Research article

The transmission of SARS-CoV-2 from mother to child – anxieties versus reality: a systematic review and discussion

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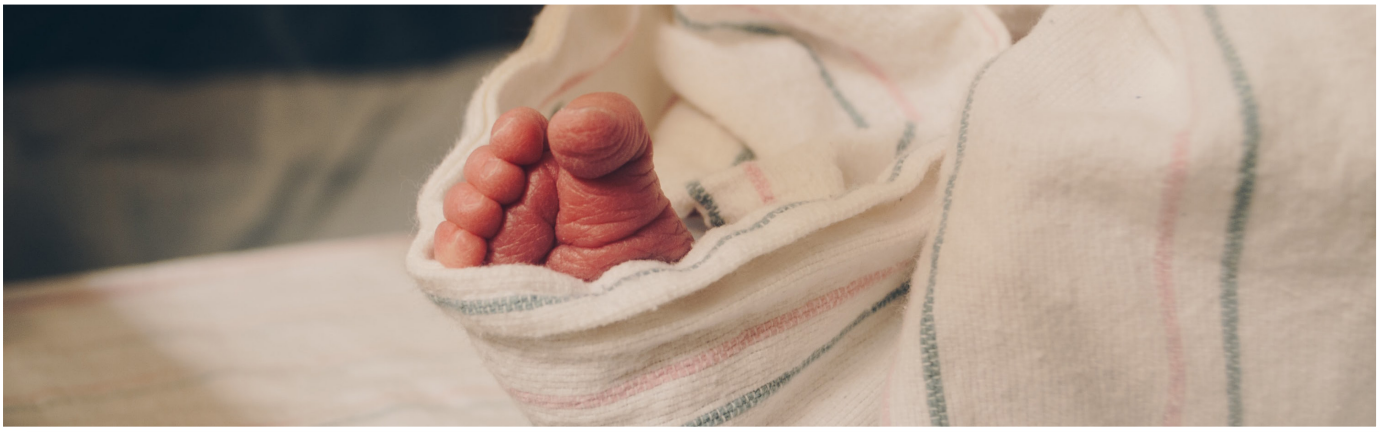

Abstract

Introduction
Increasing levels of anxiety have been observed among pregnant women surrounding vertical transmission of SARS-CoV-2 and the subsequent effects on the fetus. Therefore, the primary aim of the review is to summarise the available literature suggesting vertical transmission of SARS-CoV-2 with the secondary aim being the outcomes of neonates infected with SARS-CoV-2.

Methods
A MedLine search was conducted, 415 articles were screened based on title and abstract, 26 articles were assessed for eligibility and eight articles were critically analysed.

Results
The eight articles included a collective total of 988 confirmed SARS-CoV-2 positive women and 822 neonates, who were tested for infection. Twenty-four neonates had a positive SARS-CoV-2 test after birth and therefore the rate of vertical transmission is approximately 2.55%. 75% of articles did not observe an increase in neonatal morbidity.

Conclusion
The risk of vertical transmission is negligible and adverse outcomes in infected neonates are rarely seen. Maternal SARS-CoV-2 infection has been linked to preterm delivery. Antibodies may be transferred transplacental or via breastmilk.

Abbreviations

ACE2 - Angiotensin-converting enzyme receptor 2
CMV - Cytomegalovirus
HSV - Herpes simplex virus
NICU - Neonatal intensive care unit
PCR testing - Polymerase chain reaction testing
SARS-CoV-2 - Severe acute respiratory syndrome coronavirus 2
UKOSS - United Kingdom Obstetric Surveillance System
Viral RNA - Viral ribonucleic acid

