Editorial

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Vertical Transmission of Severe Acute Respiratory Syndrome Coronavirus 2: Current Evidence and Perspectives

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With the widespread transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the medical community has organized efforts to determine a series of clinical questions about the virus. Critical questions have also arisen in the field of maternal-fetal medicine and have received increasing attention, as physiological and immunologic changes in pregnancy might potentially increase the susceptibility to SARS-CoV-2 infection and complications of the virus.[1]

Many early reports indicated that pregnant women with SARS-CoV-2 infection were not prone to experiencing severe disease.[2–4] However, later studies supported pregnancy as a risk factor for severe disease associated with SARS-CoV-2 infection, such as intensive care unit admissions, invasive ventilation, extracorporeal membrane oxygen (ECMO) utilization and death.[5,6] Additionally, pregnant women with severe or critical SARS-CoV-2 infection are at risk for various perinatal complications, such as cesarean section, hypertensive disorders of pregnancy, and preterm birth.[2,7] Risk factors for severe or critical SARS-CoV-2 infection include advanced maternal age, increased body mass index, and underlying medical comorbidities such as asthma, chronic hypertension, and pregestational diabetes.[2,7] However, the risk of fetal infection due to vertical transmission of SARS-CoV-2 is still a major concern and debated issue.[8]

Vertical transmission is defined as the transmission of the infectious pathogen from the mother to fetus via the placenta or ascending infection in utero (intrauterine), body fluid contact during delivery (intrapartum), or through breastfeeding after birth (postpartum). At present, the extent to which vertical transmission of SARS-CoV-2 occurs and when it occurs is unclear. This article reviews the current evidence and perspectives.

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Incidence

Yan *et al.*[3] conducted a cohort study with 116 pregnant patients with SARS-CoV-2 infection who delivered 100 babies. Of these neonates, 86 tested negative for SARS-CoV-2 via nasopharyngeal swab testing. An analysis by three major Harvard-affiliated hospitals showed that among 149 of 159 newborns (94%) that underwent testing for SARS-CoV-2 within 24 hours of delivery, none showed a positive result for SARS-CoV-2 (0/149).[9] The largest cohort study was from the United Kingdom, which included 427 pregnant women with SARS-CoV-2 infection. In that study, 12 of 244 neonates who were tested by nasopharyngeal swabbing after birth were positive for SARS-CoV-2 (12/244); six of them were tested within 12 hours of birth.[10] A systematic review and meta-analysis that included 38 cohort and case series studies showed that a pooled proportion of 3.2% for vertical transmission through testing 936 neonatal nasopharyngeal SARS-CoV-2 RNA, either immediately after birth or within 48 h of birth.[11] A recent meta-analysis that included 206 cohort studies and 266 case series and case reports showed that in cohort studies, 1.8% of the 14,271 babies born to mothers with SARS-CoV-2 infection had positive results for SARS-CoV-2 based on reverse-transcriptase polymerase chain reaction (RT-PCR) analysis after birth. When the analysis was limited to babies tested in the first 24 hours after birth, the positivity rate was 0.9%. When combined the cohort studies with case series and case reports to further assess the timing of mother-to-child transmission based on the in utero exposure testing and viral persistence testing according to the categorization of World Health Organization (WHO) classification system.[12] The results showed that of the 536 SARS-CoV-2–positive babies with sufficient data to apply the WHO classification system for the timing of exposure and likelihood of infection, 14 were categorized as having confirmed mother-to-child transmission: seven with in utero transmission (448 assessed), two with the intrapartum transmission (18 assessed), and five with early postnatal exposure (70 assessed).[13]

