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Opinion

Intrauterine vertical transmission of SARS-CoV-2: what we know so far

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The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly worldwide and is now a global pandemic. One of the major concerns is whether SARS-CoV-2 can be vertically transmitted from mothers to their fetuses, thus causing congenital infection.

The most conclusive evidence of intrauterine transmission of COVID-19 would be to confirm the replication of SARS-CoV-2 in fetal pulmonary tissues, but this is almost infeasible technically. Practically, the approach to investigate whether there has been intrauterine viral infection is to test for the presence of the virus in placental, amniotic-fluid, cord-blood and neonatal pharyngeal swab samples. It is important to emphasize that all of these samples need to be collected immediately after delivery using aseptic technique, in order to guarantee that the samples are not contaminated and that they represent intrauterine conditions. In the first study investigating the possibility of intrauterine vertical transmission of COVID-19 in nine pregnant women with mild to moderate manifestation of laboratory-confirmed COVID-19 in the third trimester, matched amniotic-fluid, cord-blood and neonatal pharyngeal swab samples from six neonates were tested for SARS-CoV-2, using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). All samples tested negative, suggesting that intrauterine fetal infection did not occur during the third trimester of pregnancy[1]. Utilizing similar methodology, Lei *et al.* demonstrated no evidence of vertical transmission in four pregnant women with COVID-19 in the third trimester, and vaginal secretion samples also tested negative for SARS-CoV-2 RNA[2]. In the study by Chen *et al.*[3], paired placental tissues from three pregnant women with confirmed COVID-19 in the third trimester and neonatal pharyngeal swab samples were used to evaluate the potential risk of intrauterine vertical transmission, and all samples tested negative for SARS-CoV-2 RNA. Notably, a neonate born to a pregnant woman with COVID-19 tested positive for SARS-CoV-2 RNA in the pharyngeal swab sample obtained 36 h after birth, but it was subsequently confirmed that qRT-PCR testing of the placental and cord-blood samples was negative for SARS-CoV-2, suggesting that intrauterine vertical transmission might not have occurred[4,5]. Thus, based on existing data, there is currently no evidence of intrauterine infection caused by vertical transmission in women with COVID-19 in the late third trimester.

However, some questions remain unanswered. In the studies described above, most pregnant women had mild to moderate COVID-19 symptoms, and in all cases, symptoms manifested during the third trimester of pregnancy, therefore, the time interval from clinical manifestation of SARS-CoV-2 to delivery was short. Since the placental barrier may temporarily delay the transfer of the virus from the mother to the fetus, as observed in cytomegalovirus infection, it is uncertain whether there could be a risk of vertical transmission when SARS-CoV-2 infection occurs in the first or second trimester, or when there is a long interval between clinical manifestation and delivery. Additionally, there appear to be some mechanisms by which SARS-CoV-2 could potentially cause intrauterine infection by transplacental vertical transmission. Zhao *et al.* demonstrated that angiotensin-converting enzyme 2 (ACE2), which was recently identified as the putative surface receptor of sensitive cells for SARS-CoV-2[6], is expressed in the human placenta[7]. This opens up the possibility of SARS-CoV-2 spreading transplacentally through ACE2. In addition, damage to the placental barrier caused by severe maternal hypoxemia in women with COVID-19 could potentially lead to vertical transmission of SARS-CoV-2 causing intrauterine infection.

Most recently, two studies explored the possibility of vertical transmission of SARS-CoV-2 in a combined total of seven affected pregnancies, by testing for SARS-CoV-2-specific antibodies (immunoglobulin G (IgG) and immunoglobulin M (IgM)) in neonatal serum samples using recently developed automated chemiluminescence immunoassays[8,9]. Based on the detection of anti-SARS-CoV-2 IgM antibodies in blood samples obtained following birth from three neonates, the two studies concluded that SARS-CoV-2 could be transmitted *in utero*. However, in all three neonates, pharyngeal swab samples were negative for SARS-CoV-2 RNA and testing of cord-blood and placental samples was not performed thus there was no direct evidence of infection. Of note, the sensitivity and specificity of the immunoassays used in the two studies have not been evaluated extensively[10]. Furthermore, it is well known that IgM assays are prone to false-positive results[10].

