | Value | Range |
|---|---|---|
| Leukocytes $*10^9$ / L | 7.9 (5.4–9.8)* | 3.53–42.8 |
| Erythrocytes $*10^{12}$ / L | 3.91 (3.6–4.3)* | 2.79–5.26 |
| Hemoglobin, g/L | 116.5 ± 14.6 | 75–160 |
| Platelets $*10^9$ / L | 238 (197–293)* | 91–1058 |
| Lymphocytes % | 20 (15.6–28)* | 5–62 |
| Ferritin, ng/ml | 53.5 (20.9–151.5)* | 5.1–14.750 |
| PCT, ng/ml | 0.08 (0.05–0.24)* | 0.028–36 |
| CRP, mg | 6.4 (11.7–19.9)* | 0.08–229 |
| AST, UI/L | 19.8 (12.1–32)* | 10.1–103 |
| ALT, UI/L | 22.7 (18.8–31)* | 6.1–104 |
| LDH, UI/L | 398 (306–436)* | 237–1984 |
| Albumin, g/L | 33 ± 4.8 | 22.3–43.5 |
| Creatinine, mmol/L | 75.3 (68.3–80.7)* | 54.3–80.5 |
| Fibrinogen, g/L | 4.76 (4–5.7)* | 2.02–9.04 |
| INR | 1.01 ± 0.08 | 0.9–1.17 |
| PR sec | 11.5 (10.7–12.3)* | 10.2–20.8 |
| Antithrombin III % | 96.5 (87.3–114.3)* | 78–146 |
| D-dimer, ng/L | 1361 (822–2045) | 25–34.280 |

PCT: procalcitonin; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; INR: International Normalized Ratio; PR: prothrombin ratio. Data are shown as the mean value and standard deviation (M ± SD).
*Data are shown as the median value and interquartile range (Me (IQR)).

## Results

The mean age of patients was (30.3 ± 6.25) years, the mean height was (166 ± 6.8) cm, the mean body mass index was (27.1 ± 4.6) kg/m$^2$. The mean gestational age was (31.3 ± 10.4) weeks ranging from 5 to 38 weeks. 5 (7.6%) patients were COVID-19 positive in the Ist trimester, while in IInd and IIIrd trimesters the disease diagnosed in 7 (10.6%) and 54 (81.8%) cases, respectively. The mean duration of the disease was 17.6 (6–34) days. Hospital stay was 14.9 (4–30) days. PCR tests for SARS-CoV-2 became negative on average after 15.6 (6–31) days. The main clinical symptoms were cough (51.5%), loss of smell (34.9%), and hyperthermia (33.3%) (Table 1). Asymptomatic course of COVID-19 was reported in 15 (22.7%) of cases. Mild, moderate, or severe COVID-19 accounted for 25 (38%), 20 (30.2%), and 6 (9.1%), respectively (Table 2).

The laboratory changes most often included the increased levels of LDH, creatinine, D-dimer, and CRP, anemia, and leukopenia (Tables 3 and 4). Lymphopenia featured the viral infection in 42 cases (63.6%). CRP level as the main laboratory marker of inflammation activity, indicator of the antibacterial therapy necessity and criterion of treatment efficacy was measured in patients with pneumonia every 3 days.

D-dimer levels, along with the patient's clinical condition and severity of pneumonia according to CT data, were used to determine the dosage of low molecular weight heparins (LMWH).

Laboratory changes were analyzed in accordance with the severity of the disease. Main predictors of severe COVID-19 course in pregnant women were the decrease in the levels of erythrocytes and lymphocytes and increase in the levels of ALT and CRP (Table 5).

CT showed no features of viral pneumonia (COVID-19 Reporting and Data System-1-2 (CO-RADS-1-2)) with 0% of affected lung tissue (CT-0) in 5 cases (25%). High probability of viral pneumonia (CO-RADS-4-6) with minimal (<25%) volume of lung tissue affected (CT-1) was reported in 8 women (40%). High probability of viral pneumonia (CO-RADS-4-6) with moderate (25-50%) volume of lung tissue affected (CT-2) was reported in 2 women (10%). High probability of viral pneumonia (CO-RADS-4-6) with significant (50–75%) volume of lung tissue affected (CT-3) was reported in two cases (10%). High probability of viral pneumonia (CO-RADS-4-6) with critical (>75%) volume of lung tissue affected (CT-4) was reported in three cases (15%).