Evidence of SARS-CoV-2 intrauterine vertical transmission

Since the onset of the pandemic, worldwide efforts were made to explore the possibility of vertical transmission of SARS-CoV-2. The first study from China reported a retrospective cohort of nine pregnant women with SARS-CoV-2 infection, by RT-PCR analyses of the virus, on babies born to mothers with SARS-CoV-2 infection and their paired amniotic fluid and cord blood. The study indicated no evidence of intrauterine vertical transmission in late pregnancy.[14] Subsequently, more studies have reported similar results and failed to

demonstrate the intrauterine vertical transmission of SARS-CoV-2, including negative testing in newborn's nasopharyngeal swabs, placental tissues, umbilical cord blood, amniotic fluid, and vaginal swabs.[3,4,15,16] However, with the increasing number of published studies on SARS-CoV-2 infection during pregnancy, few cases have suggested probable intrauterine vertical transmission of SARS-CoV-2. However, most reports have been based on single positive results of neonatal nasopharyngeal SARS-CoV-2 detected by RT-PCR tests with significant differences in sample collection times.[10,17–19] Thus, although strict isolation measures were undertaken for neonates, the lag time to neonatal nasopharyngeal swab raises the possibility of postnatal transmission. However, several published literature have described the detection of SARS-CoV-2 in intrauterine tissue samples such as amniotic fluid, placenta, and umbilical cord plasma,[20–29] which further supports the hypothesis that, even uncommon, there may be intrauterine vertical transmission of SARS-CoV-2.

First trimester

Shende *et al.*[20] reported a pregnant woman tested positive for SARS-CoV-2 at 8 weeks of gestation, despite being symptomless. At 13 weeks of gestation, the ultrasound indicated fetal demise and the patient underwent dilation and curettage. SARS-CoV-2 RNA was detected in the placenta cells. In addition, viral RNA was found in the amniotic fluid and the Spike proteins of SARS-CoV-2 were immunolocalized in cytotrophoblast and syncytiotrophoblast cells of the placental villi. However, in this case, no fetal tissue was available for testing of viral particles.[20] Valdespino-Vázquez *et al.*[21] reported a case of spontaneous twin abortion in early pregnancy from a SARS-CoV-2 infected symptomatic mother. RT-PCR of the placenta, kidneys, and lungs for SARS-CoV-2 of one fetus was positive, confirmed by immunofluorescence and electron microscopy.

Second trimester

In one case, a SARS-CoV-2–positive pregnant mother miscarried at 19 gestational weeks. Fetal axillae, mouth, meconium, and blood samples obtained within minutes after the birth all tested negative for SARS-CoV-2 by RT-PCR. However, placental swabs from the fetal side taken within minutes of birth were positive for SARS-CoV-2 RNA.[22] The second case reported a patient with SARS-CoV-2 infection who delivered at 22 weeks of gestation because of severe preeclampsia and placental abruption. SARS-CoV-2 RNA detected by RT-PCR tests in the placenta and umbilical cord samples were positive; furthermore, viral capsids were found in the trophoblast cells by electron microscopy, confirming infection of the fetal side of the placenta. However, fetal tissues (lung, myocardium, liver, kidney) showed normal histology without inflammation.[23] The third case was of a premature neonate delivered at 26 weeks of gestation. SARS-CoV-2 RNA was positive in the placenta and umbilical cord blood samples. In addition, SARS-CoV-2 nucleocapsid and SARS-CoV-2 spike protein in the cytotrophoblast and syncytotrophoblast were shown to be positive by immunohistochemical analysis. No fetal tissues were tested for SARS-CoV-2.[24] Another study was of a second-trimester twin stillbirth in a woman with SARS-CoV-2 infection. Placental histology and immunohistochemistry of both fetuses demonstrated SARS-CoV-2 infection, and SARS-CoV-2 RNA was detected by using RT-PCR in all tissue samples (fetal lung, kidney, heart, and liver and maternal placenta, cords, and membranes), except for the kidney of the second fetus.[25]

