REVIEW

Being pregnant in the COVID-19 pandemic: Effects on the placenta in all aspects

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Abstract

The coronavirus disease 2019 (COVID-19), which had spread to the world from Wuhan (China) in late December, was announced as a pandemic by the World Health Organization in March 2020. In addition to acute respiratory syndrome symptoms, this virus also affects nonrespiratory organs, according to existing data. ACE2 and TMPRSS2, which play a critical role in the entrance of SARS-COV-2 into the cell, are coexpressed in placental development stages, so the placenta also carries a risk for this virus. Many studies have shown that this virus causes some histopathological changes in the placenta. The vertical transmission of the virus is not yet clear, but available data have shown that the indirect effects of the virus can be seen on the fetus. This article focuses on revealing the effects of the virus on the placenta in all aspects.

KEYWORDS

coronavirus, genital tract, pandemics, vertical transmission

1 | INTRODUCTION

A new form of coronavirus exploded in Wuhan (China) at the end of December 2019 and spread rapidly worldwide, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), additionally the disease is called coronavirus disease 2019 (COVID-19). Due to its rapid spread, it was soon declared a global pandemic by the World Health Organization (WHO) in March 2020.[1]

Existing data showed that SARS-CoV-2 uses angiotensin-converting enzyme II (ACE2) as a receptor for the entrance into the cells via its surface spike (S) proteins.[2] Additionally, the leading molecule for the successful infection process is host proteases like transmembrane serine protease 2 (TMPRSS2). TMPRSS2 shows efficiency in the fusion in the membranes of the virus and host cell because the virus becomes skillful enough to bind ACE2 through the region released after the S protein of the virus is disrupted by TMPRSS2.[3,4]

The critical point is that ACE2 and TMPRSS2 have been expressed by many other organs except the lungs, so this virus not only affects the respiratory system but also promote histopathological changes and effective in numerous nonrespiratory organs, such as the heart, liver, kidney, brain, or male reproductive system.[5-7] Additionally, some data available have also revealed fetal infection, fetal growth restriction, fetal loss, and congenital malformation that indicated the effects of the virus on the placenta.[8]

According to the data available, this paper focuses on being pregnant in the COVID-19 pandemic and aims to be a review that collects all data by now under one paper, revealing the effects of the virus on the placenta in all aspects.

2 | THE EXPRESSION AND LOCALIZATION OF THE HUMAN PLACENTAL ACE2 AND TMPRSS2

The placenta is a highly specialized organ, which provides communication between the mother and fetus during pregnancy. It defends the balance between biochemical and immunological elements that are necessary for fetal development, and it is also a regulator for the protection of the fetus from various infections.[8,9] The functional units of the placenta are chorionic villi (CV) and include syncytiotrophoblasts (STBs), extravillous trophoblasts (EVTs), and cytotrophoblasts (CTBs).

STBs locate in the external sheet of the trophoblasts, so if the maternal infection happens, the STBs provide as a barrier against invasion. EVTs locate in the base of the stem villi and, unlike the STBs, cause vertical transmission because EVTs define a direction through which pathogens can break the placental barrier. Additionally, CTBs locate in the inside of the STBs and act as stem cells.[8,10,11]

It is known that some viruses can contaminate the placental cells via receptors on trophoblasts and despite the presence of the placental barrier, they lead to fetal complications.[9] Viruses can infect STBs, CTBs, endothelial cells, hematopoietic cells, and the fetal membranes.[12] It was revealed that the incidence of positivity in infants born from COVID-19 positive mothers were 0.4%–5%.[13] Although a few number of cases have been reported, there is a need to research the vertical transmission of the SARS-CoV-2. As the mechanism is not fully clarified, the coming possibilities have been considered for crossing the placental barrier of SARS-CoV-2: (1) Direct infection of STBs via ACE2 and probably TMPRSS2, (2) either get through the maternal circulation to EVTs (3) or through the maternal immune cells, and (4) vaginal passage during childbirth.[13] Cui et al.[14] and also Qiu et al.[15] did not find any viral positivity in the vaginal fluids of COVID-19 positive patients according to their studies, but also some recent studies showed a 9.6%–21.9% positive rate of newborns from COVID-19 positive patients who gave birth vaginally.[13] These contradictory data suggest that the final possibility will occur with a lower probability.

