Definition and categorization of the timing of mother-to-child transmission of SARS-CoV-2

Scientific brief

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Introduction

Increasing numbers of pregnant women with COVID-19 are being reported globally *(1)*, and the potential for mother-to-child transmission (vertical transmission) of SARS-CoV-2, either *in utero*, intrapartum or in the early postnatal period is of concern. In general, respiratory viruses, like SARS-CoV-2, are not easily transmitted *in utero*, with no evidence for *in utero* transmission of other respiratory coronavirus infections (SARS-CoV or MERS-CoV) and only few case reports for other respiratory pathogens like influenza *(2)*.

While most neonates born to infected women test negative for SARS-CoV-2, one review found that 1.9% (95/4907) of neonates tested positive at age 24 hours or less *(3)*[1]. Neonates present largely with symptoms which are not severe *(4, 5)*. At present, the extent to which SARS-CoV-2 vertical transmission occurs, and timing of such transmission, is unclear. Indeed, determining infection of the neonate, and when it occurs, has been challenging. Although two categorization systems have been proposed *(6, 7)*, there is a lack of standardized international consensus definitions. Such consensus definitions are key to enable comparison of data across studies, and to determine potential interventions to improve clinical outcomes.

Methods

This scientific brief was prepared based on results of evidence synthesis and a WHO expert consultation. The WHO COVID-19 LENS (Living Evidence Synthesis) working group consolidated available evidence, based on rapid reviews of the literature and results of a living systematic review on pregnancy and COVID-19 (up to October 7, 2020)(3), on potential mechanisms of vertical transmission of infectious pathogens, feasibility of vertical transmission of SARS-CoV-2, data related to interpretation of positive SARS-CoV-2 virologic and serologic neonatal tests, lessons from diagnosis of other congenital infections, and existing proposed definitions to classify timing of vertical transmission of SARS-CoV-2 (6, 7). WHO convened a multidisciplinary, international panel of experts between October and November 2020 to review the evidence and propose a consensus initial classification system for the timing of vertical transmission of SARS-CoV-2 (Annex 1). The panel included experts in obstetrics, neonatology, paediatrics, epidemiology, virology, infectious disease, congenital infections, and placental pathology. The selection of the panel ensured geographic representation, gender balance, and no important conflicts of interest, in accordance with WHO standard procedures.

Review of the evidence

Mechanisms of vertical transmission of infectious pathogens

In utero transmission can occur through the haematogenous route, or more rarely the ascending route *(2)*. Most pathogens transmitted *in utero* are those in which systemic (bloodstream) infection occurs in a pregnant woman to permit the

[1] Results up to November 29, 2020. Regular updates of the results of this living systematic review before peer-review will be published on a dedicated website (https://www.birmingham.ac.uk/research/whocollaborating-centre/pregcov/index.aspx)

pathogen to access the placenta. Once the pathogen reaches the placenta, it must cross the maternal-placental interface (either through infection of placental cells or through disruption of the placental barrier) to obtain access to fetal vessels, reach the fetus and cause infection *(8)*. The risk of fetal infection may increase or decrease over the course of pregnancy depending on the pathogen *(9)*.

Intrapartum transmission occurs during labour and childbirth, and requires exposure of the neonate to the infectious pathogen in maternal blood, vaginal secretions, or faeces during the birth process, and for the pathogen to be able to reach an appropriate host cell to result in infection of the neonate *(10)*.

Postnatal transmission can occur through breastfeeding, and requires infant exposure to breast milk containing an infectious pathogen, the pathogen to reach target sites in the infant through the oral/gastrointestinal route, and for the pathogen to overcome infant defence systems *(11)*. Postnatal transmission may also occur from an infected mother to her infant through respiratory or other infectious maternal secretions, or through contact with other infected caregivers or fomites *(12)*.