Third trimester

Zamaniyan *et al.*[26] described the detection of SARS-CoV-2 in the amniotic fluid obtained during cesarean section from a pregnant woman with severe SARS-CoV-2 infection who delivered at 32 gestational weeks. Neonatal nasopharyngeal SARS-CoV-2 just after birth was negative, but positive on the second test within 24 hours of birth. Kirtsman *et al.*[27] reported a woman with SARS-CoV-2 infection who delivered at 35 gestational weeks by cesarean section, and SARS-CoV-2 PCR testing of the placental tissue had a positive result, as did the RT-PCR test of the neonatal nasopharyngeal swabs, plasma, and stool samples, highly suggestive of utero vertical transmission. Vivanti *et al.*[28] reported a probable case of transplacental transmission of SARS-CoV-2 during late pregnancy. The amniotic fluid and placental sample tested positive for SARS-CoV-2 by RT-PCR. In addition, the placenta showed signs of intervillous inflammation that was consistent with the severe maternal systemic inflammatory status triggered by SARS-CoV-2. RT-PCR on neonatal nasopharyngeal and rectal swabs collected 1 hour after birth and blood and nonbronchoscopic bronchoalveolar lavage fluid collected in the first 6 hours after birth were all positive for SARS-CoV-2 genes. This is probably the best evidence to date for intrauterine vertical transmission of SARS-CoV-2.[28]

A recent multicenter prospective study including 31 pregnant women with confirmed SARS-CoV-2 infection showed that two of 31 newborns tested positive for SARS-CoV-2. In addition, the SARS-CoV-2 genome was detected in one umbilical cord blood sample and in two at-term placentas.[29] A systematic review by Kotlyar *et al.*[11] indicated that vertical transmission of SARS-CoV-2 infection in the third trimester is possible but rare. Their results showed that of 936 neonates from mothers with SARS-CoV-2 infection, 27 tested positive for SARS-CoV-2 RNA by RT-PCR with a nasopharyngeal swab. Furthermore, SARS-CoV-2 RNA was positive for one neonatal cord blood sample (1/34, 2.9%), two placenta samples (2/26, 7.7%), and three fecal or rectal swab samples (3/31, 9.7%), but 51 amniotic fluid samples and 17 urine samples tested negative. In addition, neonatal serology analysis based on the presence of immunoglobulin M was positive for three of 82 samples (3.7%).[11] Serologic assessments were also performed in neonatal serum samples to explore the possibility of intrauterine vertical transmission of SARS-CoV-2.[30–34] However, thus far, no conclusive and concrete evidence was found for in utero vertical transmission of SARS-CoV-2.[35]

Pathological basis of SARS-CoV-2 intrauterine vertical transmission

The low reported rate of SARS-CoV-2 intrauterine vertical transmission is likely because in most studies, pregnant women had mild-to-moderate symptoms that manifested during the third trimester of pregnancy, and in some cases, cesarean sections were carried out immediately given the uncertainty about the risk of mother-to-fetus transmission of the virus, especially in the early pandemic. Therefore, the nonserious condition and short time interval from clinical manifestation of SARS-CoV-2 to delivery might have weakened the fetus' chances of intrauterine infection of the virus.[14,35]

Notably, from a pathophysiologic viewpoint, the intrauterine SARS-CoV-2 infection for fetuses has a biological plausibility. First, it has been found that angiotensin-converting enzyme 2 receptor and transmembrane protease serine 2 required for SARS-CoV-2 entering the cells is expressed in the placenta.[36–38] Although the data regarding their expression is inconsistent, and whether they have different expressions due to different gestational weeks are not clear, the angiotensin-converting enzyme 2/transmembrane protease serine 2 pathway is considered the main mechanism of transplacental invasion of SARS-CoV-2. SARS-CoV-2 can directly damage the placenta by inducing apoptosis and vascular damage. As a result, the virus can infect the fetus without the need for placental cell infection.[36] In addition, the rare viraemia associated with severe SARS-CoV-2 infection may let the virus spread via the bloodstream to the uterus and then infect the fetus. Therefore, the possibility of intrauterine vertical transmission of SARS-CoV-2 requires further careful study.