Introduction

504 million cases of novel coronavirus (COVID-19) have been confirmed worldwide since the discovery of the virus in China in December 2019.[1] The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, RNA positive virus. The Spike (S) protein, which assembles the viral envelope, assists with viral entry to host cells and replication. SARS-CoV-2 is transmitted by person-to-person contact via respiratory droplets, direct contact and airborne particles and the virus enters the respiratory tract cells using the angiotensin-converting enzyme receptor 2 (ACE2).[2] The most common symptoms of this virus include dyspnoea, continuous cough, pyrexia and myalgia, with approximately 5% of patients developing acute respiratory distress syndrome and becoming critically unwell.[3]

Vertical transmission involves virus RNA crossing the placental barrier and entering fetal circulation. Transplacental transmission of viruses such as cytomegalovirus virus (CMV) has been recorded; CMV may impede placental perfusion and cytotrophoblast invasion.[4] The transmission rate of CMV is approximately 30%.[5] Herpes simplex virus can be transmitted in utero (5%), during delivery (85%) or postnatally (10%) via direct contact with an orolabial lesion.[6] Vertical transmission of SARS-CoV-2 is controversial, however, the ACE2 receptor is expressed on the human placenta, ovary, uterus and vagina and therefore, a theoretical possibility of mother-to-child transmission exists.[7]

Pregnancy has been shown to cause a more severe respiratory disease in patients infected with SARS-CoV-2. Pre-eclampsia and perinatal death have been associated with maternal COVID-19 infection, with the most adverse pregnancy outcome being preterm birth and fetal growth restriction due to microemboli at the fetomaternal exchange interface.[8] Additionally, the immunocompromised status during pregnancy may increase the susceptibility of pregnant women to COVID-19 infection.[9]

Personal informal discussions with pregnant women reveal high levels of anxiety regarding the potential for in utero transmission of the virus. Due to the potential adverse outcomes of SARS-CoV-2 for neonates, understanding the role of vertical transmission during pregnancy is imperative. Therefore, the primary aim of this literature review is to assess and summarise the current available evidence, enabling a conclusion to be drawn regarding the role of vertical transmission of SARS-CoV-2 from mother to neonate. The secondary aim of this project is to understand the neonatal outcomes of infants born to mothers infected with SARS-CoV-2.

Methods

To investigate the risk of vertical transmission from infected mothers to their child and the subsequent neonatal outcomes, a search for published articles was conducted electronically using Medline. An advanced search was run using subject heading searching which was then supplemented with text-word searching. The three main themes included in the search were 'SARS-CoV-2', 'viral transmission' and 'mother-to-child'; search terms relevant to these themes were included and a full list of search terms can be viewed in **Appendix 1**. Initially, 415 articles were found, and articles were screened based on their title and abstract. Articles were considered if they included vertical transmission as their primary aim whilst articles were not included if the research trial was incomplete or if the article consisted of secondary data, such as systematic reviews. The inclusion and exclusion criteria are summarised in the PRISMA diagram (**Figure 1**). 26 full text articles were assessed for eligibility and subsequently reduced to eight articles which were critically analysed.

