Coronavirus Infection COVID-19 and Pregnancy

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Abstract—The novel coronavirus infection SARS-CoV-2, which broke out in China in December 2019, has rapidly spread around the world. On March 11, 2020, the World Health Organization (WHO) assigned this infection pandemic status. Pregnant women and puerperae occupy a special place in the structure of the incidence of COVID-19. For more than a year and a half, the Lapino Clinical Hospital of the Mother and Child Group of Companies has accumulated significant experience in managing patients with COVID-19, including pregnant women and puerperae. This article presents the features of the course of the new coronavirus infection in pregnant women and puerperae during various periods of the pandemic, the experience of managing pregnancy and childbirth in the above group of patients, and methods of treatment.

Keywords: new coronavirus infection, COVID-19, SARS-CoV-2, course of pregnancy with COVID-19, delivery management for COVID-19, extracorporeal membrane oxygenation (ECMO), monoclonal antibodies

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Coronaviruses are important pathogens for humans and animals. At the end of 2019, a new coronavirus was identified as a source of pneumonia in Wuhan, in the Chinese province of Hubei. The viral infection quickly spread, leading to an epidemic throughout China, followed by a pandemic. In February 2020, the World Health Organization designated the disease as COVID-19, that is, coronavirus disease 2019 [1]. The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), formerly 2019-nCoV. It is a single-stranded RNA virus belonging to the Coronavidae family, genus Betacoronovirus. An important property of this virus is its tropism (that is, the ability to affect mainly specific organs and tissues) to target cells that have angiotensin-converting enzyme type II (ACE2) receptors, which are located on the endothelial and epithelial alveolar surfaces. The main target of SARS-CoV-2 is type II alveolar cells, leading to the development of diffuse alveolar damage [2–4]. With a new coronavirus infection, a cytokine storm can develop: an excessive response of the immune system, the rapid release of cytokines, and the development of blood clotting disorders.

Over 21 months (from March 2020 to December 2021), more than 5000 patients with a new coronavirus infection were hospitalized at the Lapino Clinical Hospital, including 389 pregnant women and puerperae; 145 births were performed; and 151 live children were born, including 6 twins. COVID-19 was diagnosed by PCR detecting SARS-CoV-2 RNA and IgM and IgG to SARS-CoV-2. Instrumental diagnostics included computer tomography (CT) of the chest organs and ultrasound of the lungs and pleural cavities. In mild disease, there were no characteristic manifestations (CT-0); in moderate disease, <25% of lung volume (CT-1) or 25–50% of lung volume (CT-2) was affected; in severe disease, the prevalence of the lesion reached 50–75% of lung volume (CT-3); and in extremely severe, >75% (CT-4). Treatment was carried out in accordance with the methodological recommendations of the Ministry of Health of the Russian Federation “Organization of Medical Care for Pregnant Women, Women in Childbirth, Puerperae, and Newborns with a New Coronavirus Infection COVID-19” [5]. Over the entire period, out of 389 patients with a mild course of the disease, 94 (24%) were hospitalized; with an average course, 253 (65%); with a severe course, 34 (9%); and with extremely severe one, 8 (2%).

From the start of the pandemic to December 2021, four waves of novel coronavirus infection were recorded (Fig. 3). The first wave, which was observed...
from March to May 2020, was caused by the Chinese strain of COVID-19; the second wave (October 2020–March 2021) was joined by the British strain; and the third (April–August 2021), by the Indian; the fourth wave, ongoing since September 2021, was mainly caused by the Indian strain (Fig. 1).

