Mother-to-child transmission of severe acute respiratory syndrome coronavirus 2

Ansari, Kehkashan; Kew, Tania; Allotey, John; Thangaratinam, Shakila

Title

Mother-to-child transmission of SARS-CoV-2: Review of classification systems and systematic reviews

Authors

Kehkashan Ansari[1]*, Tania Kew[2]*, John Allotey[1 3], Shakila Thangaratinam[1 4]

[1] *WHO Collaborating Centre for Global Women's Health, Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK*

[2] *Birmingham Medical School, University of Birmingham, Birmingham, UK*

[3] *Institute of Applied Health Research, University of Birmingham, Birmingham, UK*

[4] *Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK*

*Joint first author

Corresponding author:

Kehkashan Ansari

KXA088@student.bham.ac.uk

Abstract

Purpose of review: To review the various classification systems for mother-to-child transmission (MTCT) of SARS-CoV-2 and collate existing evidence on systematic reviews of MTCT of SARS-CoV-2.

Recent findings: To-date, there are three classification systems for MTCT of SARS-CoV-2, including the WHO classification developed by expert consensus, based on *in utero,* intrapartum and postnatal exposure of the babies to the virus. The systems variously classify babies tested for suspected SARS-CoV-2 infection as confirmed, probable, possible, indeterminate, and unlikely for MTCT. To-date, 68 systematic reviews have been published between December 2019 and March 2021 on SARS-CoV-2 MTCT. Most of the reviews included cases series and case reports in their pooling of data, and often used SARS-CoV-2 infection and test positivity interchangeably.

Summary: Several classification systems are available to assist in determining the timing of SARS-CoV-2 infection in new-borns. Existing reviews of MTCT are of poor quality and report variable rates of SARS-CoV-2 positivity. A high-quality systematic review is needed on the extent of confirmed vertical transmission of SARS-CoV-2, risk factors for MTCT of SARS-CoV-2, the prevalence and persistence of viral particles or immunological response in reported biological samples. Primary studies should categorise MTCT using classifications such as WHO classification system that considers the strength of the timing of classification and persistence of positivity, taking into account the sterility of the collected samples.

Introduction

Pregnant and recently pregnant women diagnosed with COVID-19 are at increased risk of severe disease (1) compared to reproductive-aged non-pregnant women with COVID-19. There are additional concerns about the potential for vertical transmission of SARS-CoV-2 from pregnant women to their offspring. Vertical transmission is defined as the transmission of an infectious pathogen from mother to child during the antenatal or intrapartum period (2,3). *In utero* transmission via the transplacental route generally requires the pathogen to circulate in the maternal bloodstream to reach the placental maternal-foetal interface (4,5). Intrapartum transmission can occur with pathogens present in the lower reproductive tract allowing direct contact of the pathogen with the infant during passage through the birth canal (e.g., group B streptococcus, human immunodeficiency virus (HIV), chikungunya virus)) (6). Breast milk transmission requires a viable infectious pathogen to be present in the milk and for the pathogen to be able to infect the infant through the oral/gastrointestinal route (e.g., HIV, cytomegalovirus (CMV)) (7). Pathogens with a primary respiratory route of infection, like SARS-CoV-2 are usually not easily transmitted *in utero* (8).

Data related to vertical transmission of SARS-CoV-2 are limited and the implications of vertical transmission on foetal development and neonatal outcomes remains to be discerned. Transplacental, intrapartum and/or breast milk transmission have been documented for a number of infectious pathogens, such as zika virus, CMV and HIV among others (4,5). In light of the known risk of vertical transmission of other infectious pathogens, there are ongoing efforts to elucidate the possibility of SARS-CoV-2 transmission from mother-to-child (MTCT). Accurate ascertainment of true infant infection through vertical transmission and timing of such transmission requires robust standardised classification systems on timing of MTCT to determine the true burden of SARS-CoV-2 MTCT. Such systems have the potential to allow for comparison of data reported across studies and facilitate development of interventions to improve clinical outcomes, including interrupting transmission.

Numerous studies, including case series and case reports, have reported possible MTCT of SARS-CoV-2 (9). Reports of detection of viral RNA in placenta, amniotic fluid, umbilical cord blood samples and breastmilk, suggest the potential for MTCT but are not by themselves proof of such transmission (10). Systematic reviews collate the available evidence to inform clinical practice and future research. In this review, we summarize the various classification systems for SARS-CoV-2 MTCT and provide an overview of the published systematic reviews on SARS-CoV-2 MTCT.

