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COVID-19 Infection and Pregnancy: Perinatal Outcomes

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Abstract. *An analysis of studies conducted in 2024–2025 shows that a previous coronavirus infection has a significant impact on the gestational process, increasing the risk of specific obstetric and perinatal complications.*

Keywords: *COVID-19, pregnancy outcomes, coronavirus infection, placenta.*

Over the two years of the SARS-CoV-2 pandemic, a certain amount of experience has already been accumulated and data on gestational complications associated with COVID-19 infection have been systematized [4,7,8]. The pathogenesis of gestational complications in COVID-19 infection is обусловлен both by the direct effect of the virus on cells expressing angiotensin-converting enzyme 2 (ACE2) receptors and indirectly against the background of physiological changes occurring in the maternal organism during pregnancy.

It is known that the SARS-CoV-2 virus infects tissues via the ACE2 receptor, and cleavage of its structural protein by the serine protease TMPRSS2 is required for viral entry into cells. Membrane expression of ACE2, in addition to alveolocytes, is present in numerous non-respiratory organs, including the heart, liver, and kidneys. The presence of ACE2 on the cell membrane is crucial for viral virulence, as cells lacking ACE2 are resistant to SARS-CoV-2 infection [4,9,18,27,33,41]. The placenta is a target organ for SARS-CoV-2, since ACE2 receptors are detected in the syncytiotrophoblast, cytotrophoblast, and the endothelium of placental villi [5].

A significant role in the pathogenesis of clinical manifestations and complications of coronavirus infection in pregnant women is played by physiological gestational changes occurring in the body. First of all, this involves deviations in cellular immunity. Increased levels of cortisol, estrogens, and progesterone, as well as the appearance of chorionic gonadotropin during pregnancy, contribute to the development of physiological immunosuppression through suppression of T-cell–mediated

immunity and a shift toward the predominance of Th2-mediated immunoregulatory mechanisms [6,7].

Recently-published data have also suggested that symptomatic women may represent only the tip of the iceberg of SARS-CoV-2 infection in pregnancy [4, 5], making it possible that registries contain data from only a small proportion of true SARS-CoV-2 positive cases, especially in countries where mass testing has not yet been adopted. It is therefore imperative that asymptomatic pregnant women are also screened for the virus in order to capture the full breadth of effects of SARS-CoV-2 infection in both pregnancy and infancy [1,12,20,25,34,39].

It has been proven that pregnancy is accompanied by changes in the hemostatic system. The level of the anticoagulant protein S decreases by 55%, fibrinogen levels increase, and fibrinolytic activity of the blood progressively decreases due to increased concentrations of plasminogen activator inhibitor type 1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI) [7,8].

Changes in the hemostatic system induced by SARS-CoV-2 infection are classified as CAC—COVID-associated coagulopathy—which is clinically manifested by thrombotic events.

The SARS-CoV-2 virus enters host cells through interaction with angiotensin-converting enzyme 2 (ACE2) receptors, resulting in involvement of a wide range of tissues and organs. ACE2 receptors have been identified in placental tissues, which is supported by an increasing number of publications reporting the detection of viral particles in placental cotyledons. To date, infectious involvement and visualization of SARS-CoV-2 localization in placental tissue have been described in a limited number of cases and occur with a relatively low frequency, estimated at approximately 21%.

According to current evidence, pregnant women infected with SARS-CoV-2 are at increased risk of miscarriage, preeclampsia, preterm birth, and perinatal mortality. Therefore, ongoing efforts are focused on the study of placentas from patients who have recovered from COVID-19 in order to better predict the effects of SARS-CoV-2 infection on pregnant women and newborns.

The aim of the present study was to analyze the clinical course and pregnancy outcomes in patients who experienced coronavirus infection during early gestation, accompanied by placental and gestational changes that led to adverse perinatal outcomes.

Investigation and analysis of the effects of coronavirus infection on pregnant women are of significant importance; consequently, an increasing number of scientific studies aim to elucidate the mechanisms of etiopathogenesis and the potential for vertical transmission of infection from mother to fetus [6,11,17,28,32,40]. The impact of SARS-CoV-2 on the course and outcomes of pregnancy remains controversial. Available data suggest that pregnancy outcomes and clinical manifestations of COVID-19 in pregnant women are comparable to those observed in non-pregnant women of reproductive age [7].

