Commentary

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Research progresses in vertical transmission of SARS-CoV-2 among infants born to mothers with COVID-19

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"Transplacental transmission is widely considered to be the most important and most likely vertical transmission route of SARS-CoV-2"

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COVID-19 is primarily transmitted through droplets and close contact and has become a global public health problem. As COVID-19-positive pregnant women manifested higher viral loads and higher rates of disease progression during infections, there has been an increasing concern about the possible effects of pregnant women with COVID-19 on their infants. To address this question, we assess the possibility of vertical propagation and its probable mechanisms during pregnancy and breastfeeding, and discuss the possible pathological changes of the placenta and the potential impact on neonatal outcomes.

Methods of vertical transmission

Vertical transmission is defined as the possibility of transmission from the mother to her fetus before and during delivery or to the neonate after delivery. Vertical transmission of viral infection usually occurs during the antenatal period by transmission through the placenta, or during delivery by ingestion or close contact with cervicovaginal secretions or perineal-infected tissue or by direct transfer across breast milk in the postpartum period.

Transplacental transmission

It is an extremely controversial issue whether SARS-CoV-2 can be transmitted by transplacental infection or not. Some preliminary studies believed that there was insufficient evidence of materno–fetal transmission of SARS-CoV-2 [1,2]. Celik *et al.* [3] brought forward that the deficiency of canonical cell in trophoblast seems to be a significant mechanism to prevent the vertical transmission of SARS-CoV-2, as SARS-CoV-2 cannot enter placental villi for a lack of caveolin, while Pique *et al.* [4] attributed this impossibility to the negligible coexpression of ACE2 and TMPRSS2 in the placenta, which mediate viral entry. Placental pathological studies have suggested that syncytiotrophoblasts are often infected with SARS-CoV-2, but the fetus is not always infected, and this indicates that the presence of placental barrier is also an important reason for the low possibility of vertical transmission of COVID-19, even if it is not completely effective. However, some scholars were surprised to discover that SARS-CoV-2 may infect human placenta through other alternative receptors (DPP4 and CD147) and proteases (Furin), which to some extent testifies to the possibility of vertical transmission [5,6]. Part of the existing studies have found through real-time PCR detection on fetal placental tissue, umbilical cord blood, amniotic fluid, vaginal secretions, nasopharyngeal swabs and other specimens of pregnant women and newborns with COVID-19, that SARS-CoV-2

can indeed traverse the placenta and migrate from mother to fetus [7,8]. The mother-to-child vertical transmission rate is inconclusive and fluctuates between 1.6 and 6.3% [9,10], and may have nothing to do with maternal disease severity.

Transplacental transmission is widely considered to be the most important and most likely vertical transmission route of SARS-CoV-2; however, there are inadequate high-quality data to describe the molecular pathway of SARS-CoV-2 vertical transmission through the placenta. Based on the current understanding of the vertical transmission route of the main TORCHES microorganisms and nonviral TORCHES pathogens through the placenta, we propose some possible mechanisms for the SARS-CoV-2 virus to pass through the placenta: virus particles directly infect the syncytiotrophoblasts on the placental villi through the maternal–fetal interface, trigger an inflammatory response and enter the villi matrix and fetal capillaries through syncytial trophoblasts. Direct infection and rupture of syncytial trophoblasts, FcR-mediated antibody-dependent enhancement could promote the virus to pass through the placenta. Viremia: the maternal blood containing the virus could travel from the uterine artery to the placenta, so the virus enters the interstitial space, and then enters the fetal circulation through the chorion, via the ascending route from virus or infected cells in the cervicovaginal compartment. Entering the extravascular trophoblast as well as other placental cells through endothelial microcirculation. The virus first infects maternal immune cells such as decidual immune cells, monocytes, Hofbauer cells and then transfers to the proximal extravillous trophoblast cells, which act as a carrier, allowing downstream transmission to the villus core and fetal vasculature. The virus passes through the placenta through the action of other alternative receptors ([CD26 and CD147] and proteases [Furin]).

Contact transmission during vaginal delivery

Beyond all question, the risk of contact with vaginal and perineal-infected tissues or aspiration of cervicovaginal secretions is higher in the case of vaginal delivery. At present, most researchers considered no SARS-CoV-2 virus to exist in the vaginal fluids of pregnant women with COVID-19, which to some extent supports that vaginal delivery may be a safe delivery option. Most existing studies indeed indicated that vaginal delivery may not increase the incidence of neonatal SARS-CoV-2 infection, and cesarean section may not prevent vertical transmission [11,12]. Though Sinaci *et al.* [13] proved that SARS-CoV-2 can be detected in the placenta or vaginal secretions of COVID-19-positive pregnant women, the risk of contracting COVID-19 in these vaginally delivered newborns has not increased. Therefore, the method of delivery should be based on the obstetric situation, and not all COVID-19-positive pregnant women should be delivered by cesarean section.