According to several data that support the first way of vertical transmission was mentioned above, coexpressions of ACE2 and TMPRSS2 have been found in STBs (in the first trimester), in EVTs (in the second trimester), and also in chorioamniotic membranes (in the third trimester).[8,9,12,16] In addition to allowing the virus to enter into the cell, ACE2 and TMPRSS2 coexpressing cells are also linked to genes associated with mitochondrial metabolism and glucose transport.[9] Gengler et al. investigated the localization of ACE2 in the placenta throughout pregnancy; they made immunohistochemical stainings with placental samples between 14 and 40 weeks gestation from 28 COVID-19 positive patients. They found strong membranous ACE2 stainings through STBs, CTBs, and EVTs. COVID-19 negative patient's materials were also used in this study for the control, and they found strong ACE2 expression in the relevant cells throughout the entire pregnancy, regardless of COVID-19.[17]

Taken together, ACE2 and TMPRSS2, which play an active role in the entry of the SARS-CoV-2 into the cell, are also coexpressed in the placenta, indicating that the placenta is an increased-risk organ for the COVID-19.

3 | COVID-19 SENSITIVITY IN PREGNANCY: IMMUNE CLOCK AND CYTOKINE STORM

Pregnancy is a special immunological process in which maternal immunity fights with microbial challenges while protecting the allogeneic fetus on the one hand. In this process, immune suppression does not occur, but instead, a different immunological adaptation is provided during different developmental stages of the fetus through a process also called "immune clock."[18] (1) A pro-inflammatory state occurs in the first trimester to be useful for the embryo placentation and implantation; (2) an anti-inflammatory condition occurs in the second trimester to be useful for the fetal growth; (3) a pro-inflammatory state occurs in the third trimester to prepare for starting of birth.[19]

Pregnant women are more sensitive to respiratory pathogens than the general population, especially caused by "cytokine storm" passed during the pro-inflammatory states through the gestational stages.[18] If we consider this point more closely, COVID-19 infection is also associated with a cytokine storm (characterized by a reduction in the number of lymphocytes relative to inflammatory monocytes, which could increase plasma concentrations of interleukins [IL] 2, 7, 10; granulocyte-colony stimulating factor, monocyte chemoattractant protein 1, macrophage inflammatory protein 1α, and tumor necrosis factor [TNF]-α), so the cytokine storm induced by SARS-CoV-2 may trigger a more severe inflammatory state in pregnant women who have already been through this storm.[18–21] Additionally, aberrant cytokine storm leads to acute respiratory distress syndrome and multisystem organ failure.[21]

There is no definitive evidence of vertical transmission of SARS-CoV-2 infection from mother to child in the existing data, but some pregnancy complications have been reported, like premature birth, intrauterine growth restriction, and spontaneous abortion through COVID-19 positive mothers. Therefore, the potential risk of infected pregnant women and the fetus is not ignored; even these complications may be caused by the direct effect of the virus on mothers.[18]

If we return to the pregnancy cytokine storm, whose severity increases with COVID-19, abnormal maternal inflammation as a result of the viral infection during pregnancy causes some complications, such as pregnancy loss, premature rupture of membranes, intrauterine growth restriction, preterm birth or stillbirth, preeclampsia, also fetal brain development abnormalities, neuronal dysfunctions, or behavioral phenotypes in postnatal life.[18,19,21]

Choi et al.[22] showed that maternal immune activation of IL-17a induces an autism spectrum-like phenotype and brain development abnormalities. Yockey and Iwasaki[23] declared that elevated levels of maternal TNF-α can be associated with defects in early embryo development and also high fever can be associated with postnatal hyperactivity according to Dreier et al.'s study.[24] Additionally, SARS-CoV-2 among pregnant women have greater risk for autism, mental health disorders, or schizophrenia in neonates according to studies.[21] Additionally, preterm birth before 34 or 37 weeks of gestation, nearly 50% were reported among COVID-19 positive mothers according to some studies.[21,25]

There is currently no evidence to support the fetal SARS-CoV-2 infection by vertical transmission, but more articles began to report maternal deaths; for instance, 124 maternal deaths were reported in Brazil.[26] Additionally, about five newborns who showed positive results for COVID-19 were reported according to their swab tests