During the first wave of COVID-19, 84 pregnant women and puerperae were hospitalized at the Lapino hospital, mostly (85.2%) with mild and moderate severity of the disease. The age of the patients ranged from 21 to 46 years. The mean age in the severe group was greater than in the other groups and was 35.8 ± 3.4 years. The gestation period was also longer than average, 32.2 ± 3.8 weeks. In the management of patients during the first wave, regardless of the gestational age, oseltamivir and influenzaferon were used. In moderate and severe cases, the majority used an inhibitor of HIV-1 and HIV-2 protease—lopinavir + ritonavir (Kaletra). Most pregnant women and puerperae received antibiotic therapy. In puerperae, hydroxychloroquine (Plaquenil) was used. The IL-6 inhibitor tocilizumab (Actemra) was used when the perceived benefits outweighed the risks. Indications for the introduction of IL-6 blockers (introduced only to puerperae) were CT data—CT2-3 in combination with two or more signs: decreased SpO2, CRP > 30 mg/L, fever >38°C for three days, leukocyte count <3.0 × 10⁹ L⁻¹, and the absolute number of lymphocytes <1.0–10⁹ L⁻¹. No side effects were observed during treatment with Actemra. By the end of the first wave, glucocorticosteroids (dexamethasone, 8 mg twice a day) began to be used, which made it possible to stop the cytokine storm much faster and more efficiently and improved saturation and laboratory markers, prolonging pregnancy.

Of the features of the course of the disease in the first wave, it should be noted that pregnant women at gestation periods up to 32 weeks suffered more often from severe forms of the disease; there was no increase in the level of IL-6 more than 100; there was no rapid progression of interstitial changes; regardless of the period of illness and fever, the changes increased gradually. OAC, CRP, IL-6, and D-dimer were used as laboratory markers to assess the dynamics. The management of pregnancy was expectant; with an increase in respiratory failure and/or deterioration of the fetal condition, an emergency delivery was performed, which improved the condition of the patients.

Of the 84 patients admitted, 79 were pregnant: 50 of them (63%) were discharged with recovery and with a prolonged pregnancy; 23 had timely or premature births; 4 had spontaneous abortions; and 1 was diagnosed with an ectopic pregnancy. One patient, transferred to the hospital from another medical institution in an extremely serious condition, died on the 13th day after delivery as a result of bilateral polystemal total pneumonia, sepsis, and multiple organ failure. All 5 postpartum women admitted to the hospital were discharged with recovery.

During the second wave of the new coronavirus infection, 127 pregnant women and puerperae were hospitalized at the Lapino hospital, 91.2% of them with mild and moderate severity. Their ages ranged from 19 to 49 years. The mean age in the groups with varying degrees of severity did not differ. Pregnant women were hospitalized in the period from 6 to 41 weeks of gestation. On average, the longest gestation period was in the group with moderate severity, 29.6 ± 10.3 weeks. In the 2nd wave, patients with mild severity were hospitalized for delivery. Approaches to treatment changed: they stopped using Kaletra and Plaquenil; Triazaverin and favipiravir were used in puerperae; glucocorticosteroids and antibacterial drugs were actively used, which made it possible to prolong

![Fig. 1. Severity of COVID-19 disease in four waves.](image-url)
pregnancy. At gestation periods up to 32 weeks, with an ineffectiveness of hormonal and antibacterial therapy, and with an increase in pneumonia and pro-inflammatory markers (cytokine storm), to maximize the prolongation of pregnancy, tocilizumab was administered more often, after which the process stabilized, and it was possible to avoid premature delivery. For health reasons, the following IL inhibitors were used: sarilumab (Kevzara), levilimab (Ilissir), and olokizumab (Artlegia). The hospital used cytokine columns Jafron HA 330 (cytokine sorption) and extracorporeal membrane oxygenation (ECMO). Cytokine columns were used in 9 patients on days 1–3 after caesarean section with an increase in the level of IL-6 over 40 pg/mL. Hemosorption was carried out through a Jafron HA 330 column for 3–5 h (or treatment of 20–30 L of blood). Each patient received one to three treatments (one treatment per day). As a result, we observed a decrease in interleukin-6, detoxification, and an increase in saturation (during the procedure).

The peculiarities of the course of the disease in the second wave include the gradual development of a total lesion of the lung tissue, despite the ongoing therapy. Fibrinogen, LDH, and ferritin were added to laboratory markers.