A systematic review including 107 cases of COVID-19 in pregnant women demonstrated that only 3% required admission to intensive care units, with no reported cases of maternal mortality [2,13,21,24,35,38]. In contrast, Di Mascio et al. reported a significantly increased risk of miscarriage, preeclampsia, preterm birth, and perinatal mortality in patients infected with coronaviruses, including SARS-CoV-1 and MERS [2,7]. However, it should be noted that the number of SARS-CoV-2 infection cases included in that analysis was limited.

The SARS-CoV-2 virus invades and affects cells of a wide range of tissues and organs, leading to various clinical manifestations. The infection may be asymptomatic or may follow a severe course with the development of respiratory failure, multiple organ dysfunction, and can result in death [5,10,16,23,30,42]. Most commonly, the disease presents as acute respiratory distress syndrome (ARDS), reflecting the predominant tropism of the virus for the respiratory tract; however, the infectious process is not limited to the lungs.

This is supported by a growing number of publications reporting placental tissue involvement and the detection of viral particles in placental cotyledons, as well as isolated cases of vertical transmission of SARS-CoV-2 from mother to fetus [11].

Histological manifestations of COVID-19 in the placenta remain a subject of considerable interest and ongoing research.

The immune system undergoes a change during pregnancy, outside the implantation site where suppression occurs. The response to microorganisms varies depending on the type of pathogen and stage of pregnancy. The trophoblastic and mother's immune system reach a state of agreement where the immune response during pregnancy is a combination of the mother's systemic response and the local fetal-placental response. Therefore, the signals from the placenta are the ones that alter mother's immune system, and the immune system during pregnancy is focused on integrating the actions of placenta, foetus and pregnant woman [3,14,19,26,31,37]. Caring for the immune system is one of the elements of pre-conception, prenatal and perinatal education. Therefore, important are protective vaccinations before getting pregnant as well as proper diet and supplementation during pregnancy. Vitamin D3 facilitates the immune adaptation necessary to maintain pregnancy. It regulates the concentration of calcium and phosphate in the plasma, affects the state of mineralization of mother and foetal bones and alters the work of the system, among others immune system [9]. Vitamin D3 deficiency may affect up to 50% of pregnant women in the first trimester. The new guidelines assume that women planning pregnancy and during pregnancy should take vitamin D3 supplements, preferably in doses calculated based on blood tests. If it is not possible to determine D3 in the blood — the use 2000 IU/d is recommended [10]. During lactation, D3 supplementation does not differ from that taken during pregnancy - the dose is selected based on the vitamin D3 levels in the blood or 2000 IU/d [7,8,15,22,29,36].

Clinical manifestations and the course of COVID-19 disease.

A prospective study revealed the relationship between the severity of COVID-19 and the occurrence of preeclampsia-like syndrome in the affected pregnant women [2]. In their study, 34 non-severe and eight cases of severe COVID-19 were enrolled, and five out of eight (62.5%) severe COVID-19 developed preeclampsia-like syndrome [3]. This finding crystalizes the induction of preeclampsia-like syndrome by COVID-19 and suggesting that the presence of COVID-19 during pregnancy might

face a greater risk for maternal-related complications. A study assessing the role of comorbidities on mortality of pregnant women with COVID-19 found that patients who died were older and more likely to have co-morbidities [3]. COVID-19 associated multisystem inflammatory syndrome has been described in a pregnant woman as a rare but severe complication causing critical illness and cardiogenic shock requiring mechanical ventilation, wherein intravenous immunoglobin and high-dose corticosteroids were necessary for the recovery.

Once COVID-19 symptoms start, pregnant women are more likely to have severe illness than other people, particularly if they have certain conditions (such as diabetes or heart disease).

The risk of problems during pregnancy (such as preterm labor, birth of a premature newborn, and preeclampsia) is increased if symptoms are moderate or severe.

Some patients require admission to the Intensive Care Unit, of which, according to the authors, the risk of death was estimated at 7% [6]. Zaigham et al. performed systematic review based on 18 articles, covering 108 cases of pregnant women infected with SARS-CoV-2. Among the symptoms analysed, high fever (68%) and cough (34%) were the most common ones, while fatigue (13%) and shortness of breath (12%) were less common. Three percent of patients required admission to the Intensive Care Unit. There were no deaths in pregnant women, however one case of neonatal and one case of intrauterine death were recorded [1].