All pregnant women received LMWH and interferon alfa-2b according to National clinical recommendations and international experience [14,15]. Antimicrobial drugs included Amoxicillin/Clavulanic acid (46%) and macrolides (28%). Carbapenems were the antibiotics of choice in severe cases of disease. Side effects of Lopinavir/Ritonavir, risk of intrauterine growth restriction as well as an unproved efficacy of this group of drugs in COVID-19 treatment were the reasons for their limited application in our study. Lopinavir/Ritonavir was used in the severe cases of disease only.

Additional oxygenation was required in six cases (9%): four (6%) patients received CPAP therapy and two (3%) – mechanical ventilation. Corticosteroids

(dexamethasone 12 mg/day for 3–4 days) and immuno-globulin therapy (0.5 g/kg for 3–4 days) were also prescribed.

In the majority of cases, prophylactic doses of LMWH (Enoxaparin or Nadroparin Calcium) were administered. However, therapeutic doses of LMWH were given to the patients under mechanical ventilation who had high of D-dimer levels (up to 34,280 ng/l).

Abortions before 20 weeks of gestation occurred in 4 cases (6.1%) out of 66: 2 spontaneous abortions before 12 weeks of gestation in women with mild form of Covid-19, one spontaneous abortion at 18th week in a woman with severe Covid-19 infection, and one medical abortion at 19th week for fetal abnormalities. Births and on-going pregnancy were reported in 42 (63.6%) and 20 (30.3%) cases respectively. Eight preterm (19%) and 34 term deliveries (81%) occurred.

**Table 4.** Laboratory changes reported in pregnant women with novel coronavirus infection.

| Parameter | N = 66 | % |
|---|---|---|
| Anemia (<110 g/L) | 11 | 16.6 |
| Leucocytosis (>12*10⁹/L) | 8 | 12.1 |
| Leukopenia (<5,5*10⁹/L) | 11 | 16.6 |
| Lymphopenia (<19 %) | 42 | 63.2 |
| Thrombocytosis (>350*10⁹/L) | 3 | 4.5 |
| Thrombopenia (>150*10⁹/L) | 7 | 10.6 |
| CRP increase (>10 mg) | 17 | 25.8 |
| AST increase (>40 UI/L) | 5 | 7.6 |
| ALT increase (>40 UI/L) | 5 | 7.6 |
| Creatinine increase (>80 mmol/L) | 18 | 27.2 |
| LDH increase (>300 UI/L) | 36 | 54.5 |
| D-dimer increase (>600 ng/L) | 27 | 40.9 |
| PCT increase (>0,5 ng/ml) | 4 | 6 |

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

6 preterm operative deliveries were performed due to obstetric conditions (a scar after previous cesarean section, increase in severity of preeclampsia, placenta accreta). Seven women who delivered preterm had mild form of infection and one had a moderate form of the disease. Due to fetal distress, cesarean section was performed in 17 (40.5%) cases, vacuum extraction – in 2 (4.8%) cases, normal vaginal delivery accounted for 23 cases (54.7%). Cesarean section was performed due to fetal conditions including malformations in 7 cases (41.2%) and due to maternal obstetric conditions (cephalopelvic disproportion, previous cesarean section, placenta previa, etc.) in 10 cases (58.8%). The mean birth weight in neonates was (3283 ± 477) g. The mean length was (52 ± 2.75) cm. The 1-min Apgar score was 7.8 ± 0.6 and 5-min Apgar score was 8.7 ± 0.5.

Neonates after birth were immediately isolated from their mothers until 2 negative SARS-CoV-2 results were obtained. After that the breastfeeding was allowed. All neonates were tested for SARS-CoV-2 immediately after birth and on the 3rd and 10th days after birth. In all newborns the tests appeared negative, and no clinical signs of COVID-19 were documented. No cases of perinatal death were reported.

