

Influence of COVID-19 infection on placental function

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ABSTRACT

Objectives: Pregnant women are more susceptible to infectious diseases because of their natural immunosuppression. SARS-CoV-2 seems to be a potential risk for the condition of women and the fetus. Unfortunately, knowledge of the influence of coronavirus disease 19 (COVID-19) on pregnant women and their children is still very limited, and further investigation and analysis are needed.

The aim of the study was to conduct a meta-analysis of research about the impact of COVID-19 on the placenta.

Material and methods: Articles published between 2020 and 2021 and contained in the PubMed and Elsevier databases were analyzed.

Results: The SARS-CoV-2 infection also led to pregnancy complications in the patients. The most common pregnancy complications include caesarean delivery (80%), preterm delivery (26%), fetal distress (8%), premature rupture of the membranes (9%) and stillbirth (2%). Among the observed patients, neonatal complications occurred, such as premature delivery (25%), respiratory distress syndrome (8%), pneumonia (8%) and deaths of 4 newborns SARS-CoV-2 was found mainly in syncytiotrophoblast cells at the maternal-fetal border of the placenta. Histological examination of the placenta revealed dense macrophage infiltration. Abnormal perfusion of fetal blood vessels or fetal vascular thrombosis was observed. Elevated levels of SARS-CoV-2 IgG or IgM antibodies in the umbilical cord blood were observed in nine newborns, reported as evidence of vertical infection.

Conclusions: The features of placental damage in women with COVID-19 are clearly different from the control group. Further research is needed to better understand how SARS-CoV-2 infection affects the placenta.

Key words: SARS-CoV-2 infection; placenta; COVID-19 in pregnancy; umbilical cord

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INTRODUCTION

The pandemic outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) surprised and affected millions of people around the world. The infection broke out very quickly and the disease spread to countries all over the world within a few months. The first confirmed case of COVID-19 occurred on December 8, 2019, in Wuhan, China [1]. Nowadays, nearly 219 million people worldwide have contracted COVID-19, and more than 3 million people have died from the infection.

SARS-CoV-2 is an enveloped, single-stranded RNA virus. SARS-CoV-2 uses the SARS-CoV ACE2 receptor for input and the TMPRSS2 serine protease to stimulate the S protein. The mechanism of SARS-CoV-2 infection is that the virus enters cells by cleavage of the S protein spike at

the S1/S2 and S1' sites by the TMPRSS2 serine protease. These activities enable the fusion of viral and cell membranes [2].

Pregnant women are more susceptible to infectious diseases because of their natural immunosuppression [3]. SARS-CoV-2 is a potential risk for the condition of women and the fetus. Unfortunately, knowledge of the influence of the coronavirus on pregnant women and their children is still very limited, and further investigation and analysis are needed [4].

The SARS-CoV-2 epidemic has been compared to the SARS-CoV-1 epidemic in 2002–2003. It is possible to observe better health of the mother and the newborn with SARS-CoV-2 [5, 6]. SARS-CoV-2 infection in pregnant women can be asymptomatic, which increases the risk of virus transmission to family members, medical personnel or the newborn.

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The aim of the study was to conduct a metaanalysis of research about the impact of SARS-CoV-2 infection on the placenta.

MATERIAL AND METHODS

Articles published between 2020 and 2021 and contained in the PubMed and Elsevier databases were analyzed. All publications described pandemic situation of COVID-19 and consequences of morbidity.

RESULTS

Description of the state of knowledge

The placenta is a temporary organ developed from trophoblasts up to 18 weeks of pregnancy which allow for transmission of substances in the maternal fetal circulation. It contains the anchoring villi and umbilical cord with two umbilical arteries and one umbilical vein [7, 8]. The core of the chorionic villi contains several types of cells, including immune cells such as Hofbauer cells (fetal macrophages). The villi enable nutrition to the fetus as well as excretion of waste products from the fetus to mother. Additionally, the placenta releases hormones such as progesterone, estrogen, and human placental lactogen. Another task of this organ is to function as an immunological barrier [9, 10]. There is no difference in appearance of placenta in healthy and COVID-19 infected patients (Fig. 1).

Case reports indicate that vertical transmission between mother and child is rarely observed. Ghema et al. [11] published a study of pregnant women infected with the coronavirus, where two out of 30 newborns had a positive qRT-PCR test for SARS-CoV-2, which confirmed vertical transmission.