Of the 127 hospitalized patients, 53 (42%) were discharged with recovery and with prolonged pregnancy; 60 delivered; eight miscarried; and two were diagnosed with an ectopic pregnancy on admission. All three puerperae admitted to the hospital were discharged with recovery. One patient, transferred to the hospital from another medical institution in an extremely serious condition, died on the 29th day after delivery as a result of bilateral polycystic damage to total pneumonia, a condition after hemicraniectomy and decapitated diabetes mellitus.

The third wave of COVID-19 was mainly caused by the Delta strain. According to the US Centers for Disease Control and Prevention, this strain is characterized by increased transmissibility, a possible decrease in neutralization by some EUA monoclonal antibody treatments, and a possible decrease in neutralization by sera after vaccination. The Delta variant of the coronavirus has a double mutation in the spike protein, which allows the virus to enter the cells of the body more quickly [6].

In the third wave, there were 109 pregnant women and puerperae among those hospitalized in the Lapino CH. Their age ranged from 22 to 45 years. The mean age in the groups with different degrees of severity did not differ and amounted to 33.2 ± 6.9 years. Pregnant women were hospitalized for a period of 4 to 41 weeks of gestation. The mean gestational age was 31.6 ± 7.9 weeks.

Note that, compared with previous waves, this period saw an increase in the number of patients hospitalized in serious condition, 20 (18.3%), of which six were on mechanical ventilation, three were on non-invasive mechanical ventilation, and 11 received high-flow oxygenation. The duration of hospitalization in the intensive care unit of the hospital was 21.2 ± 3.1 days, in total 29.2 ± 5.6 days in the hospital.

The third wave had its own characteristics in the course of the disease and in therapy: a rapidly progressive course with an increase in respiratory failure and a daily progression of the volume of lung damage. In this regard, before delivery (or immediately after), tocilizumab was used more often. In the absence of a cytokine storm, the ineffectiveness of standard anti-biotic therapy and corticosteroid therapy, a single or double administration of tocilizumab led to positive dynamics and the possibility of pregnancy prolongation. In connection with the progressive increase in the level of IL-6, olokizumab (Artlegia) was used. For periods of more than 32 weeks, with the height of the disease, a rapid increase in respiratory failure, IL-6 > 100, poorly controlled fever, a decision was made on immediate delivery.

In a cytokine storm, the preferred method of delivery is caesarean section. In a severe course of the disease, even timely delivery (regardless of the method) could not lead to the expected improvement in the condition, but only made it possible to use biological therapy, cytostatics, and powerful antimicrobial and antiviral agents that are not used during pregnancy. Note that after timely delivery, the symptoms of respiratory failure often worsened, lung damage progressed to CT 3–4 in a few hours, which was also due to an increase in the symptoms of edematous syndrome. Diuretic therapy allowed reducing the phenomena of respiratory failure, as well as the size and density of consolidation.

After delivery, despite the arrest of the laboratory picture of the cytokine storm by biological immune-mediated therapy, the volume of lung tissue damage continued to increase up to 80–95% with the formation of extensive areas of consolidation, including due to hemophagocytic lymphohistiocytosis, in which cytostatics are used to prevent early fibrosis. During this period, we actively used cytokine sorption.

Of the 109 hospitalized patients, 105 were pregnant, of which 46 (44%) were discharged pregnant with recovery, 51 had timely or premature births, seven had spontaneous abortions, and one was diagnosed with an ectopic pregnancy. Two patients who were admitted to the hospital in an extremely serious condition died: one puerperal death occurred on the 57th day after birth, and the second, after an artificial termination of pregnancy at a period of 20–21 weeks of gestation (death on the 22nd day after termination of pregnancy).

During the fourth wave of COVID-19, 69 pregnant women and puerperae were admitted to the hospital: 60 of them with an average severity of the disease and nine in a serious condition. The average age of the
patients was the same as in other periods of the epidemic, 32.4 ± 3.4 years, and the average gestational age at the time of hospitalization was 31.3 ± 8.1 weeks (from 6 to 39 weeks).