One case of maternal death occurred on the 33rd day after the patient's admission to the hospital. The patient aged 40 years old was hospitalized on the 19–20th week of gestation and had primary myelofibrosis, portal hypertension with a history of bleeding from esophageal varices grade 2 on the 18th week of gestation. The patient was admitted with bilateral

**Table 5.** Main parameters of laboratory tests of pregnant women with novel coronavirus infection.

| Parameter, units | Asymptomatic (n = 15) Value | Mild (n = 25) Value | Moderate (n = 20) Value | Severe (n = 6) Value | p |
|---|---|---|---|---|---|
| Leukocytes *10⁹/L | 8.7 (7.2–9.7)* | 8.0 (5.9–8.9)* | 7.7 (5.1–8.8)* | 14.6 (5.8–22)* | 0.18 |
| Erythrocytes *10¹²/L | 4.4 (3.46–4.76)* | 4.1 (3.8–45)* | 4 (3.8–4.2)* | 3.4 (2.8–4)* | 0.0024 |
| Hemoglobin g/L | 119.9 (113–125.3)* | 116.7 (109.8–124)* | 117.3 (106–124)* | 101.2 (81.8–113.3)* | 0.06 |
| Platelets *10⁹/L | 225.1 (186.5–263.5)* | 231 (178.5–267)* | 218.3 (179–242.5)* | 359.2 (207–455)* | 0.6 |
| Lymphocytes % | 19.29 (14,8–23,8)* | 22.5 (12.8–30)* | 15.5 (10.6–18.3)* | 11.9 (5.9–15.5) * | 0.04 |
| Ferritin ng/ml | – | 56.5 (5.3–117)* | 59.2 (14.6–120)* | 139 (56.4–216)* | 0.1 |
| PCT ng/ml | – | 0.06 (0.05–0.08)* | 0.1 (0.05–0.3)* | 0.3 (0.05–0.7)* | 0.5 |
| CRP mg | 3.2 (1.7–5.3)* | 5.4 (0.7–10.1)* | 19 (2.5–24)* | 58.5 (4.8–105)* | 0.03 |
| AST UI/L | 17.5 (15.3–20.2)* | 21.8 (15.2–23.9)* | 24 (15.2–27.1)* | 32 (21.5–43.3)* | 0.09 |
| ALT UI/L | 10.16 (7.25–12.7)* | 18.6 (11.2–27)* | 21.3 (11.2–27)* | 26.4 (16–33.4)* | 0.04 |
| LDH UI/L | 387.3 (374–413)* | 357.3 (286.5–423)* | 394 (308.3–409)* | 691 (298–1224)* | 0.7 |
| Albumin g/L | 28.3 (+0.6) | 33.6 (+5.4) | 34 (+4.2) | 29.9(+3.5) | 0.09 |
| Creatinine mmol/L | 70.7 (65.1–70.1)* | 75.7 (69.4–79)* | 74.2 (68–80)* | 73.5 (66.4–79)* | 0.8 |
| Fibrinogen g/L | 4.8 (4.1–5.2)* | 4.7 (4.1–5.3)* | 5 (4.1–6.4)* | 5.3 (3.1–7.3)* | 0.9 |
| INR | 1 (+0.06) | 1(+0.06) | 1 (+0.1) | 1.1 (+0.1) | 0.4 |
| PR sec | 11.5 (11–12.5)* | 11.2 (10,4–11.8)* | 11.5 (10.6–12.5)* | 12.3 (11.2–13.5)* | 0.36 |
| Antithrombin III % | – | 96.6 (83.3–110.9)* | 102 (90–117)* | 104 (80–120)* | 0.76 |
| D-dimer ng/L | 3838 (1007–5527)* | 2255 (1287–4354)* | 1425 (945–1905)* | 10,600 (1632–26,932)* | 0.1 |

CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; PCT: procalcitonin. Data are shown as the mean value and standard deviation (M ± SD).
*Data are shown as the median value and interquartile range (Me(IQR)).

pneumonia caused by coronavirus infection (CO-RADS-5), with up to 90% affected volume of lung tissue according to CT (CT-4) and type 2 respiratory failure of stage 2. On the 3rd day her medical condition worsened and required transfer to the ICU and mechanical ventilation. Spontaneous abortion with fetal death occurred on the 21–22nd week of gestation. Pulmonary embolism and progression of multiple organ failure on the background of severe hematologic disease were the causes of death.