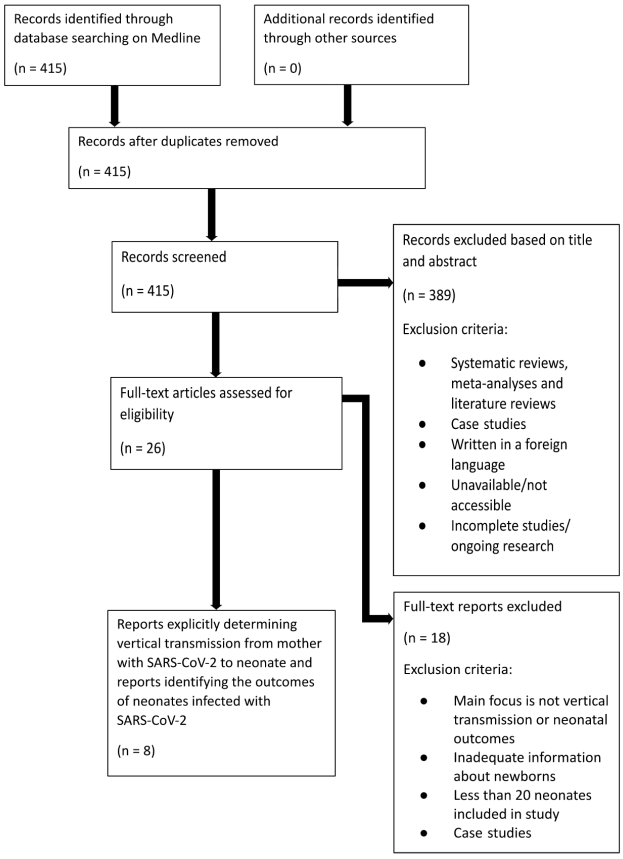

Figure 1. PRISMA diagram summarising exclusion criteria for article selection.

Results

The eight articles have been summarised in **Table 1**, where the presence of vertical transmission and neonatal outcome has been assessed. Fifty per cent of the articles noted the presence of vertical transmission. A retrospective study by Halici-Ozturk et al investigated the potential for vertical transmission in early pregnancy by analysing placental biopsies and samples from abortion material. 210 women with an early pregnancy loss were included in the study and 24 women were positive for COVID-19. There was no evidence of SARS-CoV-2 in any samples taken.[10]

Zhang et al completed a large prospective study in New York involving 142 neonates born to SARS-CoV-2 positive mothers, and of the 138 tested for COVID-19 via a nasopharyngeal swab, one neonate tested positive. This neonate was delivered via Caesarean section and the infection was likely due to vertical transmission. Two more neonates tested positive after seven days, this infection was likely acquired at home. Therefore, this study demonstrated a vertical transmission rate of 0.72%. All three neonates were asymptomatic. This study also investigated the placental histopathology and found no pathologies when compared with placentas from non-infected mothers.[11]

Similarly, Di Guardo et al took cord blood, amniotic fluid and placental samples from 145 pregnant women with SARS-CoV-2 in Italy during a retrospective analysis. Seven of 145 (5%) neonates tested positive for SARS-CoV-2 on PCR testing. Di Guardo also found that there was a higher percentage of term birth compared to preterm birth (62% vs 38%). There were 10 neonatal deaths in total (6%), two of which tested positive for SARS-CoV-2 after death.[12]

A large retrospective cohort analysis in New York by Dumitriu et al supports the previously mentioned studies by Zhang et al and Di Guardo et al. One hundred and one neonates born to 100 COVID-19 positive mothers were testing during this study using nasopharyngeal swabs. Two neonates (2%) had positive results, one born via vaginal delivery and the other via Caesarean; both were asymptomatic. All neonates born to COVID-positive mothers remained well at follow-up appointments.[13]

Contrasting with previously mentioned studies, a retrospective cohort analysis in Jamaica by Moreno et al tested 21 neonates born to 19 mothers who were infected with SARS-CoV-2. Samples were taken using nasopharyngeal swabs 24 hours after birth; these were negative in 100% of neonates and there was a 0% rate of vertical transmission. Unlike in previously mentioned studies, where there was no increase in neonatal morbidity, 61.9% of neonates in this study were admitted to NICU. The most common cause of NICU admission was prematurity. No mechanical ventilation, sepsis or neonatal mortality were observed. Preterm labour occurs in eight out of 21 (38.1%) births and seven (33.3%) neonates had a low birthweight.[14]

Furthermore, Yan et al had similar findings to Moreno et al. This study involved 116 COVID-19 positive women in a retrospective cohort study in China. Sixty-five women were laboratory confirmed COVID-19 cases and 51 were clinically diagnosed. Ninety-nine out of 116 infected women delivered and 86 out of 100 (86%) neonates were tested for SARS-CoV-2 using pharyngeal swab; the results were 100% negative; the vertical transmission rate was 0%. Amniotic fluid and cord blood was also taken from 10 neonates and the samples were 100% negative for COVID-19. No viral nucleic acid was detected in vaginal secretions and breast milk samples. Of the births observed, 21.2% were preterm, 6.1% before 37 weeks. Forty-seven out of 100 (47%) neonates received further treatment in NICU and there was one neonatal death.[15]

