Review Article

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Current State of Knowledge about Transplacental Transmission of SARS-CoV-2 Infection

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ABSTRACT

Background: To date, some cases of perinatal transmission of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) have been reported. However, it is unanswered if these occurred via the trans-placental or the trans-cervical route or through environmental exposure.

Methods: To address this question, we conducted this study to review the current state of knowledge about the transplacental transmission of COVID-19.

Results: There are no known placental findings associated with the COVID-19 infection. The possibility of intrauterine infection has been based mainly on the detection of IgM in the neonatal blood. Real time-PCR tests on amniotic fluid, placenta, and cord blood are required to ascertain the possibility of intrauterine vertical transmission.

Conclusion: There is currently no sufficient and convincing evidence about the transplacental transmission of SARS-COV-2 infection in pregnant mothers. However, the paucity of placental expression of ACE-2 involved in the cytoplasmic entry of SARS-CoV-2 may explain its relative insensitivity to transplacental infection.

Introduction

SARS-CoV-2 infection, the first pandemic of the century, causes the new coronavirus disease (COVID-19). Since the first case of a COVID-19 infection was detected in Wuhan (Hubei Province, China), China, a series of confirmed cases of the COVID-19 were found globally.[1-5] After the SARS-CoV epidemic which in 2003 caused outbreaks in six countries, some studies revealed that the infection led to some adverse outcomes in pregnant women, such as spontaneous pregnancy loss, preterm delivery, and restricted intrauterine growth (IUGR).[6] However, a matched study comparing the clinical course and outcomes of pregnant mothers infected with SARS-CoV with non-pregnant mothers found that pregnant and nonpregnant women had similar clinical symptoms and presentation, but that pregnant mothers had evidence of more severe symptoms of SARS.[7] Moreover, the association between adverse pregnancy outcomes and physiopathological changes connected to the Middle East respiratory syndrome (MERS) was reported.[8] Recent data showed that COVID-19 may be associated with a higher rate of caesareans (CS), preterm births, miscarriage, stillbirth and the virus may be able to cross the placenta to a fetus.[9-11] However, it is unclear yet whether these obstetrical outcomes were as a result of the coronavirus.[12,13] Some studies reported that the COVID-19 infection in pregnant mothers may be associated with mild or moderate disease in most cases, with a low morbidity and mortality rate.[14-16]

Evidence showed that the neonatal infection with COVID-19 is usually asymptomatic and detection rates of Real time-PCR (RT) and the interpretation of IgM, IgG and IL-6 antibodies levels in cord and samples of products of conception (placenta, amniotic fluid and umbilical cord blood) are discussed concerning the immaturity of the fetal and neonatal immune system.[17] COVID-19 could be recovered by RT-PCR from nasal and throat swabs, sputum and feces of symptomatic neonates but not from vaginal swabs, amniotic fluid, placenta, cord blood, neonatal blood or mother's milk. A study including 247 deliveries from infected mothers reported that 63 cases were preterm. One in 20 of neonates born to the tested positive for Covid-19, and five of the neonates died. Three of the deaths appear to have been unrelated to the Covid-19, but two of them might have been linked to virus. Another study including 108 infected mothers revealed that 91% of the neonates were delivered by CS. The first case series have described the clinical features and outcomes of pregnancy in infected mothers with COVID-19 in Wuhan, China reported adverse perinatal outcomes including increased risks of miscarriage, preeclampsia, preterm birth, and stillbirth in the infected mothers.[18,19]

There is an imperative need for conclusive data and research on the possibility of trans-placental migration of COVID-19 as well as pregnancy comorbidity is needed.[20] Previously, in a study, we reported that COVID-19 did not transfer vertically from pregnant women to their neonates.[13] Similarly, Silva et al., in a review concluded that there was no convincing evidence for vertical transmission of COVID-19 in pregnant mothers infected during the third trimester of pregnancy, as also reported for COVID-19 infection.[21] However, some studies which examined the placenta for the presence of COVID-19 using molecular, immunohistochemical techniques and electron microscopy have revealed COVID-19 invasion of the placenta, highlighting the potential for severe morbidity among pregnant women with Covid-19.[22] Thus, questions concerning vertical transmission of COVID-19 from infected mothers to neonates remain unanswered. To address this issue, we performed this review to confirm maternal-fetal infection and known mechanisms that COVID-19 virus was used to trans-placental pathogen migration.