Feasibility of vertical transmission of SARS-CoV-2

In utero transmission: From a pathophysiologic viewpoint, *in utero* SARS-CoV-2 transmission is possible. Viraemia due to SARS-CoV-2 although infrequent (10%; 95% CI 5-18%, 200/1512 blood samples), appears to be more likely to occur in those with severe disease *(13)*. In addition, the cell-membrane associated angiotensin-converting enzyme 2 (ACE-2) receptor and transmembrane protease serine 2 (TMPRSS2) required for SARS-CoV-2 cellular entry have been identified in placental cells, although there are conflicting data related to the extent of co-expression and whether there is differential expression by gestational age *(14, 15)*. Finally, SARS-CoV-2 can be associated with vascular damage, including hyper-coagulopathy in pregnant women. In a systematic review, histopathologic placenta findings of fetal and/or maternal vascular malperfusion were seen in 35.3% (95% CI 27.7–43.0%, 53/150 cases) and 46% (95% CI 38.1–53.9%, 69/150 cases) of placentas examined, respectively *(16)*. With ischaemic injury to the placenta, SARS-CoV-2 could reach the fetus without requiring placental cell infection. ACE-2 and TMPRSS2 can be found in the human fetal lung as well as other fetal tissues *(17, 18)*. Thus, should virus reach the fetus, fetal infection is possible.

Intrapartum transmission: SARS-CoV-2 appears to rarely be detected in vaginal swabs in pregnant women (5 cases reported) *(3)*[1]. However, SARS-CoV-2 RNA shedding is frequent (43% (934/2149)) in the faeces of infected individuals *(19)*. Faecal contamination of the vaginal canal/vulva during labour and childbirth could potentially allow SARS-CoV-2 viral contamination of the neonatal oro/nasopharynx during vaginal birth *(20)*. There may also be viral contamination in the environment during labour and childbirth or immediately after birth, due to droplets and aerosols generated by infected women during active labour, as well as maternal faecal contamination of the nearby environment, particularly during vaginal birth, which can lead to viral infection by the neonate immediately following birth *(21)*. This may make it difficult to distinguish infant viral infection during passage through the birth canal from horizontal viral infection of SARS-CoV-2 in the immediate postnatal period.

Postnatal transmission: Postnatal transmission of SARS-CoV-2 appears to account for the majority of infections reported in neonates, likely representing exposure to the infected mother, other caregivers or fomites *(3, 4)*. While SARS-CoV-2 has been detected by reverse transcription polymerase chain reaction (RT-PCR)-based assays in breast milk, it appears to be uncommon and to date no replication-competent virus has been detected *(22)*. SARS-CoV-2-specific IgG, IgM and IgA have been detected in breast milk *(11, 23)*; it is unknown if these antibodies would be protective against infection in a breastfed infant. In the postnatal period, infants may be exposed to SARS-CoV-2 from an infected mother, other caregivers and/or the neonate's environment, making the source of postnatal infection, should it occur, difficult to determine.

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System for classifying timing of SARS-CoV-2 vertical transmission

The evaluation of the frequency and timing of vertical transmission of SARS-CoV-2 raises some methodological challenges. The virus is primarily transmitted through the respiratory route and respiratory samples are primarily used for diagnosis, making it difficult to differentiate *in utero* or intrapartum transmission from postnatal transmission. Based on a review of other congenital infections *(9, 24)* and what is known about modes of transmission and diagnosis of SARS-CoV-2, a number of issues were considered during the development of the classification system, as described below.

1. *Definition and timing of maternal infection:* Maternal infection is defined as per WHO COVID-19 case definitions *(25)*. There are only limited data on fetal outcomes of women who had SARS-CoV-2 in early pregnancy. There are some case reports of first or early second trimester pregnancy loss in women with symptomatic COVID-19, but several of these cases lack data on SARS-CoV-2 detection in the corresponding placenta and/or fetus *(26, 27)*. The rate of spontaneous abortion (<13 weeks gestation) in women with SARS-CoV-2 infection in the first trimester does not appear to be increased when compared to women with ongoing pregnancies (11% (11/100) vs 9.3% (12/125)) *(28)*. The few reports of amniocentesis in women with recent/recovered SARS-CoV-2 infection have not shown evidence of amniotic fluid infection *(29, 30)*. However, because the potential for *in utero* transmission with maternal infection in early pregnancy is unknown, for the diagnosis of *in utero* infection, documented SARS-CoV-2 maternal infection at any time during pregnancy is considered appropriate; for diagnosis of intrapartum and postnatal transmission, maternal infection must be diagnosed near the time of childbirth (from 14 days prior to 2 days after birth. See Annex 1).