Review of classification systems for SARS-CoV-2 MTCT

There are currently three classification systems to categorise the timing of mother-to-child transmission of SARS-CoV-2 (3,11,12): The World Health Organization (WHO) expert consensus classification system, the Shah and Blumberg classifications (3,11,12). While all three are based on the type and timing of maternal and neonatal testing, they vary on the criteria used to characterize the timing of transmission (3,11,12). Broadly, all systems categorise SARS-CoV-2 MTCT into three exclusive possible modalities of *in utero*, intrapartum, and postnatal transmission.

The classification by Shah et el (11) categorises maternal and infant infection into four classifications of infant infection based on timing of infection: congenital infection with intrauterine foetal demise; congenital infection in live born neonate; neonatal infection acquired intrapartum; and neonatal infection acquired postpartum, and is further stratified by the symptom status of mother and infant. The authors did not report how they arrived at the proposed definitions, and only report that it was based upon existing evidence of perinatal infection. The classification system includes five categories indicating the strength of the classification of timing of infection: confirmed – strong evidence of infection with confirmatory microbiology; probable – strong evidence of infection but a lack of absolute proof; possible –

suggestive of infection but incomplete; unlikely – little support for diagnosis but infection cannot be completely ruled out; and not infected – no evidence infection.

The classification by Blumberg et al (12) does not consider maternal or infant symptoms, nor include categorisation by strength of the classification of timing of infection. There are two classifications of confirmed infant infection – intrauterine and combined intrapartum or early postnatal, with a third classification of superficial exposure to SARS-CoV-2 or transient viremia. Confirmed infant infection requires persistence of SARS-CoV-2 assay positivity in either infant respiratory samples or a SARS-CoV-2-specific immunologic IgM response, to confirm an initial positive test. Intrapartum and early postnatal transmission are combined, as the classification system assumes that it will be difficult to distinguish between intrapartum infection due to exposure to infected maternal blood, vaginal secretions, and/or faeces during passage through the birth canal versus infection from in the nearby environment soon after birth via respiratory route or due to direct contact with infected mother or other caregivers, or potential transmission through breast milk. The authors also make assumptions that SARS-CoV-2 may be transiently detected for up to 24 hours after birth due to superficial contamination, transient viremia, or due to neonatal resuscitation in delivery room leading to aspiration of potentially infectious secretions into infant airway (respiratory, faecal), and this transient colonization with SARS-CoV-2 will not be associated with an infant immune response indicating active infection had occurred. Except for the underlying assumptions for their classification, the authors do not report any methods on how these definitions were reached.

The WHO classification was an international consensus classification outlining definitions for determination of infant SARS-CoV-2 vertical infection and timing of such infection (3). This was driven by data obtained from the WHO COVID-19 Living Evidence Synthesis (LENS) in conjunction with a WHO expert consultation. Transmission is delineated into four main groups: *in utero* transmission in the case of a live birth; *in utero* transmission in the case of

foetal demise; intrapartum transmission; and early postnatal transmission. Diagnosis is conditional to the assessment of both *in utero* exposure and viral persistence or immune response through confirmatory testing for live new-borns. *In utero* transmission in the case of foetal demise requires evidence of SARS-CoV-2 infection in foetal tissue and specimens including the placenta or amniotic fluid. The strength of the determination of timing of SARS-CoV-2 transmission is delineated into mutually exclusive categories based on the likelihood of infection (confirmed, possible, unlikely, and indeterminate), based on results of confirmatory investigations or absent testing procedures. Sampling modalities are additionally distinguished by sterility, consisting of samples such as neonatal blood, cerebrospinal fluid, or lower respiratory secretions as sterile, and samples such as upper respiratory tract nasopharyngeal or oropharyngeal or faecal swabs as non-sterile samples, respectively (3). Features of the classification systems are summarized in Table 1.