A prospective study by Liu et al based in China involved 48 pregnant women: 15 confirmed cases of COVID-19, 17 suspected cases and 16 women without COVID-19. Neonates were separated from mother after birth and samples from amniotic fluid, placental swab, gastric lavage fluid, neonatal serum, throat swab and faeces were tested

using PCR. All 48 neonates (100%) had a negative PCR swab, no neonates showed COVID-19 symptoms and there were no differences found between samples taken from the neonates born to infected mothers and those born to mothers negative for COVID-19. The mean gestational age of neonates born to confirmed mothers was on average one week earlier than the neonates born to mothers without SARS-CoV-2 (37.41 weeks).[16] These findings are similar to previously mentioned studies by Moreno et al and Yan et al.

Contrasting with this, Knight et al completed a large prospective cohort study in the UK using the UK Obstetric Surveillance System (UKOSS). Here, 427 pregnant women with COVID-19 were included and 265 neonates were tested using nasopharyngeal swab or blood samples. Twelve out of 265 (4.5%) neonates showed a positive PCR result. Details regarding the outcomes of neonates with COVID-19 were not recorded, however one neonate of the 12 was admitted to intensive care.[17]

Discussion

Across all studies included in this review, a total of 988 women with confirmed SARS-CoV-2 were included and 822 neonates were tested for infection. Shah et al developed a classification system whereby congenital infection in live born neonates is confirmed by PCR detection of viral RNA in the umbilical cord or neonatal blood within 12 hours of birth or in amniotic fluid prior to membrane rupture.[18]

> *Twenty-four neonates had a positive PCR SARS-CoV-2 swab test after birth, indicating the vertical transmission rate is approximately 2.55%.*

There was some conflict between studies with regards to the outcomes of infected neonates. Di Guardo et al and Knight et al both described a higher rate of vertical transmission than other studies, with Di Guardo et al reported mortality in 6% of neonates. most commonly due to acute foetal distress. Despite finding a 0% rate of vertical transmission, 61.9% of infants were admitted to NICU in the study by Moreno et al. Prematurity and low birthweight were the most common causes for NICU admission in the study. A limitation of Di Guardo's study is that only 21 neonates were included, whilst other studies focused on many more participants.

Five of the eight studies included in this review have used samples such as cord blood or amniotic fluid, rather than solely nasopharyngeal swabs to test vertical transmission. It is suggested that vertical transmission should be tested for using placental biopsies, whilst vaginal secretions can be used to detect intrapartum transmission.[19] Therefore, the studies including cord blood and amniotic fluid samples may be a more reliable example of vertical transmission than those which exclusively included pharyngeal swab testing. Furthermore, it is difficult to distinguish if the neonate was infected with COVID-19 in utero, during birth or post-partum as the neonate was not isolated from the mother after birth in most studies. Wei et al separated the neonates from mothers at birth for 14 days and no neonates tested positive for COVID-19. The other seven studies had neonates roomed in and breast fed by mothers. In all studies nasopharyngeal swab testing occurred within 48 hours of birth, however, Zhang et al found two neonates had a positive test after seven days post-partum – it is likely these were infected via droplet spread rather than in utero.

A study by Schwartz et al investigated the placentas from six neonates who were suspected of acquiring COVID-19 via transplacental transmission and all six placentas demonstrated chronic histiocytic intervillositis and necrosis of the syncytiotrophoblast (inflammatory change at the placental interface). These placental findings were similar to the placentas of stillborn infants and contrasted to healthy placentas from non-infected neonates. Chronic histiocytic intervillositis and syncytio necrosis are associated with poor obstetric outcomes including miscarriage, intrauterine growth restriction and preterm delivery.[20] Microvasculopathy, which may be due to altered coagulopathy seen in SARS-CoV-2 and pregnancy, has been demonstrated in placentas taken from women with SARS-CoV-2 in a separate study. This resulted in maternal and fetal malperfusion, however no transplacental transmission was observed, despite the detection of viral RNA in placental tissue and umbilical cord.[21] On the other hand, Zhang examined 101 placentas from positive mothers and did not find an increase of placental pathologic features when compared to negative mothers.