Jaiswal et al. [12] conducted a prospective study with comparison of 27 pregnant women with asymptomatic or mild SARS-CoV-2 infection and 27 women without infection. The study showed that pregnant women with a positive SARS-CoV-2 result show significantly more symptoms of placental disorders than healthy women according to histological analysis after birth. In the placenta of pregnancies with COVID-19, there were features of vascular malperfusion, e.g., retroplacental hematomas, accelerated villous maturation, distal villous hyperplasia, mural hypertrophy of membrane arterioles, fibrinoid necrosis, chorangiomas and intramural fibrin deposition. Also, thrombosis of the fetal chorionic plate was detected in some cases. All these changes were present either on the maternal or fetal part of the placenta [12].

Gajbhiye et al. [13] observed 441 pregnant women with COVID-19. Pneumonia was diagnosed in 96% of the examined women. Two percent of pregnant women had placenta disorders. Based on the results, it was estimated that the vertical transmission rate of SARS-CoV-2 is 8%. Some women enrolled in the study suffered from comor-

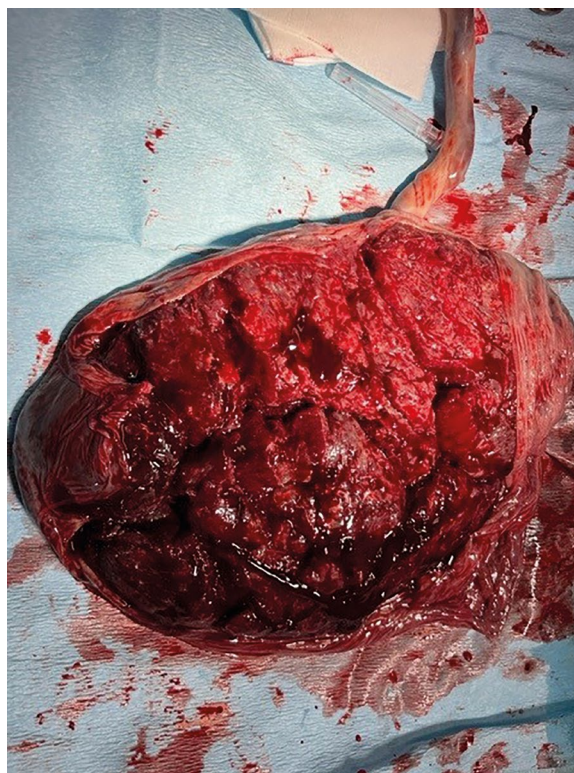


Figure 1. Placenta of COVID-19 infected patient

bidities such as hypertension (10%), diabetes (9%), placental disorders (2%), co-infections (3%), uterine scarring (3%) and hypothyroidism (3%). The SARS-CoV-2 infection also led to pregnancy complications in the patients. The most common pregnancy complications include caesarean delivery (80%), preterm delivery (26%), fetal distress (8%), premature rupture of the membranes (9%) and stillbirth (2%) (Fig. 2). Among the observed patients, neonatal complications occurred, such as premature delivery (25%), respiratory distress syndrome (8%), pneumonia (8%) and deaths of four newborns [13].

In 2020 Hosier et al. [14] described a second-trimester pregnancy with symptomatic COVID-19 complicated by severe pre-eclampsia and placental abruption. The research showed the presence of SARS-CoV-2 virus in histological examination of the placenta using electron microscopy as well as molecular and immunohistochemical tests. SARS-CoV-2 was found mainly in syncytiotrophoblast cells at the maternal-fetal border of the placenta. Histological examination of the placenta revealed a dense macrophage infiltration, but no evidence of vasculopathy typical of pre-eclampsia was found. This case shows the invasion of SARS-CoV-2 on the placenta, indicating the possibility of severe morbidity and serious complications among pregnant women with COVID-19. The histological results of placental infection by the SARS-CoV-2 virus examined

