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SARS-CoV-2: Is it the newest spark in the TORCH?

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ABSTRACT

Amid the rapidly evolving global coronavirus disease 2019 (COVID-19) pandemic that has already had profound effects on public health and medical infrastructure globally, many questions remain about its impact on child health. The unique needs of neonates and children, and their role in the spread of the virus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) should be included in preparedness and response plans. Fetuses and newborn infants may be uniquely vulnerable to the damaging consequences of congenitally- or perinatally-acquired SARS-CoV-2 infection, but data are limited about outcomes of COVID-19 disease during pregnancy. Therefore, information on illnesses associated with other highly pathogenic coronaviruses (i.e., severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome [MERS]), as well as comparisons to common congenital infections, such as cytomegalovirus (CMV), are warranted. Research regarding the potential routes of acquisition of SARS-CoV-2 infection in the prenatal and perinatal setting is of a high public health priority. Vaccines targeting women of reproductive age, and in particular pregnant patients, should be evaluated in clinical trials and should include the endpoints of neonatal infection and disease.

1. Introduction

Since the World Health Organization (WHO) declaration of a COVID-19 pandemic [1], infections with SARS-CoV-2 have exacted a profound impact on public health. As of this writing, nearly 2.5 million cases of SARS-CoV-2 infection have been identified globally, with over 165,000 deaths reported to date [2]. It is generally believed that these are under-estimates, given continuing resource restrictions that preclude wide-spread testing in many countries. The range of manifestations of illness is expanding, with recent evidence of transmission by aerosol route in addition to droplet spread. Infections during pregnancy are increasingly being described, but the frequency and severity of infections in the newborn are incompletely defined. A critical and as yet unanswered question is whether SARS-CoV-2 can be transmitted *in utero*. The possibility of maternal-fetal transmission has been suggested by several observational studies, including the documentation of neonatal disease in some cases, reviewed below. Still, it remains uncertain whether these are post-natally acquired infections or represent vertically transmitted infections.

In this review, we summarize the state of knowledge acquired to date about potential risks of transmission of SARS-CoV-2 to the fetus and newborn. By analogy with animal models of coronavirus disease, congenital transmission of SARS-CoV-2 is feasible, and this literature is reviewed. The possibility of analogous congenital transmission of coronaviruses in humans requires continued study. Perinatal and postnatal environmental routes of transmission appear to be clear risks to the newborn infant, and measures to prevent the acquisition of SARS-CoV-2 in this setting are warranted. Reassuring information has been reported that suggests a lack of breast milk-mediated transmission [3,4], although this needs to be confirmed by more extensive studies. Of considerable interest is the question of whether SARS-CoV-2 should be considered as a “TORCH” infection. The TORCH acronym, first coined by Nahmias [5], was initially defined as a group of infections (toxoplasmosis, “other” infections, rubella, CMV, and herpes simplex virus [HSV]) that were commonly encountered in the newborn and acquired from a maternal source. Numerous variants of this acronym have evolved over the past four decades [6–13], and the definition of TORCH infection is today more broadly recognized as a heterologous collection of infections that can cause neonatal disease following acquisition by either trans-placental or perinatal routes. We submit that SARS-CoV-2

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should be included in the grouping of TORCH infections and that efforts should be made both to more fully define the mechanisms of transmission and the scope of disease in the fetus and neonate. Strategies to prevent transmission, including virologic monitoring of pregnant women, are likely to be of great value. Therapeutic interventions to prevent transmission in the newborn period, including vaccines and immunotherapies, also warrant investigation.

2. Is SARS-CoV-2 a congenital or perinatally-acquired pathogen for the neonate?

2.1. Lessons from animal models

Animal models for SARS and MERS coronaviruses have been described [14], although relatively little attention has been devoted to the prospects for congenital or perinatal transmission in these studies. Murine coronavirus (M-CoV) is a species of coronavirus which infects mice, and experiments using a virulent strain of this virus in a pregnancy/challenge model demonstrated infection of both placenta and fetus in susceptible BALB/cByJ mice [15,16]. Fetuses were infected during all three trimesters of pregnancy, although there was variation among different strains of mice, insofar as infection of resistant CD-1 mice was limited, with no fetal infection [16]. *Betaarterivirus suid* 1 virus (formerly known as porcine reproductive and respiratory syndrome virus) is a porcine arterivirus related to coronaviruses and was commonly associated with early fetal demise in pigs in another study following challenge during pregnancy [17]. Infection of cats with the coronavirus feline infectious peritonitis virus results in newborn kittens becoming carriers of the virus [18]. Interestingly (and paradoxically), increased morbidity compared to controls was observed in kittens born to queens pre-sensitized with a vaccinia virus-vectored spike (S) protein vaccine, following challenge with feline infectious peritonitis [19]. The mechanism of increased mortality in the vaccine group was not clear but may be related to vaccine-induced immune enhancement of infection [20]. Antibody-mediated enhancement of coronavirus entry into Fc receptor-expressing cells has been described for antibodies targeting the receptor binding domain of the MERS coronavirus [21]. These observations may be relevant to COVID-19 vaccines as they move forward in clinical evaluation.