The role of antibodies in vertical transmission in the above studies is unclear. A study by Flannery et al detected IgG antibodies in the cord blood of 87% of neonates born to asymptomatic women and women with severe symptoms. IgM was not detected in cord blood. Therefore, Flannery et al suggest that transplacental transfer of SARS-CoV-2 IgG antibodies assist in neonatal COVID-19 immunity.[22] The transfer of antibodies in breastmilk has also been investigated: Pace et al analysed milk samples from 18 women following SARS-CoV-2 diagnosis and found that they did not contain SARS-CoV-2. 76% of milk samples from infected mothers contained IgA whilst 80% contained IgG, therefore breastmilk is a beneficial source of SARS-CoV-2 antibodies.[23] The study by Pace et al therefore supports the WHO guidance to continue breastfeeding during maternal COVID-19 illness.[24] The ability for infected mothers to breastfeed was a large concern raised during discussions with pregnant women, therefore, understanding the role of antibody transfer in breastmilk is useful to provide advice for women who are considering breastfeeding.

Filiz Halici-Ozturk et al was the only study to investigate early transmission of SARS-CoV-2 as most of the other available literature included mothers in their third trimester. No evidence of transmission was detected in this study, however, more research must be done to determine the effect of infection in early versus late pregnancy. A further limitation of the literature discussed was that most studies were retrospective and only Liu et al included a case group for comparison. Studies with a strong suggestion for vertical transmission were most commonly case studies, which are less reliable than large cohort studies and therefore not included in this literature review.

Discussions amongst pregnant women also reveal a large concern surrounding preterm labour. Zhang et al did not find an increase in preterm delivery, however, Di Guardo et al and Yan et al observed preterm labour in 38% and 21.2% of pregnancies respectively, suggesting higher rates of preterm delivery than the national average, which was 7.8% in the UK in 2019.[25] Dumitriu indicated that severe SARS-CoV-2 is associated with a preterm labour of one week earlier on average than babies born to mothers with mild SARS-CoV-2. Preterm labour may be a result of previously mentioned placental changes. Yan et al also recorded iatrogenic preterm birth, fetal distress, poor obstetric history and preeclampsia as causes of preterm birth in their study. Despite finding the risk of any preterm birth before 37 weeks is increased in COVID-19 infection, their study did not indicate there is an increased risk of spontaneous preterm birth before 37 weeks.

Conclusions

Informal discussions with women reveal anxieties experienced during pregnancy surrounding the health of their unborn neonate and the potential for in utero infection, leading to distress and, in some cases, social isolation. However, vertical transmission is a very rare complication of SARS-CoV-2 infection in late pregnancy, with a transmission rate of approximately 2.55%. Infected mothers may be at increased risk of preterm delivery and placental abnormalities, although the evidence regarding placental abnormalities is conflicting.