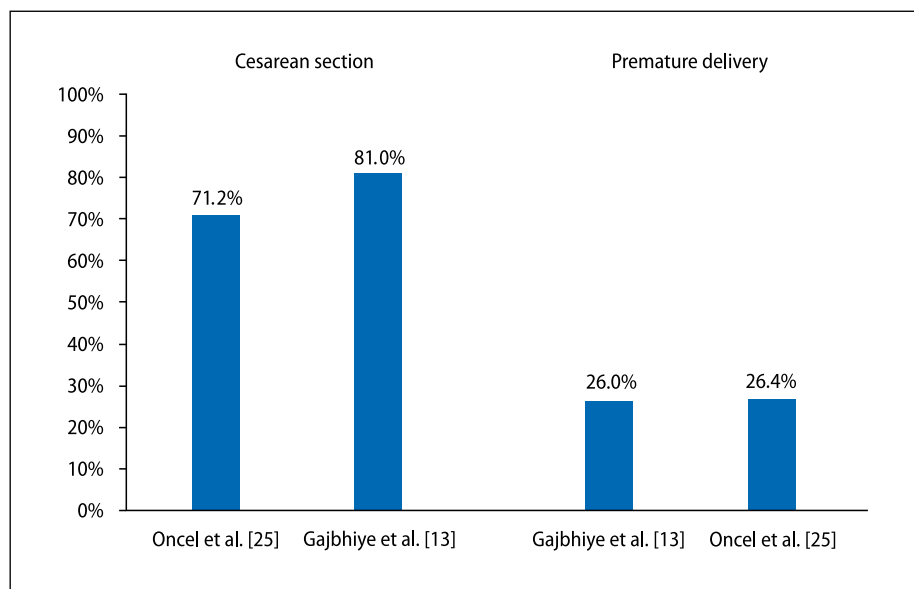


Figure 2. Comparison of the most common complications in pregnant women with SARS-CoV-2

by electron microscopy were published in 2020. For better assessment molecular and immunohistochemical tests were used. SARS-CoV-2 was found mainly in syncytiotrophoblast cells at the maternal-fetal border of the placenta. Histological examination of the placenta revealed a dense macrophage infiltration, but no evidence of vasculopathy typical of pre-eclampsia was found [14].

Shanes et al. [15] examined 16 placentas obtained from women infected with SARS-CoV-2 and compared them with the control group. It was found that the placenta of virus-infected women in the third trimester of pregnancy was significantly more likely to present maternal vascular malperfusion. In particular, abnormal or damaged maternal vessels and intercellular clots were observed in the third trimester of pregnancy. The presence of acute or chronic inflammation was not noted. The analysis was based on 15 placentas after delivery in the third trimester of pregnancy and after caesarean section of one patient in the second trimester because of intrauterine fetal death. In the latter case, villous swelling and a hematoma outside the placenta were observed [15].

Baergen et al. [16] examined 20 placentas from mothers infected with SARS-CoV-2. In 50% of analyzed cases abnormal perfusion of fetal blood vessels or fetal vascular thrombosis was observed.

Hecht et al. [17] examined 19 placentas from women with COVID-19 using immunohistochemical tests with the expression of ACE2 and TMPRSS. No changes in placentas were found in the histopathological examination. However, two cases of infection were detected in the villous trophoblast. No expression of ACE2 was found. On the other hand, activity of TMPRSS2 was weak. The study showed

no correlation of SARS-CoV-2 infection and congenital COVID-19 infection [17].

Schwartz et al. [18] analyzed the influence of SARS-CoV-2 on 38 pregnant women with COVID-19 and their newborns in China to assess the effects of it on mothers and infants. Data were compared with two previous epidemics of coronavirus infections: severe acute respiratory syndrome (SARS) caused by SARS-CoV-1 and Middle East respiratory syndrome (MERS) caused by MERS-CoV. The results of the metaanalysis showed no death from SARS-CoV2 and MERS-CoV. Moreover, there were no confirmed cases of intrauterine vertical transmission of SARS-CoV-2 from mothers with COVID-19 to their infants. All newborns and all the placentas were RT-PCR negative for SARS-CoV-2 [18].

The impact of SARS-CoV-2 infection on the embryo or fetus is difficult to predict. Probably risk factors vary depending on the type of viral infection, the age of pregnancy during the infection and the general condition of the mother. The SARS-CoV-2 virus can affect children of every age. In 2020, Lu et al. [19] published a study investigating 31 children under the age of one year. The youngest child had confirmed SARS-CoV-2 infection in the first 24 hours after birth. Predominant symptoms of the upper respiratory tract in children were infection, pneumonia, fever, cough and throat erythema.

SARS-CoV-2 infection also causes neurological symptoms in children. Dugue et al. [20] reported a case of a 6-week-old patient with COVID-19 infection who developed fever, cough and twice short 10–15-second episodes of looking up and bilateral stiffening of the legs.