Nine patients (13%) were in serious and extremely serious condition; eight of them were breathing on their own; one was on a ventilator and ECMO. The duration of hospitalization in the intensive care unit was 31.5 ± 4.4 and 15.4 ± 5.9 days in the hospital.

Of the features of the course of the disease in the fourth wave, it is necessary to note the rapidly progressive (sometimes fulminant) course of the disease in pregnant women with an increase in respiratory failure and daily progression of the volume of lung damage according to multislice computer tomography (MSCT) of the chest organs. MSCT of the chest organs and ultrasound of the lungs (in the first and early second trimester) turned out to be the most informative for diagnosis. Glucocorticosteroids were used no earlier than the fifth day of the disease; tocilizumab, levilimab, sarilumab, and olokizumab (Artlegia) were actively used.

A new treatment method at the end of 2021 was the use of covid-globulin, a human immunoglobulin against COVID-19, consisting of human plasma proteins, of which at least 95% is IgG, which has the activity of antibodies to SARS-CoV-2, and monoclonal antibodies. The monoclonal antibodies bamlanivimab + etesevimab, casirivimab + imdevimab, and sotrovimab are used to treat COVID infection in adults and children weighing over 40 kg. The drug is administered in hospital to 6 pregnant women at 3–6 days of the disease in the presence of clinical manifestations and CT results of 0–1. Five patients did not develop pneumonia, and one had a regression of clinical symptoms. None of the patients required early delivery.

As in the third wave, at terms of more than 32 weeks of gestation at the height of the disease, with a rapid increase in respiratory failure, IL-6 > 100, and poorly controlled fever, a decision was made on immediate delivery. Of the 69 patients hospitalized in the fourth wave, 39 (59.4%) were discharged with recovery as pregnant women; 22 had timely or premature births; three had spontaneous abortions; and one was diagnosed with an ectopic pregnancy upon admission.

According to the US Centers for Disease Control and Prevention, the rate of preterm birth among pregnant women with COVID-19 was 11.6%, and the rate of caesarean section was 33.1% [10]. According to our data, the proportion of preterm births ranged from 13% in the first wave to 45% in the fourth. The frequency of caesarean section in the Lapino CH was the lowest in the second wave, 28.3%, and the maximum in the first wave, 73.3%.

If adequate oxygenation is not possible against the background of mechanical ventilation and a high risk of death, veno-venous (VV) extracorporeal membrane oxygenation (ECMO) can be used [11]. VV ECMO is aimed at maintaining oxygenation and unloading the pulmonary circulation, which increases the necessary time limits for the restoration of the lung tissue. The most popular VV ECMO approaches are right femoral vein drainage cannula and right jugular vein return cannula. Oxygenated blood flows directly to the right side of the heart, reducing pulmonary circulation resistance and right ventricular afterload.

Indications for VV ECMO are [12, 13] the following:
- $\frac{PaO_2}{FiO_2} < 80$ mm more than 6 h;
- $\frac{PaO_2}{FiO_2} < 30$ mm more than 30 h;
- pH < 7.25 with PaCO2 > 60 mm Hg more than 6 h.

Here is an example of the successful use of VV ECMO in a pregnant patient with severe ARDS caused by COVID-19 infection.

Patient S., 37 years old, with a diagnosis of pregnancy at 21–22 weeks, a new coronavirus infection of an extremely severe course, community-acquired bilateral polysegmental pneumonia, the volume of lung damage is more than 90%. She was admitted to the intensive care unit of the Lapino CH. Delivered by an ambulance from another medical institution on the 16th day of illness with a positive PCR result for SARS-CoV-2. She was hospitalized for 12 days. At the previous stages of treatment, antibacterial, anticoagulant, and symptomatic therapies were carried out. On admission, the patient’s condition was considered critical. During transportation to the hospital and in the first 12 h of hospitalization, noninvasive ventilation of the lungs was carried out through a face mask in the CPAP + PS mode with PEEP parameters of 9 mbar, $P_{support}$ 10 mbar, and oxygen fraction in the inhaled mixture ($FiO_2$) 90%. Hemoglobin saturation ($SpO_2$) of 95% was achieved, the patient’s hemodynamics remained stable, and other organ systems were without dysfunctions. Upon admission, according to ultrasound and Doppler, the development of the fetus corresponded to the gestational age.