Author	Study Location	Duration	Study Design	Total Number of Pregnant Women and mean gestational age	Number of Pregnant Women with SARS-CoV -2	Total Number of neonates	Number of Neonates positive for SARS-CoV -2 after birth	Samples taken	Vertical Transmission	Vertical Transmission Confirmed By	Neonatal Outcome
Halici-Ozturk et al	Turkey	September – December 2020	Prospective Study	210 women with pregnancy loss before 24 weeks of gestation	24	NA (early pregnancy loss)	NA (early pregnancy loss)	Maternal Nasopharyngeal Swabs Placental biopsy and samples from abortion material	No (0%)	SARS-CoV-2 Quantitative RT-PCR	NA (pregnancy loss) No difference between SARS-CoV-2 positive and negative mothers
Zhang et al	New York	March – August 2020	Prospective Study	219	142	143	1/138 (tested after birth) (2 more positive after 7 days)	Nasopharyngeal Swabs of Mother and child Placental Histopathology	Yes (0.72%)	SARS-CoV-2 Quantitative RT-PCR	Infected babies were asymptomatic
Di Guardo et al	Italy	March – July 2020	Retrospective Analysis	145 (36 weeks)	145	145	7	Amniotic fluid, placenta samples Cord blood	Yes (5%)	SARS-CoV-2 Quantitative RT-PCR	2 deaths among covid positive neonates
Dumitriu et al	New York	March – April 2020	Retrospective Cohort analysis	100	100	101	2	Nasopharyngeal swab for mother and neonate	Yes (2%)	SARS-CoV-2 Quantitative RT-PCR	Both infected babies were asymptomatic
Moreno et al	Jamaica	March – April 2020	Retrospective observational study	19 (37 weeks)	19	21	0	Nasopharyngeal swabs on mother and neonate	No (0%)	SARS-CoV-2 Quantitative RT-PCR	61.9% admitted to NICU No neonatal mortality
Yan et al	China	January – March 2020	Retrospective Cohort Study	116 (38 weeks)	116 (99 delivered)	100	0	Maternal and neonatal Nasopharyngeal swab. Amniotic fluid, cord blood, vaginal secretion and breast milk samples.	No (0%)	SARS-CoV-2 Quantitative RT-PCR	47% admitted to NICU No neonatal mortality
Liu et al	China	January – March 2020	Prospective Study	48	15 confirmed 17 Suspected	48	0	Samples from amniotic fluid, placental swab, gastric lavage fluid, neonatal serum, throat swab and faeces Oropharyngeal and faeces swab	No (0%)	SARS-CoV-2 Quantitative RT-PCR	No difference in neonatal outcomes in those born to mothers positive for COVID19 and those born to negative mothers
Knight et al	United Kingdom	March – April 2020	Prospective Cohort Study using UKOSS	427 (34 weeks)	427	265	12	Nasopharyngeal swab or blood for mothers and neonates	Yes (4.5%)	SARS-CoV-2 Quantitative RT-PCR	1 infected neonate was admitted to a neonatal unit 25% neonates admitted to NICU

Table 1. Table of results summarising the eight articles analysed for vertical transmission and neonatal outcomes

> *Further studies should be conducted to determine if preterm delivery is truly an adverse outcome of antenatal COVID-19 infection.*

Neonates infected with SARS-CoV-2 are most commonly asymptomatic and there is little evidence for increased neonatal morbidity. Vertical transmission is not affected by mode of delivery. Breastfeeding is safe and may provide antibodies against SARS-CoV-2. Further studies using more samples from amniotic fluid, cord blood and vaginal secretions must be conducted to determine whether the virus is transmitted in utero, during delivery or postpartum. With the recent development of the vaccine, further studies should be conducted to determine the role of vaccination in reducing rates of vertical transmission and improving neonatal outcomes.

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Appendix

Appendix 1: Search terms input on Medline

1. Exp COVID19
2. SARS-CoV-2
3. COVID19
4. Novel coronavirus
5. 2019 novel coronavirus
6. SARS-CoV2
7. COVID-19
8. Exp infectious disease transmission. Vertical
9. Vertical transmission
10. Contact transmission
11. Transplacental transmission
12. Delivery transmission
13. Post partum
14. Mother-to-child
15. Maternal
16. Fetal
17. Foetal
18. Fetus
19. Child
20. Baby
21. Embryo
22. Mother adj3 child
23. Mother adj3 baby

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I'm currently in my 4th year at Cardiff University studying medicine and I have a keen interest in obstetrics and gynaecology. I have explored my passion for women's health by participating in the committee for the 'CoppaFeel!' University society, raising awareness for breast cancer amongst the public. I hope to pursue these interests throughout my career.