Kyle et al. [21] analyzed 836 newborns among whom only 35 (4.2%) were positive for SARS-CoV-2. Infants from

mothers in critical stages of COVID-19 infection were observed; however, a much greater percentage of newborns infected with SARS-CoV-2 were mildly infected. Elevated levels of SARS-CoV-2 IgG or IgM antibodies in the umbilical cord blood were observed in nine newborns, reported as evidence of vertical infection.

On the other hand, specificity and sensitivity of serological tests in diagnosing SARS-CoV-2 are undefined according to passive crossing of the maternal placental barrier, which can potentially provide protection against the disease. Moreover, these newborns had a PCR test result and showed no symptoms suggesting infection [22, 23].

On the other hand, infected mothers were not isolated with their newborns [21]. The separation of the mother and the newborn immediately after delivery is associated with long-term deficits in the mother's behavior and an interrupted mother-child relationship. Nevertheless, it has not been proven that direct breastfeeding after washing hands increases the risk of SARS-CoV-2 infection in newborns. For this reason, a COVID-19 infected mother and her baby should be treated in the same way as healthy women after childbirth [24].

Oncel et al. [25] conducted a multicenter cohort study of 125 newborns of mothers with COVID-19 in 34 neonatal intensive care units (NICUs) in Turkey. The study included 125 women who tested positive for RT-PCR and their newborns. The most common complications of SARS-CoV-2 infection included cesarean section (71.2%), prematurity (26.4%) and low birth weight (12.8%). Eight mothers (6.4%) were admitted to the intensive care unit, among whom six died (4.8%). 3.3% of newborns tested positive for coronavirus by RT-PCR. Comparison of complications in COVID-19 infected patients is located in Table 1.

Due to increasing morbidity of COVID-19 infection it seems to be important to identify predictive factors and placental features in ultrasound. To date, no studies have been conducted in this area.

CONCLUSIONS

Both asymptomatic and symptomatic SARS-CoV-2 infection in pregnant women can cause disorders of the placenta, as confirmed in histological presentation. The features of placental damage in women with COVID-19 are clearly different from the control group.

Nowadays, there are no adverse effects of placental injury in the course of SARS-CoV-2 infection for the child. However, long-term health effects in children whose mothers suffered from COVID-19 during pregnancy cannot be excluded. For this reason, pregnant women infected with SARS-CoV-2 should be taken care of by an interdisciplinary team consisting of a gynecologist, midwife, neonatologist and psychologist. Newborns should also be monitored for

Table 1. Complications of patients COVID-19 infected

Author of the publication	Reported complications in pregnant women with COVID-19
Ghema et al. [11]	Vertical transmission of coronavirus to a child
Jaiswal et al. [12]	Features of vascular malperfusion were present in the placenta, e.g., post-placental hematomas, accelerated villous maturation, distal villus hypertrophy, parietal membrane arteriolar hypertrophy, fibrinous necrosis, choroidal vessels, and intramural fibrin deposition. The thrombosis of the fetal chorionic plate
Gajbhiye et al. [13]	Pneumonia in women. Vertical transmission of coronavirus to a child. The caesarean delivery, preterm delivery, fetal distress, premature rupture of the membranes and stillbirth. In newborns: respiratory distress syndrome, pneumonia and deaths
Hosier et al. [14]	The severe pre-eclampsia and placental abruption
Shanes et al. [15]	The placenta of virus-infected women in the third trimester of pregnancy was significantly more likely to present maternal vascular malperfusion. In particular, abnormal or damaged maternal vessels and intercellular clots were observed in the third trimester of pregnancy The intrauterine fetal death, villous swelling and a hematoma outside the placenta
Baergen et al. [16]	The abnormal perfusion of fetal blood vessels or fetal vascular thrombosis
Hecht et al. [17]	The infection in the villous trophoblast
Schwartz et al. [18]	No confirmed vertical transmission from mother to child
Lu et al. [19]	Infection, pneumonia, fever, cough and erythema in children under 1 year of age
Dugue et al. [20]	The fever, cough and twice short 10–15-second episodes of looking up and bilateral stiffening of the legs in child
Kyle et al. [21]	Vertical transmission of coronavirus to a child
Oncel et al. [25]	The cesarean section, prematurity and low birth weight. Death of a pregnant woman. Vertical transmission of coronavirus to a child

long-term effects of COVID-19 on their health and psychomotor development.

Conflict of interest

All authors declare no conflict of interest.

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