Review of reviews on SARS-CoV-2 MTCT

From our ongoing work on living systematic reviews of COVID-19 infection in pregnancy (1,13), we identified 68 systematic reviews on SARS-CoV-2 MTCT. There was considerable overlap in the periods of literature search between the various systematic reviews, and searches covered 1 to 9 months. Review articles interchangeably (and incorrectly) used infant infection and neonatal sample SARS-CoV-2 assay positivity when reporting on rates positive tests in the neonates. The number of primary studies included in the reviews varied from 6 - 121, and the number of SARS-CoV-2 positive neonates reported ranged from 0-39, and this variation was not always explained by publication date of the review. Diagnosis of infant infection was often based on a single positive neonatal sample. A total of 66 studies were traditional systematic reviews, with 2 living systematic reviews evaluating the presence of SARS-CoV-2 specific antibodies in neonates born to infected mothers, and potential for transmission through breast milk, respectively (14,15).

The rates SARS-CoV-2 positive tests in the neonates were reported in 61 review articles, often with by pooling or meta-analysing case reports and case series along with cohort studies, which is known to produce biased estimates (16). This has the potential to exaggerate the true burden of SARS-CoV-2 infection in neonates, because of the inherent selection bias in primary studies that are case reports or series. Some reviews aggregated data on biological samples (i.e., placenta, amniotic fluid, umbilical cord blood, neonatal peripheral blood, infant nasopharyngeal samples, faecal samples, and maternal breast milk) which were reported with varying degrees of frequency and completeness in the individual primary studies included in the systematic reviews. Most primary studies did not collect appropriate specimens at appropriate times or confirm persistence of the virus in the neonate with repeat tests. Definitions of vertical transmission and neonatal test positivity were heterogeneous across the systematic reviews, and only one review (17) used a classification system to determine whether the infant SARS-CoV-2 assay positivity indicated true infant infection. Reviews varied in the outcomes reported despite often including the same primary studies. Table 2 summarizes the key characteristics of the reviews.

Potential pathways for vertical transmission of SARS-CoV-2

For *in utero* transmission of SARS-CoV-2 to occur, the pathogen should be present in the maternal blood to enable it to reach and cross the placenta and infect the foetus. SARS-CoV-2 viremia has been rarely reported and may be more common in infected individuals with severely symptomatic disease (18). The cell-membrane associated angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease serine 2 (TMPRSS2) associated with SARS-CoV-2 cell entry has been reported to be expressed in placental maternal-foetal interface cells, although co-expression may be limited, should viremia occur, placental cell infection could occur, allowing passage of the virus to the foetus. Additionally, placental disruption, possibly due to hyper-coagulopathy, could allow viral passage to the foetus without actual placental infection. ACE-2 and TMPRSS2 can be found in the foetal

lung, heart, and liver, suggesting foetal infection is possible should the virus reach the foetus (19,20).

Intrapartum transmission requires foetal or infant exposure to the pathogen during labour and delivery (ascending infection or contact with infected secretions during passage through the birth canal) and for the virus to infect the new-born (4). SARS-CoV-2 has been rarely found in vaginal fluids, but more frequently found in the faeces of infected individuals (21). Faecal contamination of the vaginal canal and nearby environment during labour and childbirth could lead to viral infection of the neonate immediately after birth, particularly during vaginal birth (22). This may make it difficult to differentiate infant viral infection from viral infection acquired during passage through the birth canal, and from infection occurred horizontally in the immediate postnatal period.

In the postnatal period, infants may be exposed to SARS-CoV-2 via various routes including, from an infected mother during maternal-infant-skin-to-skin contact, while rooming-in or breastfeeding, via other infected caregivers/family members and/or the neonate's environment, or potentially through breast milk, making the source of postnatal infection, should it occur, difficult to determine. Postnatal transmission through breastfeeding requires foetal/infant exposure to infectious pathogen in breast milk and infection of the infant through the oral/gastrointestinal route. SARS-CoV-2 has been rarely detected by RT-PCR in breast milk, is often only transiently detected, and to date, no replication competent virus has been detected (15). Additionally, SARS-CoV-2-specific immunoglobulin (IgG, IgM, and IgA) has been detected in breast milk (23); whether the presence of SARS-CoV-2 antibody in breast milk is protective against infection in the infant is not known.