Transmission through breast milk

Although the ACE-2 receptor is expressed in breast tissue, most reports have not detected SARS-CoV-2 in breast milk and almost all infants have no evidence of SARS-CoV-2 infection [14,15]. A small number of studies have found that breastfed infants have tested positive for SARS-CoV-2, but the mode of infection cannot be determined (breast milk or close contact). Considering the immune characteristics of breast milk, most scholars currently do not recommend interrupting breast feeding. For exposed or infected mothers, mothers should wear surgical masks when feeding their babies to take additional droplet protection measures. Further research is needed to distinguish whether breast milk or breastfeeding (i.e., related bodily fluids, such as blood, sweat and respiratory droplets) cause the vertical propagation of SARS-CoV-2.

Placental pathology

Studies have found that the pathological manifestations of the placenta infected with SARS-CoV-2 are diverse, which can be manifested as: fetal vascular malperfusion, fetal vascular thrombosis, maternal vascular malperfusion, acute and chronic placental inflammation (e.g., lymphohistiocytic villitis, histiocytic intervillositis, chorioamnionitis and choroiditis), intervillous thrombosis, perivillous fibrin deposition, Hofbauer cell hyperplasia and syncytiotrophoblast necrosis [16–18]. Although the placenta of SARS-CoV-2-infected women may show a series of different pathological changes, most trials believe that none of these pathological changes are specific. However, Garrido-Pontnou *et al.* [19] recently have proposed that trophoblastic damage may be a specific marker of placental SARS-CoV-2 infection, and diffuse trophoblast cell damage may become a hallmark of SARS-CoV-2-related fetal death.

Neonatal outcome

Newborns born to mothers with COVID-19 may be asymptomatic. However, most researchers currently have confirmed that newborns delivered by COVID-19-positive pregnant women are at higher risk of fetal distress, intrauterine growth restriction, premature delivery, low birth weight, respiratory distress, unstable body temperature and gastrointestinal and cardiovascular dysfunction. Pawar *et al.* [20] considered that the maternal infection of SARS-CoV-2 would lead to the production of protective IgG antibodies against the viral spike protein. These antibodies cross the placenta and enter the newborn's body. In some children with genetic susceptibility, the antibodies may interact with neutrophils and macrophages, causing an immune response that results in development of neonatal multisystem inflammatory syndrome, thrombosis and early neonatal heart involvement, including QTc prolongation, atrioventricular block, cardiogenic shock and coronary artery dilation. In addition, studies have also found that newborns delivered by mothers with COVID-19 confirmed in late pregnancy can have kidney developmental damage, which is manifested by increased cystatin C and β2 microglobulin [8]. It is not clear whether some of the reported mother-to-child complications are caused by viruses or are iatrogenic (for example, caesarean section can cause premature delivery and newborn breathing problems).

Conclusion

As there is a lack of impactful preventive or therapeutic measures against SARS-CoV-2 infection in utero during pregnancy, elucidation of the molecular pathways and host defense events associated with SARS-CoV-2 infections during pregnancy is a key area for future investigation and is critical for the effective control of the COVID-19 epidemic. Vaginal delivery and postpartum breastfeeding are unlikely to transmit SARS-CoV-2. Selective cesarean section or separation of the baby from the mother is controversial and is not generally recommended. Based on our understanding of the transplacental transmission of common viruses, we propose some possible molecular pathways for the vertical transmission of SARS-CoV-2 which needs to be clarified in subsequent experimental studies. The placenta infected with SARS-CoV-2 showed a variety of non specific pathological changes. Whether one or more specific pathological changes can be determined in placenta infected with SARS-CoV-2 is the top priority of future research. Maternal infection with COVID-19 may have adverse effects on the newborn's various systems.

Future perspective

Future studies should confirm whether SARS-CoV-2 can indeed be transmitted vertically through the placenta, by reliably isolating the SARS-CoV-2 virus from the placenta and fetal blood or tissue. The future research focus is to further explore the potential molecular pathways of placental vertical transmission, specific placental pathological changes and to find biomarkers for early prediction of placental vertical transmission.

Author contributions

M Yi: ideas; formulation or evolution of overarching research goals and aims; Z Peng: development or design of methodology; creation of models; J Zhang: preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation); Y Shi: preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre-or post publication stages.

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