The PCR results were SARS-CoV-2-negative for all samples of vaginal discharge, amniotic fluid, placenta, and colostrum obtained from 32 women. However, in 11(34,4%) patients SARS-CoV-2 was revealed in rectal swabs.

## Discussion

### Principal findings

Even though previous outbreaks of coronavirus infection (SARS and MERS) were associated with the growth of maternal mortality up to 25% [2,3], according to our research the rate of severe cases of novel form of coronavirus infection accounted for 9.1% and mechanical ventilation was required in 3% of the cases. Main clinical symptoms included cough (51.5%), loss of smell (34.9%) and hyperthermia (33.3%); this corresponds to other literature reports [16,17]. Asymptomatic course of COVID-19 was found in 22.7% of cases, which is significantly lower than in general population (50–75% of cases) [18].

### Results

There was an inverse correlation between the elimination of the virus from the body and severity of the disease. The process took more time in asymptomatic carriers than in patients with severe course of the disease, lasting in average 11 days (8.5–18) versus 20 days (16–27), respectively. PCR-positive tests persisted on average for 15.6 days. This significantly exceeds average time required for virus elimination reported by Gautret et al., which was 6 days for 70–100% of patients who received medical treatment (hydroxychloroquine and azithromycin) and only for 12.5% of patients in the control group without these medications [19].

According to several communications cesarean section was the most often method of delivery due to high rates of fetal distress [20,21]. In our study, normal vaginal delivery prevailed (54.7%). Operative delivery (including vacuum extraction) due to fetal hypoxia was performed in four cases (9.5%) which is slightly more than previously reported in other publications (4–6%) [22–24].

Though our study did not demonstrate strong correlation between COVID-19 severity and adverse perinatal outcomes, possibly due to a small patients sample and/or timely and appropriate medical care at mild/moderate stages of the disease, other publications do, rising awareness on this issue [25–27].

### Clinical implications

Main predictors of severe COVID-19 course in pregnant women were a decrease in the levels of erythrocytes and lymphocytes and an increase in the levels of ALT and CRP; further research may contribute to better understanding of the mechanism and value of this correlation. The main cause of maternal death with COVID-19 was a severe comorbid disease.

### Research implications

In our study, all neonates were SARS-CoV-2-negative. We have also found no evidence of the virus in the amniotic fluid and placenta (similarly to Schwartz et al. [28]), as well as in the vaginal discharge of women in labor; these observations may reduce the concerns of vertical transmission of the infection during pregnancy and labor, but still are subject to further investigation in larger populations.

Although we found non SARS-CoV-2 in the colostrum, Wu et al. detected virus in breast milk by PCR [29]. Therefore, the issue of the mother to baby virus transmission through breastfeeding should be carefully addressed.

Herein we demonstrate the data obtained during the "first wave" of COVID-19 in Russia, indicating that there is no risk of transmission of the virus to the babies born from the mothers infected with SARS-CoV-2 shortly before the childbirth managed with appropriate precautions. Early publications also suggested a low risk of intrauterine transmission of COVID-19 from infected pregnant women to their fetuses. Karimi-Zarchi reported about 31 infected pregnant mothers with COVID-19, with no infection detected in the newborns and placenta [30]. Later, several observational studies on the possibility of vertical transmission of infection during pregnancy were published [31–33].

### Strengths and limitations

Our study is the first experience in Russian Federation in analysis of the clinical course of novel COVID-19

infection in pregnant women. We managed to correlate laboratory findings with the clinical characteristics of the disease. The main limitations of the study were small patients sample from one center and the absence of comparative group (e.g. pregnant women with other respiratory infections).

## Conclusions

Mostly, the manifestations of COVID-19 were mild. However, 9% of cases were severe, and could contribute to preterm delivery, abortion or maternal and fetal morbidity. Main clinical predictors of severe COVID-19 outcomes in pregnant women were a decrease in the levels of erythrocytes and lymphocytes and an increase in the levels of ALT and CRP. Elimination of the virus in pregnant women required more time due to physiological immunosuppression. No evidence of vertical transmission during pregnancy and delivery was found; however, such possibility cannot be excluded.

## Disclosure statement

The authors report no conflict of interest.

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