SARS-CoV-2 test positivity in babies
A positive SARS-CoV-2 RT-PCR in the infant can indicate active infection with replicating virus, the presence of residual non-infectious viral gene fragments ('dead virus'), or

contamination, where the virus is present on a surface (skin, mucus membrane) but not causing actual infection in the infant. A positive RT-PCR in a normally sterile tissue (e.g., cord blood, neonatal blood, bronchoalveolar lavage) is more likely to indicate infection than a positive test in non-sterile samples (neonatal upper respiratory or faecal samples). False-negative RT-PCR tests can occur with inappropriate sample collection, handling, and transport, as well as stage of disease (e.g., if the specimen is obtained when viral load is very low) (24). Persistent RT-PCR positivity is needed in determining that an active replicating infection is present, but repeat testing is rarely carried out in studies. Therefore, detection of the virus on surface (skin, nasopharyngeal specimen) at a single time point may represent transient contamination not infection, and a single positive test in babies should not be reported as SARS-CoV-2 infection.

Conclusion

International classifications should be routinely used to determine and classify timing of SARS-CoV-2 MTCT in studies that report on SARS-CoV-2 testing of babies. The WHO classification system developed by international consensus, which combines the strength of classification of timing of transmission, with the persistence of positivity, and considers the sterility of the evaluated samples is preferred. Clinicians and parents should be aware that a single test with SARS-CoV-2 positivity in new-borns is not necessarily indicative of true neonatal infection. Primary studies on MTCT should obtain relevant maternal samples for SARS-CoV-2 testing when possible, including vaginal fluid, amniotic fluid, placental, cord blood; and neonatal blood, respiratory and faecal samples for SARS-CoV-2 virologic testing, as well as blood for SARS-CoV-2 IgM testing should be obtained at multiple timepoints to confirm viral persistence/immune response, starting at or near birth. High quality systematic reviews are needed to synthesize available evidence to determine the extent to which vertical transmission of SARS-CoV-2 occurs and obtain precise estimates of the rates and risk factors of neonatal positivity, including evaluating the timing and routes of possible transmission of the virus using the WHO standardised definition and categorisation system.

Key points

- Amongst the various classifications for SARS-CoV-2 MTCT, the WHO classification provides detailed and comprehensive information needed to accurately classify the babies born to mothers with SARS-CoV-2 infection and suspected to be infected.

- Systematic reviews will need to take into account previous evidence published by other systematic reviews to minimize research waste and their qualities need to be improved.

- Large cohort studies are needed to ascertain the rates of SARS-CoV-2 MTCT.

Acknowledgements: None

Financial support and sponsorship: None

Conflicts of interest: Shakila Thangaratinam and John Allotey are members of the WHO COVID-19 LENS (Living Evidence Synthesis) working group. The other authors report no conflict of interest.

References

1. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020 Sep 1;

2. RCOG. Coronavirus (COVID-19) Infection in Pregnancy. Royal College of Obstetricians and Gynaecologists. 2021.

3. WHO team. Definition and categorization of the timing of mother-to-child transmission of SARS-CoV-2. World Health Organization. 2021.

4. Mahyuddin AP, Kanneganti A, Wong JJL, Dimri PS, Su LL, Biswas A, et al. Mechanisms and evidence of vertical transmission of infections in pregnancy including <scp>SARS-CoV</scp> -2s. Prenatal Diagnosis. 2020 Dec 4;40(13).

5. Arora N, Sadovsky Y, Dermody TS, Coyne CB. Microbial Vertical Transmission during Human Pregnancy. Cell Host & Microbe. 2017 May;21(5).

6. Patras KA, Nizet V. Group B Streptococcal Maternal Colonization and Neonatal Disease: Molecular Mechanisms and Preventative Approaches. Frontiers in Pediatrics. 2018 Feb 22;6.

7.	Blackshaw K, Valtchev P, Koolaji N, Berry N, Schindeler A, Dehghani F, et al. The risk of infectious pathogens in breast-feeding, donated human milk and breast milk substitutes. Public Health Nutrition. 2021 May 16;24(7).

8.	Schwartz DA, Dhaliwal A. Infections in Pregnancy With COVID-19 and Other Respiratory RNA Virus Diseases Are Rarely, If Ever, Transmitted to the Fetus: Experiences With Coronaviruses, Parainfluenza, Metapneumovirus Respiratory Syncytial Virus, and Influenza. Archives of Pathology & Laboratory Medicine. 2020 Aug 1;144(8).