When using specific IgG and IgM antibodies as a method to detect a viral infection, it is important to

observe the kinetic changes of the antibodies. Zeng *et al.* did not evaluate the dynamic changes of anti-SARS-CoV-2 IgM and IgG antibodies in the neonates[8]. In the study of Dong *et al.*, the observed decline of anti-SARS-CoV-2 IgG and IgM levels from 140.32 AU/mL (normal range is 0–10 AU/mL) and 45.83 AU/mL (normal range is 0–10 AU/mL), respectively, at 2 h after birth, to 69.94 AU/mL and 11.75 AU/mL, respectively, at 14 days of age, is not consistent with the typical profile of the body's antibody response to acute viral infection[9]. As the half-life of IgG antibodies is around 21–23 days and the time lag between the development of anti-SARS-CoV-2 IgM antibodies and the production of IgG antibodies is about 1 week[11,12], the rapid decline $((140.32 - 69.94)/140.32 = 50\%)$ of anti-SARS-CoV-2 IgG antibody level in the infant within 14 days, in addition to the decline in anti-SARS-CoV-2 IgM antibody level, strongly indicates that the neonatal anti-SARS-CoV-2 IgG antibodies were derived transplacentally from the mother and their production was not actively induced by the presumed neonatal infection. In our opinion, these two studies do not provide concrete evidence to prove that SARS-CoV-2 infection can be acquired *in utero*.

In a cohort study by Zeng *et al.*[13], three of 33 (9%) infants were diagnosed with neonatal early-onset infection with SARS-CoV-2 based on positive qRT-PCR result in two consecutive nasopharyngeal and anal swab samples obtained on day 2 and day 4 of age. Though strict infection control and prevention measures were implemented during the delivery, the possibility of postpartum neonatal infection cannot be completely excluded because of the delay in testing. All three infants tested negative for SARS-CoV-2 RNA on day 6 ($n = 2$) or 7 ($n = 1$) of age[13]. Whether neonatal SARS-CoV-2 infection has the same virological profile as that of adult infection requires further investigation.

High-quality research is needed to elucidate whether SARS-CoV-2 can be transmitted *in utero* from the mother to the fetus. First, we propose that cohort studies evaluating the risk of fetal adverse outcome, including structural malformation, miscarriage and fetal growth restriction, in pregnant women with COVID-19 contracted during the first or second trimester are essential in investigating whether vertical transmission of SARS-CoV-2 can occur. Second, collection of appropriately matched biological samples immediately after delivery, using aseptic technique, from pregnant women with COVID-19 is important to help determine whether SARS-CoV-2 can be transmitted vertically. Biological samples should include cord blood, placental tissue, amniotic fluid and amnion–chorion interface swab. Though we do not assume that the fetus can acquire the virus through the respiratory route, we believe that neonatal pharyngeal swab is also a suitable biological sample for the detection of SARS-CoV-2 RNA, as the virus is detectable in the upper airway because it is propagated proximally by epithelial cilia of the respiratory tract. In the event that a pregnant woman with COVID-19 experiences a miscarriage, testing of the miscarried fetus and placenta for SARS-CoV-2 should be undertaken, if possible. Third, in addition to testing for SARS-CoV-2 RNA by qRT-PCR, serological tests could be an important supplement to help clarify the question of vertical transmission of SARS-CoV-2. However, longitudinal follow-up of infants born to women with COVID-19 during pregnancy is required. For example, if biological samples collected immediately after birth are negative for SARS-CoV-2 RNA, but the newborn tests positive for IgM and IgG antibodies against SARS-CoV-2, longitudinal follow-up of the IgG antibody concentrations in the infant is required. If the IgG antibodies in the infant become negative within 6 months, the possibility of intrauterine infection can be ruled out, and if the IgG antibodies in the infant persist till the age of 18 months or beyond, the diagnosis of congenital infection can be confirmed after excluding the possibility of infection during infancy.

In conclusion, there is currently no concrete evidence of intrauterine vertical transmission of SARS-CoV-2, but further high-quality research is needed. Virological and serological evidence is valuable to clarify this issue, however, the study design should be scientifically sound and reliable assays should be used, and longitudinal follow-up of infants for 6–18 months after birth is essential to draw reliable conclusions when serological results are used.

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