2. *Virologic testing:* The SARS-CoV-2 RT-PCR assay detects the presence of virus genetic fragments and does not assess whether there is replicating virus. Thus, a single positive RT-PCR in a respiratory sample in a neonate may indicate either active viral replication; viral fragments acquired during passage through the birth canal or from the immediate postnatal environment; or transient superficial contamination of the neonate that does not result in actual neonatal infection *(7)*. In a report of universal SARS-CoV-2 nasopharyngeal RT-PCR screening, 2.2% (9/418) of neonates tested positive within 24 hours of birth; of those, eight had mothers with negative nasopharyngeal RT-PCR tests and no symptoms, and seven retested neonates were negative on the second test *(31)*. This illustrates the difficulty in interpreting a single positive SARS-CoV-2 RT-PCR test in neonates. Persistence of a positive test on subsequent specimens is critical to differentiate whether there is superficial contamination (resulting in a false positive test) or actual neonatal infection. Viral isolation could similarly be falsely positive due to superficial contamination. The presence of additional positive tests of normally sterile specimen types (e.g. neonatal blood, lower respiratory tract samples, cerebrospinal fluid) can provide important information to enable differentiation of contamination from neonatal infection.

3. *Serologic testing:* Due to transplacental maternal antibody transfer during the second and third trimester, IgG found in the neonate is primarily reflective of maternal antibody and hence cannot be used to diagnose *in utero* infection. Maternal IgM and IgA do not cross the placenta unless there is placental disruption and are thought to represent the fetal immune response to infection. However, the sensitivity and specificity of IgM tests vary and usually are less reliable than molecular diagnostic tests based on nucleic acid amplification and detection *(32)*. Both false negative IgM tests in infants with a variety of other congenital pathogens and false positive tests in healthy infants without infection have been reported *(9, 10)*. Thus, a positive serological test always requires confirmatory testing of a second specimen, preferably using molecular diagnostic tests to directly detect the pathogen or otherwise a later serological test. SARS-CoV-2 IgM in the neonate between birth and less than7 days after birth is assumed to represent fetal response to *in utero* infection whereas negative IgM at less than7 days followed by detection of neonatal immune response after day 7 is assumed to reflect intrapartum or early postnatal infection *(7)*.

4. *Mode of birth:* Sampling during a caesarean section, where both placenta and fetus may be delivered under sterile conditions, is less prone to contamination than through a vaginal birth, although there is still significant exposure to maternal blood during a caesarean section. For example, detection of virus by RT-PCR on the placental surface from a caesarean birth may be less likely to reflect potential contamination from maternal virus than a placenta that has been obtained via vaginal birth.

5. *Placental tissue and/or fetal tissue assays:* To definitively determine placental or fetal infection, placental or fetal tissue (as opposed to a surface swab, which can be contaminated) is needed *(10)*. In a study comparing SARS-CoV-2 detection by in situ hybridization (ISH) or immunohistochemical (IHC) assay to the gold standard of tissue quantitative SARS-CoV-2 RT-PCR, the specificity of a positive test was far higher using ISH than IHC (100% vs 53.4%)*(33)*. Additionally, identification of viral particles by electron microscopy may potentially yield false positive results *(34)*. Hence, identification of SARS-CoV-2 in placental or fetal tissue with RT-PCR or ISH assays (with appropriate positive and negative controls) is viewed as more definitive than use of IHC, microscopy, or placental swab PCR testing.
6. *Placental tissue and amniotic fluid specimens for diagnosis:* While a placental tissue or amniotic fluid specimen positive for a pathogen is viewed as diagnostic of infection in the woman, it is not necessarily diagnostic of congenital infection in the neonate and requires confirmatory testing. While SARS-CoV-2 has been reported to be detected by RT-PCR in the placenta in several case reports, the presence of virus in the placenta has not always correlated with a positive RT-PCR test in the fetus/neonate *(35, 36)*. Similarly, the finding of a pathogen in amniotic fluid alone does not necessarily correlate with fetal infection. While SARS-CoV-2 has been reported to be detected by RT-PCR in amniotic fluid in a small number of case reports, not all neonates had confirmed infection *(37, 38)*. Thus, a positive SARS-CoV-2 assay on placenta or amniotic fluid alone is not viewed as confirmatory evidence of *in utero* infection.
7. *Umbilical cord blood*: Contamination of umbilical cord blood may occur due to cross-contamination with maternal blood during sample collection, maternal blood cells entering the fetal circulation through the placenta during pregnancy, or more frequently, maternal blood cells entering the fetal circulation during labour as a result of uterine contractions *(39)*. Thus, a positive PCR in cord blood requires confirmation with either a fetal/neonatal peripheral blood sample or testing of another sterile or non-sterile sample.
8. *Viral detection in sterile vs non-sterile samples*: Viral detection in an otherwise sterile sample (e.g. neonatal blood, lower respiratory tract samples, cerebrospinal fluid) is preferred to samples from a more superficial, non-sterile sample (e.g. neonatal nasopharyngeal swab, saliva, stool) which is more likely to represent transient contamination.
9. *Timing of sample collection:* In general, definitive diagnosis of *in utero* infection requires a positive diagnostic test near the time of birth (see Annex 1) that is confirmed with a second positive specimen, while definitive diagnosis of intrapartum infection requires a negative diagnostic test near the time of birth, with a later test in the first few days after birth being positive and confirmed with a later second specimen.
10. *Persistence of the pathogen:* Persistence of a pathogen, documented through confirmatory testing of a second specimen collected within a few days (see Annex 1) of the first positive specimen, is important to be able to distinguish transient colonization, without infection, from true neonatal infection.
11. *Neonatal symptoms and signs*: SARS-CoV-2 infection in neonates may be asymptomatic; in a meta-analysis of 74 studies, 45% of 176 neonates with positive RT-PCR from a nasopharyngeal swab and/or the presence of specific IgM were asymptomatic *(4)*. Clinical manifestation, such as neonatal respiratory distress, are not specific to SARS-CoV-2 infection, particularly in preterm infants *(10)*. Therefore, neonatal symptoms and signs are not included in the classification system.