30 h after birth or 17 days after birth, although they did not show any symptoms.[21,26] There was no direct evidence of vertical transmission among these neonates, but it should be noted that amniotic fluid, umbilical cord blood, or placenta of these newborns were not tested.[26] Unlike, according to the study of Vivanti et al.,[27] COVID-19 positive pregnant at 35 + 2 weeks of gestation had given birth due to increased respiratory distress, and after that, RT-PCR (reverse transcription polymerase chain reaction) on the placenta was positive for SARS-CoV-2 genes. Therefore, although everything has not yet been fully demonstrated, pregnant women and newborns need special attention in order to be prevented from COVID-19.[26]

Taken together, because of the direct effects of the virus on mothers, a healthy pregnancy needs an early diagnosis of COVID-19 and to take appropriate protection at an early stage by calculating the potential risks of treatment on the fetus.

4 | PLACENTAL HISTOPATHOLOGY IN COVID-19

According to the existing data, the effects of COVID-19 on placenta histology are divided into two ways. Some researchers found the presence of COVID-19 in the placenta but argued that no differences in placental histopathology were observed, while some studies showed that some pathological changes occurred. We will examine these studies a little more closely below. All placentas in the described studies belong to subjects whose mother tested positive for COVID-19.

Baergen et al. examined 20 placentas according to Amsterdam criteria, and they found fetal vascular malperfusion or fetal vascular thrombosis as the most common lesion. Intramural fibrin deposition in one or two foci, foci of villous stromal-vascular karyorrhexis, multiple lesions, intramural nonocclusive thrombi, meconium macrophages, and chronic villitis were reported as other findings. All of these findings were not seen in each placenta, distributed in different samples, and COVID-19 might be related to the tendency for thrombosis in the fetal circulation were concluded.[28] Shanes et al. studied 16 placentas, 15 with a live birth in the third trimester and 1 delivered in the second trimester after intrauterine fetal demise. Compared to control samples, they showed an increased prevalence of decidual arteriopathy and maternal vascular malperfusion due to abnormal or injured maternal vessels and intervillous thrombi through the placentas of the third trimester. Additionally, villous edema and a retroplacental hematoma were observed among the placenta of the second trimester.[29] Fifty-one third-trimester placentas were examined according to Amsterdam Criteria by using in situ hybridization (ISH) and immunohistochemistry (IHC) techniques in the study of Smithgall et al.,[30] and they identified maternal or fetal malperfusion with villous agglutination and subchronic thrombi as the most common findings. A total of seven placentas, two placentas from pregnant women regaining from COVID-19 in the first trimester (Group I), three placentas from women that gave birth during the acute stage of COVID-19 (Group II), and two placentas from

pregnant women regaining from COVID-19 in the third trimester (Group III) were examined in the study of Wenling et al. According to the study, placental histopathology was found normal through Group I, intervillous and subchronic fibrin were identified in the placentas of Group II, and extensive thrombotic vasculopathy on the fetal side was observed in the placentas of Group III. Additionally, intrauterine growth restriction, oligohydramnios, and small for gestation newborns were reported for Group III.[26] Menter et al.[31] found prominent lymphohistiocytic villitis and intervillositis, signs of maternal and fetal malperfusion, among the placentas of 40th and 41st gestational weeks, and Mongula et al.[32] reported increased perivillous fibrin deposition and intervillositis according to their study.

Zhang et al. examined 74 placentas and tested placental tissues for SARS-CoV-2 viral particles by using the ISH technique. Accordingly, they demonstrated viral particles within the STBs, atrophic endometrial glandular epithelium, and subchronic plate but they did not report any histopathological changes among these placentas. So, they concluded that no relationship exists between the maternal COVID-19 status and placental pathology.[33] Algarroba et al.[34] studied the placenta of a woman at 28 weeks' gestation caused by severe COVID-19 by using electron microscopy for examining the coronavirus virions. According to this study, researchers found a single virion in STB and also in a microvillus; however, Kniss[35] stated in a letter to the editor that the structures, which were identified as SARS-CoV-2 virions, looked exactly like clathrin-coated pits or vesicles.