Based on the analysis of the available studies and literature, it can be concluded that no significant differences in clinical symptoms have been described in the pregnant women group infected with SARS-CoV-2 in relation to the general population [7]. Although, in most of the cases mentioned above the course of the disease was mild or even asymptomatic, some of them required intensive care and mechanical ventilation.

A systematic review of 57 studies involving 1,009 pregnant women with SARS-CoV-2 infection demonstrated that placental involvement is characterized by the development of fetal–maternal vascular malperfusion syndrome. Its pathomorphological features include perivillous fibrin deposition and inflammatory

lesions such as villitis, intervillitis, and chorioamnionitis, as well as villous edema and retroplacental hematomas.

The most characteristic consequences of prior COVID-19 include placental insufficiency, which occurs in 30–50% of patients regardless of the gestational age at the time of infection. The virus may damage placental vessels, thereby limiting oxygen transport to the fetus. The risk of developing preeclampsia, particularly severe forms, is significantly higher in women who have recovered from COVID-19, reaching up to 16% of cases, with the risk increasing when infection occurs during the second trimester.

Vertical transmission**.** There have been many studies regarding the possibilities of vertical transmission in COVID-19, with few revealing no vertical transmission to the possibility of vertical transmission from COVID-19 infected pregnant women to fetus [10]. Early data from nine pregnant women in China who were in the third trimester of pregnancy and without any underlying chronic disease conditions found no evidence of intrauterine transmission using samples collected from the amniotic fluid, blood from the umbilical cord, and throat swabs from the neonate [6]. A study involving 38 pregnant women also did not find any evidence of vertical transmission of the SARS-CoV-2 from mothers to their fetuses, supporting the observations made by previous studies during the MERS-CoV and SARS-CoV epidemics [70]. In one more study, out of 19 pregnant COVID-19 positive women, none of the neonates were tested positive for COVID-19 [1]. Other studies also have been conducted in China, Iran [4], and the US [5] and suggested no significant scientific evidence of vertical transmission of SARS-CoV-2. A study also reported the possibility of maternal to the fetal transmission of SARS-CoV-2 [9]. In the third trimester of pregnancy, COVID-19 infection resulted in serious renal developmental injury, which is indicated by high cystatin C and β2-microglobulin levels in all neonates.

Fetal growth restriction (FGR) and oligohydramnios are diagnosed in approximately 20% of c**ases** following infection. The risk of developing gestational diabetes mellitus (GDM) is also increased, particularly after moderate and severe forms

of COVID-19. Symptoms of threatened miscarriage are reported in 46.7–53.6% of women following SARS-CoV-2 infection.

Pregnancy and Delivery Outcomes. Preterm birth: the incidence reaches 15–22%, which is several times higher than average population rates. Severe forms of infection are associated with a higher risk of preterm delivery. In women who experienced symptomatic COVID-19, cesarean section is performed significantly more frequently. Cases of antenatal fetal death are reported in 3–5% of observations.

Neonatal Outcomes

Neonatal condition: due to preterm birth and fetal growth restriction (FGR), newborns are often born with low birth weight and reduced adaptive capacity.

Respiratory complications: up to 16% of newborns require admission to neonatal intensive care units (NICUs). A history of maternal COVID-19 allows prediction of the risk of neonatal pneumonia with high accuracy (up to 98%).

Vertical transmission: as of 2025, there is insufficient convincing evidence of transplacental transmission of SARS-CoV-2 from mother to fetus; however, transplacental transfer of protective antibodies has been confirmed.

Anthropometric parameters: newborns of infected mothers have significantly lower birth weight.

Apgar score: the risk of a low Apgar score (less than 7 points at 5 minutes) increases by 1.44 times.

Fetal distress: the risk increases by 1.76 times.

Neonatal respiratory distress syndrome: occurs almost twice as often.

Prevention of COVID-19 during pregnancy

The best way to prevent COVID-19 is to avoid being exposed to the virus, which can be difficult because some infected people do not know they have the virus. The Centers for Disease Control and Prevention (CDC) has issued recommendations for preventing the spread of COVID-19. These recommendations apply to all people (see also Prevention of COVID-19). If a pregnant woman may be infected, separating her from her baby after delivery may be necessary to avoid passing the infection to the baby.

Conclusion. The severity of pregnancy and neonatal outcomes directly depends on the gestational age at the time of infection—particularly during the first and second trimesters, which are critical for placental formation—and on the severity of the infection itself. Patients who have recovered from COVID-19 require enhanced monitoring of placental blood flow and fetal growth dynamics.

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