9.	Kotlyar AM, Grechukhina O, Chen A, Popkhadze S, Grimshaw A, Tal O, et al. Vertical transmission of coronavirus disease 2019: a systematic review and meta-analysis. American Journal of Obstetrics and Gynecology. 2021 Jan;224(1).

10.	Groß R, Conzelmann C, Müller JA, Stenger S, Steinhart K, Kirchhoff F, et al. Detection of SARS-CoV-2 in human breastmilk. The Lancet. 2020 Jun;395(10239).

11.	Shah PS, Diambomba Y, Acharya G, Morris SK, Bitnun A. Classification system and case definition for SARS-CoV-2 infection in pregnant women, fetuses, and neonates. Acta Obstetricia et Gynecologica Scandinavica. 2020 May 21;99(5).

12.	Blumberg DA, Underwood MA, Hedriana HL, Lakshminrusimha S. Vertical Transmission of SARS-CoV-2: What is the Optimal Definition? American Journal of Perinatology. 2020 Jun 5;37(08).

13.	Yap M, Debenham L, Kew T, Chatterjee SR, Allotey J, Stallings E, et al. Clinical manifestations, prevalence, risk factors, outcomes, transmission, diagnosis and treatment of COVID-19 in pregnancy and postpartum: a living systematic review protocol. BMJ Open. 2020 Dec 2;10(12).

14.	Bwire GM, Njiro BJ, Mwakawanga DL, Sabas D, Sunguya BF. Possible vertical transmission and antibodies against SARS-CoV-2 among infants born to mothers with COVID-19: A living systematic review. Journal of Medical Virology. 2021 Mar 10;93(3).

15.	Centeno-Tablante E, Medina-Rivera M, Finkelstein JL, Rayco-Solon P, Garcia-Casal MN, Rogers L, et al. Transmission of SARS-CoV-2 through breast milk and breastfeeding: a living systematic review. Annals of the New York Academy of Sciences. 2021 Jan 28;1484(1).

16.	Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ Evidence-Based Medicine. 2018 Apr;23(2).

17.	Raschetti R, Vivanti AJ, Vauloup-Fellous C, et al. Neonatal SARS-CoV-2 Infections: Systematic Review, Synthesis and Meta-Analysis of Reported Cases. SSRN Electronic Journal. 2020;

18.	Andersson MI, Arancibia-Carcamo C v., Auckland K, Baillie JK, Barnes E, Beneke T, et al. SARS-CoV-2 RNA detected in blood products from patients with COVID-19 is not associated with infectious virus. Wellcome Open Research. 2020 Oct 12;5.

19.	Faure-Bardon V, Isnard P, Roux N, Leruez-Ville M, Molina T, Bessieres B, et al. Protein expression of angiotensin-converting enzyme 2, a <scp>SARS-CoV</scp> -2-specific receptor, in fetal and placental tissues throughout gestation: new insight for perinatal counseling. Ultrasound in Obstetrics & Gynecology. 2021 Feb;57(2).

20.	Li M, Chen L, Zhang J, Xiong C, Li X. The SARS-CoV-2 receptor ACE2 expression of maternal-fetal interface and fetal organs by single-cell transcriptome study. PLOS ONE. 2020 Apr 16;15(4).

21. Khalil A, Kalafat E, Benlioglu C, O'Brien P, Morris E, Draycott T, et al. SARS-CoV-2 infection in pregnancy: A systematic review and meta-analysis of clinical features and pregnancy outcomes. EClinicalMedicine. 2020 Aug;25.

22. Hermesch AC, Horve PF, Edelman A, Dietz L, Constant D, Fretz M, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Environmental Contamination and Childbirth. Obstetrics & Gynecology. 2020 Oct;136(4).

23. Demers-Mathieu V, Do DM, Mathijssen GB, Sela DA, Seppo A, Järvinen KM, et al. Difference in levels of SARS-CoV-2 S1 and S2 subunits- and nucleocapsid protein-reactive SIgM/IgM, IgG and SIgA/IgA antibodies in human milk. Journal of Perinatology. 2021 Apr 1;41(4).

24. Bahreini F, Najafi R, Amini R, Khazaei S, Bashirian S. Reducing False Negative PCR Test for COVID-19. International Journal of Maternal and Child Health and AIDS (IJMA). 2020 Oct 8;9(3).