Due to the rapid increase in respiratory failure (tachypnea up to 40 breaths per minute, decrease in saturation to 80%), the patient was transferred to invasive ventilation with the following initial ventilation parameters: $P_{purt}$ 28 mbar, frequency 18 min$^{-1}$, PEEP 11 mbar, $FiO_2$ 100%, and $SpO_2$ 96%. Prolonged sedation with propofol and dexmedetomidine and muscle relaxation were started. According to CT scan of the chest, the volume of the lesion was more than 90%. Antibacterial therapy with broad-spectrum drugs, anticoagulant and anti-inflammatory therapy, and symptomatic treatment were continued. On the second day, the patient developed hemodynamic instabil-
ity, which required the administration of norepinephrine at a dosage of 0.05 µg/kg/min.

During the first 3 days of hospitalization, progression of hypoxemia occurred with the following ventilator parameters: Pupr. 29 mbar, tidal volume 280 mL, rate 18 breaths per minute, PEEP 11 mbar, and FiO2 100%. Attention was drawn to a significant decrease in the dynamic compliance of the lungs and tidal volume. Pronation of the patient did not improve oxygenation. Despite ongoing respiratory support and muscle relaxation, progression of critical hypoxemia continued. On an emergency basis, a multidisciplinary council was assembled together with specialists from the ECMO center of City Clinical Hospital no. 52. A decision was made to start the veno-venous ECMO procedure. A 26 Fr cannula was inserted into the right femoral vein, and a 19 Fr cannula, into the right internal jugular vein. Starting parameters: blood flow 4.5 L/min, speed 7300 rpm, fresh gas flow 7 L/min, and oxygen fraction 100%. An SpO2 of 90% was reached. Ventilation in the BiPAP mode continued with protective parameters: Pupr. 20 cm H2O, tidal volume 180 mL, rate 16 min−1, PEEP 10 mbar, and FiO2 70% (Fig. 2).

Given the extremely serious condition of the patient, after the start of ECMO, a decision was made to terminate the pregnancy by surgery. In terms of the ward of the intensive care unit, a lower median laparotomy was performed, a small caesarean section at a period of 20–21 weeks of gestation. A live premature fetus weighing 420 g, 24 cm long, with an Apgar score of 1–3 points was removed by the leg. The child died on the 12th day of life in the neonatal intensive care unit. After surgery, the patient underwent percutaneous dilatational tracheostomy. ECMO continued with the following parameters: flow 4.3 L/min and speed 6500 rpm.

The postoperative period proceeded smoothly. According to the control ultrasound of the pelvic organs, free fluid was not detected, and the uterine cavity was slit-like. Six hours after the operation, heparin infusion was resumed to the target APTT values of 60–70 s. The next morning, sedation was turned off, and clear consciousness was restored. On the 11th day of ECMO, the patient developed hypofibrinogenemia and thrombocytopenia, against which hemorrhagic and anemic syndromes developed, which required numerous transfusions of blood components (Table 1). Starting from the 14th day of treatment, further ECMO was carried out without the introduction of heparin.

On the 17th day of inpatient treatment, despite the ongoing therapy, progression of the hemorrhagic syndrome was noted, manifested in the development of nosebleeds, bleeding from the tracheostomy hole, postoperative suture. According to the ultrasound of the abdominal organs, no free fluid was detected. A revision of the surgical wound within the subcutaneous fat was made, and hemostatic sutures were applied. On the 15th day, a spontaneous right-sided pneumothorax developed, and the pleural cavity was drained. The lung expanded, and the drainage was removed on the 26th day. In connection with an increase in the general edematous syndrome, in order to control the volemic status, renal replacement therapy was carried out for seven days in the mode of hemodiafiltration. Throughout the entire period of mechanical ventilation, the patient regularly underwent sanitation fibrobronchoscopy; there was a pic-

| Component                                | Transfused in total, L |
|------------------------------------------|------------------------|
| Fresh frozen plasma                      | 11.84                  |
| Platelet mass                            | 4                      |
| Frozen cryoprecipitate                   | 1.35                   |
| Erythrocyte suspension depleted of leukocytes | 9.3                   |
| Total                                    | 26.49                  |
ture of hemorrhagic tracheobronchitis. Improvement of the endoscopic picture occurred on the 46th day.