The proposed classification system to determine timing of vertical transmission of SARS-CoV-2 is thus based on three elements:

1) documented maternal infection, using the WHO COVID-19 case definitions *(25)*, anytime during pregnancy for *in utero* infection; near the time of birth for intrapartum and early postnatal infection;

2) tests to evaluate the likelihood of early *in utero* or intrapartum exposure; and

3) tests to evaluate the later exposure/persistence of the virus or virus-specific immune response in the fetus/neonate.

The timing of vertical transmission (*in utero*, intrapartum and early postnatal) is classified in mutually exclusive categories, as follows:

1) confirmed;

2) possible (evidence is suggestive but not confirmatory for infection);

3) unlikely (little support for diagnosis but infection cannot be completely ruled out); and

4) indeterminate (when tests required to define classification have not been performed).

Detailed classification system tables for classification of *in utero* transmission in the case of a live birth; *in utero* transmission in the case of fetal demise; intrapartum; and early postnatal transmission are provided in Annex 1. Annex 2 provides an overall summary of time of sample collection, types of neonatal samples and test results required to categorize the timing of infection for neonates born alive to women with documented SARS-CoV-2 infection. Annex 3 summarizes the types of samples that are required to categorize in utero infection for fetal demise in women with documented SARS-CoV-2 infection.

Related WHO recommendations

A WHO scientific brief on breastfeeding and COVID-19, published on June 23 2020, concluded that data remain insufficient to conclude that SARS-CoV-2 can be transmitted postnatally from an infected mother to her infant through breast milk and that the benefits of breastfeeding, combined with adherence to infection prevention and control measures by breastfeeding mothers, outweigh the potential risk *(11)*. WHO recommends that mothers with suspected or confirmed COVID-19 should be encouraged to initiate and continue breastfeeding *(40)*.

Limitations/ Knowledge gaps

Defining vertical transmission of SARS-CoV-2 based on reports in the literature to date has been difficult. Most reports of vertical transmission have been based on a single positive neonatal RT-PCR in an upper respiratory tract specimen, with significant variation in the timing of sample collection. The mechanism by which potential *in utero* acquired fetal infection would result in neonatal naso-or oro-pharyngeal positivity is unclear. The specificity of SARS-CoV-2 positive placental or amniotic fluid specimens alone to represent *in utero* infection is unclear, and the utility of SARS-CoV-2 IgM/IgA alone to diagnose neonatal infection is problematic given reports of positive IgM tests in asymptomatic neonates who have tested negative by nasopharyngeal RT-PCR. Thus, a combination of initial and confirmatory tests is required in the classification system to determine infection occurrence and timing.

Conclusions

At this time, there is limited evidence on the extent of SARS-CoV-2 vertical transmission and its timing, due to limitations related to the sensitivity and specificity of diagnostic testing, and lack of collection of appropriate specimens at appropriate times. This paucity of data is partly due to the lack of standardized definitions which would allow comparisons of data from different studies. The definitions proposed in this brief aim to increase our understanding of SARS-CoV-2 vertical transmission and its clinical consequences for the neonate. The classification system presented here may be updated in the future as new information becomes available.

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