A group of researchers stated that the SARS-CoV-2 localized predominantly in STBs,[36] but despite that, they reported that there was no statistically significant difference in placental histopathological evaluations through the placentas of COVID-19 positive women following the second opinion mentioned above.[37–39]

5 | PLACENTAL CELL THERAPY AGAINST COVID-19 DUE TO ITS ANTIVIRAL PROPERTIES

In addition to its very significant role in the development of the fetus in the intrauterine period, the placenta also includes a broad range of biologically active components. Because of these rich content, the placenta shows antiviral, anti-inflammatory, antibacterial, immunoregulatory activities, and also plays a critical role in therapeutic efficacy on wound healing, tissue regeneration, cellular proliferation, osteoarthritis, antiaging, chronic pain, brain or liver damage, and so forth. Because of these properties, placenta extracts have been considered "biological drugs" for over centuries and have been used in experimental and clinical trials.[40–42]

Growth factors (GFs), such as hepatocyte-nerve-epidermal-fibroblast-insulin-like colony-stimulating vascular endothelial GFs; cytokines or chemokines like IL-1,2,3,4,6,8,10 and IFN (interferon)-γ, TNF-α, TGF (transforming growth factor)-β; metabolic compounds such as nicotinamide adenine dinucleotide (NADH), nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), nitric oxide

(NO); antioxidants like superoxide dismutase (SOD), catalase, glutathione peroxidase; amino acids, such as alanine, arginine, histidine, tyrosine; vitamins and trace elements like zinc, copper, iron, selenium, manganese; and other components, such as collagen, elastin, carotenes, can be summarized as biologically active components in the placenta.[40] Each component has important roles in different functions; also it would be more appropriate to study more closely the antiviral activity of placenta extracts for COVID-19.

The placenta shows a protective property due to GFs, chemokines, and cytokines that are described above so that viruses do not infect the fetus from the mother's circulation. Especially IFNs play an important role in the protection process; additionally, it has shown that placental trophoblast-derived IFNs and TNF-α responsible to impair virus replication and activity.[40,43] Production of IFN-1 control infection systemically and IFN-3 control it locally at the barrier surface of the placenta. Additionally, Hofbauer cells (placental macrophages) show intrinsic antiviral activity in the placenta. Also, small, heat and pH stable "placental factor (PF)," which has recently been found, exhibit antiviral properties in addition to IFNs, for protection of the fetus during gestation.[40,44] According to another study, extracellular vesicles from human trophoblasts suppress the replication of viruses and show antiviral activity like IFNs in the placenta.[45]

In addition to IFNs, GFs within EVTs, CTBs, and STBs form the barrier for the viruses between mother and fetus from the 6th month of gestation. Because of this important property of placental GFs, if they use as antiviral drugs, the third trimester is suitable for the isolation because GFs peak during the third trimester.[40] Taken together, after the isolation process, the use of placental GFs, cytokines, and chemokines as an agent to improve the patient's immunological responses to COVID-19 may be new hope in the treatment process.

For this purpose, Barkama et al. used placenta-derived cell therapy in the case of COVID-19 in their preliminary uncontrolled study. They injected placental expanded cells (containing placenta-derived mesenchymal stem-like cells) (300×10^6 cells) by the intramuscular way to eight critically ill COVID-19 patients, and finally, they found an overall improvement in the clinical status of most patients.[46]

6 | CONCLUSION

In conclusion, ACE2 and TMPRSS2, which play an important role in the cellular entry for SARS-COV-2, are co-expressed in different cells during different periods of placental development, so the placenta also carries a risk for this virus. Researchers have identified the presence of the virus in the placenta. Additionally, many studies have also shown that this virus causes some histopathological changes in the placenta. Although the vertical transmission of the virus is not yet clear, available data have shown that the indirect effects of the virus can be seen on the fetus, from spontaneous miscarriage to intrauterine growth restriction. Cytokine storm, which occurs during pregnancy, play an important role in the appearance of indirect

effects on the fetus and is also effective in making pregnant women more sensitive to the virus compared to nonpregnant women. Furthermore, because of their antiviral activities, the use of placental GFs, cytokines, and chemokines as therapeutic agents in the treatment of COVID-19 should be investigated using advanced methods.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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