During hospitalization in the ICU, the patient underwent microbiological monitoring with an assessment of the antibacterial resistance of the detected microorganisms. Correction of antibiotic therapy was carried out according to the results of the studies. In the first 10 days, respiratory support was provided in the BiPAP mode. By the 22nd day, the maximum deterioration in the elastic properties of the lung tissue was noted: the tidal volume decreased to 20–40 mL and compliance to 10 mL/cm H₂O. When the patient was transferred to the auxiliary mode of ventilation, an increase in tidal volume and dynamic compliance of the lungs was noted. From the 20th day, against the background of therapy, there was an improvement in the elastic properties of the lung tissue and restoration of the oxygenating function of the lungs, which made it possible to reduce the volume of ECMO support. On the 42nd day of hospital treatment (day 58 of illness), ECMO therapy was discontinued and mechanical ventilation was continued in the CPAP mode. After five days, the patient was successfully weaned off the ventilator. On the 51st day, the patient was transferred to the therapy department for further treatment and observation. After a complex of rehabilitation measures, she was discharged home in a satisfactory condition without oxygen support.

The first CT examination after the start of ECMO therapy was performed on the 29th day of inpatient treatment (Fig. 3). Attention was drawn to the appearance of numerous interpleural accumulations of air. In subsequent studies, there was an improvement in the CT picture of the lungs without a significant decrease in the volume of air cavities (Fig. 4). After discharge from the hospital, complex rehabilitation treatment and further activation of the patient were continued. When performing a control CT scan of the chest after 30 days, there was a persistent positive trend, and laboratory tests were within the normative values.

Note that all babies (151) born to mothers with COVID-19 were not found to have the SARS-CoV-2 virus at Lapino Clinical Hospital. Our observations coincide with the published results of foreign researchers. Thus, in the United States, according to the outcomes of more than 20 000 births, 95% of newborns from mothers infected with SARS-CoV-2 were born in a satisfactory condition. Some newborns of infected mothers have developed mild symptoms that

Fig. 3. CT scan of the chest on the 29th day of inpatient treatment. Against the background of subtotal viral damage to the lungs, the appearance of air cavities in the right lung is noted. The approximate volume of lung damage is more than 90%.

Fig. 4. CT scan of the chest on the 59th day of inpatient treatment. Moderate positive dynamics in the form of resolution of reticular changes in the right lung, improved pneumatization of the apex of the right lung. The total volume of changes is >75%. Pneumatocele of the right lung.
do not require respiratory support, and most of these cases were associated with respiratory transmission during the postpartum period [10].

For timely treatment and prevention of complications in the case of SARS-CoV-2 infection, prompt diagnosis of Covid-19 and immediate initiation of therapy are important: it is necessary to use IL-6 receptor blockers aimed at reducing the cytokine storm, and the use of monoclonal antibodies is effective. In order to improve the excursion of the lungs, for the use of therapy that is not used during pregnancy, early delivery is necessary, as is the use of cytotoxic drugs in the postpartum period.

According to the methodological recommendations of the Ministry of Health of the Russian Federation “Organization of Medical Care for Pregnant Women, Women in Childbirth, Puerperae, and Newborns with a New Coronavirus Infection COVID-19,” specific prevention is indicated for pregnant women at risk of severe COVID-19 from 22 weeks of gestation, which will help reduce the incidence of maternal morbidity and mortality in a pandemic.

CONFLICT OF INTEREST
The author declares that he has no conflicts of interest.

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