Knowledge gaps in SARS-CoV-2 intrauterine vertical transmission

The available research until now regarding the possibility of intrauterine vertical transmission of SARS-CoV-2 has mainly involved the third trimester and shows large differences in study quality and in what data were reported. Furthermore, the finding of SARS-CoV-2 in amniotic fluid or placental tissues does not necessarily correlate with a positive RT-PCR result in the fetus or neonate.[22,26,39] Thus, it is a challenge to aggregate and compare the data across studies. To date, there is a shortage of standardized international consensus definitions for the evaluation of vertical transmission of SARS-CoV-2. However, several classification systems have been initially developed to help categorize the likelihood of intrauterine transmission of SARS-CoV-2, and they all have a few requirements: (1) evidence of maternal SARS-CoV-2 infection, (2) in utero fetal SARS-CoV-2 exposure, and (3) SARS-CoV-2 persistence or immune response in the neonate.[12,40,41] The studies outlining these systems emphasize that collection of appropriate specimens at appropriate times is essential to understanding of SARS-CoV-2 vertical transmission.

Taking the WHO[12] classification system as an example to make a definite diagnosis of in utero vertical transmission, it requires two components. (1) Evidence of in utero exposure (RT-PCR from amniotic fluid, placental tissue, neonatal blood, upper and lower respiratory tract samples, stool, or cerebrospinal fluid; or immunoglobulin M positive); and (2) evidence of viral persistence, that is, a positive result upon repeat testing in 24 to 48 hours in sterile samples (amniotic fluid, neonatal blood, lower respiratory tract sample, or cerebrospinal fluid). In the case of fetal demise in early pregnancy, it requires fetal tissues (lung, liver, brain) for a confirmed positive result. However, in clinical practice, it is difficult to repeat the testing in 24 to 48 hours in amniotic fluid, neonatal blood, or lower respiratory tract or cerebrospinal fluid samples, making the definite diagnosis difficult. With increasing knowledge of SARS-CoV-2 vertical transmission and its clinical consequences for the fetus and neonate, the classification system might be further updated and refined.

Additionally, many questions remain to be answered concerning intrauterine vertical transmission of this virus. For example, whether susceptibility to the virus is different by gestational age and whether there is a period during pregnancy when the fetus is more likely to be infected. Furthermore, does the severity of maternal illness determine the likelihood of viral transmission? Are new variants—like the Delta variant which is more aggressive and highly transmissible—able to cause more severe disease?[42,43] Moreover, whether the effects of SARS-CoV-2 on the uterine vasculature and placenta can cause adverse outcomes, such as fetal growth restriction or stillbirth. To address these questions, further high-quality studies with a large sample size are needed. Longitudinal follow-up of infants born to mothers with SARS-CoV-2 infection are also needed. Furthermore, the use of animal models might accelerate our knowledge.

Evidence of intrapartum and postpartum vertical transmission of SARS-CoV-2

SARS-CoV-2 is rarely detected in the vaginal swabs in infected pregnant women.[3,11,44] Regarding studies about evaluation for SARS-CoV-2 in breast milk, although the virus was occasionally positive tested,[45] the potential for contamination is questionable. Furthermore, the detected SARS-CoV-2 RNA in the human milk was particle of the virus but not live virus.[46] Moreover, an observational cohort study reported that if correct hygiene precautions are undertaken, like consistent use of surgical masks, hand hygiene, and breast cleansing, breastfeeding can be safely carried out without the fear of SARS-CoV-2 transmission.[47]

Conclusions

Vertical transmission of SARS-CoV-2 is possible, but rare. The relevant knowledge regarding the possible risks is still limited and controversial. Further studies investigating this issue and the subsequent fetal and neonatal consequences are needed. Further conclusive evidence regarding SARS-CoV-2 vertical transmission will help guide patient counseling and provide better obstetrical care for women with SARS-CoV-2 infection.

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Author Contributions

Huixia Yang did the concept and design. Chong Shou and Chen Wang did the literature search. Chong Shou and Chen Wang did the manuscript writing. Huixia Yang did the manuscript review. The manuscript has been read and approved by all the authors.

Conflicts of Interest

None.

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