Placenta Findings

Yang et al., in a review of 20 studies including 222 neonates using data on umbilical cord blood, placenta, and/or amniotic fluid have summarized the evidence on vertical transmission of COVID-19. They showed that there is no proof to support the intrauterine vertical transmission of COVID-19.[23] In another review based on five studies from Chinese women who were diagnosed with COVID-19 late in pregnancy (3rd trimester), Cheruiyot et al., demonstrated that there is no definitive evidence of intra-uterine vertical transmission of COVID-19 in pregnant women diagnosed in the third trimester.[24] Patanè et al., in a study including 22 infected mothers by COVID-19 who delivered at Papa Giovanni XXIII Hospital, Bergamo, Italy, examined the possibility of vertical transmission of COVID-19. They have described the first report of cases of positive PCR for SARS-CoV-2 in mother, neonate and placental tissue. Two of those neonates, born from infected mothers, resulted positive for PCR of nasopharyngeal swab. The placentas of these two women who delivered infected neonates with positive nasopharyngeal swab showed chronic intervillositis, with presence of macrophages, both in the intervillous and the villous space. Moreover, the immunohistochemical tests demonstrated chronic intervillositis with macrophages CD68+ infiltration. They revealed that the Single-molecule RNA in situ hybridization raises the possibility of direct visualization of the COVID-19 virus, evaluating the molecular target COVID-19 spike protein mRNA while retaining tissue morphology, a feature that is lost in other methods such as PCR. The presence of COVID-19 virus RNA in the syncytiotrophoblast signifies presence of the virus on the fetal side.[25]In a first report, Algarroba et al., examined potential COVID-19 transmission in the placenta using electron microscopy. Their results demonstrated that the COVID-19 virus invasion in placental tissue and placental infection was associated with COVID-19.[26] Mahyuddin et al., reviewed 40 studies of COVID-19 pregnancies to confirm maternal-fetal infection and known protective mechanisms of the placental barrier that prevent transplacental pathogen migration. In the reviewed studies there was no consensus on diagnostic strategy for congenital infection during covid-19 pandemic. In those studies, the molecular RT-PCR assay of neonatal swabs and a wide range of clinical samples including vaginal secretions, amniotic fluid, breast milk and umbilical cord blood were performed. The study showed that neonatal COVID-19 was reported in eight studies, two of which were based on the detection of COVID-19 IgM in neonatal blood. Moreover, histological tests revealed sparse the virus particles, vascular mal-perfusion and inflammation in the placenta from infected mothers.[27] Shanes et al., in a study examined 16 placentas from infected mothers (15 with live birth in the 3rd trimester and one delivered in the 2nd trimester after intrauterine fetal demise). Their results revealed that third trimester placentas were significantly more likely to show at least one feature of maternal vascular malperfusion (MVM) such as abnormal or injured maternal vessels, as well as delayed villous maturation, chorangiosis, and intervillous thrombi than healthy subjects. The placenta from the infected mother with intrauterine fetal death showed villous edema and a retroplacental hematoma. However, the rates of acute and chronic inflammation were not increased. Their results suggested a systemic inflammatory or hypercoagulable state influencing placental physiology.[28]

Angiotensin-Converting Enzyme 2

Angiotensin-converting enzyme 2 (ACE2) is described as renin-angiotensin system (RAS) component and modulates blood pressure, inflammation, and fibrosis and is crucial to the pathophysiology of hypertension, cardiovascular disease, and chronic kidney disease.[29,30] ACE inhibitors are often the first-

line agents to treat the conditions in children and are among the most commonly prescribed antihypertensive medications to children.[29] ACE2 has been established as one of the main the functional host receptors for COVID-19 and may increase the risk of SARS-CoV-2 infection and COVID-19.[31,32] Like the previous SARS-CoV, it is suggested that SARS-CoV-2 binds to ACE2 to gain entry to host cells on the respiratory tract epithelium. Importantly, SARS-CoV-2 is more pathogenic, at least in part because of its 10- to 20-fold increased binding affinity to ACE2.[33,34] These findings may partially explain the easier transmissibility of SARS-CoV-2 and that raised ACE2 expression may confer increased susceptibility to host cell entry of SARS-CoV-2. However, it seems that ACE2-expressing organs do not equally participate in COVID-19 pathophysiology, implying that other mechanisms are involved in orchestrating cellular infection resulting in tissue damage.[35]

Studies demonstrated that ACE2 was highly expressed in maternal-fetal interface cells such as stromal cells and perivascular cells of decidua, and cytotrophoblast and syncytiotrophoblast in placenta.[36,37] Meng et al., collected the online available single-cell RNA sequencing (scRNA-seq) data to evaluate the cell specific expression of ACE2 in maternal-fetal interface. Their results revealed that the SARS-CoV-2 receptor was widely spread in specific cell types of maternal-fetal interface and fetal organs. Taking these functions into account, COVID-19 may disturb the female reproductive functions through regulating ACE2.[38] Moreover, the target towards the interaction between SARS-CoV-2 and ACE2 during the pandemic may be useful for treatment of the disease.[39,40]

Conclusion

A few pieces of evidence but not definitive support the possibility of trans-placental transmission of SARS-CoV-2 infection in pregnant mothers. The placentas of the infected mothers have higher rates of decidual arteriopathy and other maternal vascular malperfusion features. Practically, possible perinatal exposure such as delivery mode and time interval from delivery to the diagnosis of neonatal infection is pivotal in ascertaining congenital from perinatal infection. The paucity of placental expression of ACE-2 involved in cytoplasmic entry of COVID-19 may explain its relative insensitivity to trans-placental infection. RT-PCR tests on amniotic fluid, placenta, and cord blood are necessary to determine the possibility of trans-placental transmission of SARS-CoV-2 infection. Moreover, the in situ hybridization of COVID-19 RNA in the infected placentas increases the possibility of estimating the viral load in cells with morphological context. High quality studies are needed to further evaluate the possibility of crossing COVID-19 from placental barriers in pregnant women.

Conflict of Interests

Authors have no conflict of interests.

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