2.2. Congenital and perinatal infections with coronaviruses other than SARS-CoV-2

There has been limited evaluation of the potential for maternal-fetal transmission of coronaviruses before the current pandemic. In one prospective pilot study of the minimally pathogenic coronavirus strains 229E, OC-43, NL-63, and HKU1, vertical transmission was studied in 159 samples from maternal-infant pairs [22]. Coronavirus was detected in seven mother-infant dyads, including in newborn gastric aspirates, and the authors concluded that vertical transmission was possible and required larger-scale investigation.

During the SARS coronavirus epidemic of 2002-2003, infection during pregnancy was associated with severe maternal illness, maternal death, and risk of spontaneous abortion [23]. Over 100 pregnant women were identified during the SARS outbreak, and these pregnancy outcomes are the subject of a recent review [24]. Notably, two infants with intrauterine growth restriction (IUGR) were described in one study [25], but no evidence of neonatal infection was observed in the 14 newborns who had virologic evaluations performed in the various cases series reported in the literature [26–31]. In one study of placentas from pregnancies complicated by maternal SARS-CoV-1 infection, the most severe abnormalities observed included extensive fetal thrombotic vasculopathy and areas of avascular chorionic villi [32]. These were interpreted as chronic findings associated with fetal vascular malperfusion and were noted in pregnancies complicated by oligohydramnios in which fetal IUGR developed. However, no signs of SARS-CoV-1 RNA or viral cytopathic effects were described in this case series.

There is limited information regarding fetal and neonatal outcomes in the setting of MERS-CoV infection. Only 13 cases of MERS infection in pregnant women appear to be reported. The fetal mortality rate was described to be 27 % [24]. In the majority of these cases, no virological investigation of the fetus/infant was performed. The one exception (and the only evidence of MERS in pregnancy described outside of the Middle East) was a case reported from South Korea. In this case, a healthy infant was delivered, and although no testing for viral RNA was reported, the infant's blood did not contain any IgG, IgM, or IgA antibodies to MERS-CoV [33]. Rasmussen *et al.* [34] reported on a published case from the Philippines but this was in a healthcare worker from Saudi Arabia and she recovered. No comments about the pregnancy outcome were reported [35].

2.3. Congenital and perinatal infections with SARS-CoV-2

To date, the morbidity and mortality described for SARS-CoV-1 and MERS-CoV infections during pregnancy do not appear to be as severe for SARS-CoV-2. Most reviews have concluded there is no conclusive evidence of transplacental transfer of SARS-CoV-2 from mothers with COVID-19 disease [36,37]. A recent review and summary of COVID-19 cases [38], chiefly compiled from those published in a series of reports from China [39–42], described 38 pregnant women with COVID-19 and their newborns and included information on clinical, laboratory and virologic data. This analysis revealed that, unlike coronavirus infections of pregnant women caused by SARS and MERS, in the 38 pregnant women with COVID-19 there were no maternal deaths. Signs and symptoms of illness were described in some infants born to SARS-CoV-2 infected mothers, including shortness of breath, fever, thrombocytopenia, abnormal liver function tests, tachycardia, vomiting, and pneumothorax [41]; one infant born prematurely (at an estimated gestational age of 34 weeks) died due to refractory shock, multiple organ failure and disseminated intravascular coagulation. Despite evidence of illness in some newborns, it was noted that there had been no virologic evidence of newborn infection, and no confirmed cases of intrauterine transmission of SARS-CoV-2 from mothers.

After this review was published, another analysis of COVID-19 cases examined the outcomes of 55 pregnant women infected with COVID-19, and 46 neonates, reported in the literature and also concluded that there was no definite evidence of vertical transmission [43]. Other reports and small case series have provided similar reassuring observations [44,45]. However, standing in contrast to these reassuring observations are a series of more recent case reports that seem to document that vertical (*in utero*) transmission of SARS-CoV-2 can indeed occur. In one study reported from Zhongnan Hospital of Wuhan University in China, six women with mild COVID-19 disease gave birth via Caesarean section to infants using multiple infection control measures, including isolation of their infants immediately following delivery. Notably, two of these six infants had IgM antibodies to SARS-CoV-2 present, although neither infant had symptoms. All of these infants were repeatedly negative when tested for viral RNA upon subsequent testing [46], leaving only the demonstration of IgM antibody as a marker defining fetal transmission. In a second report from Wuhan hospital [47], viral nucleic acid testing made for a more compelling case for vertical transmission. This analysis of 33 neonates born to mothers with COVID-19 identified three neonates with SARS-CoV-2 infection. In one infant, chest radiographic image showed pneumonia within 48 h of age, and nasopharyngeal and anal swabs were positive for SARS-CoV-2 RNA on days 2 and 4 of life. A second infant born to a woman with confirmed COVID-19 pneumonia developed lethargy, vomiting, and fever. A chest radiographic image revealed pneumonia, and nasopharyngeal and anal swabs were positive for SARS-CoV-2 on days 2 and 4 of life. The third patient was born at 31 weeks gestation by Cesarean delivery; neonatal respiratory distress syndrome and pneumonia were confirmed by chest radiographic image on admission, and

nasopharyngeal and anal swabs were positive for SARS-CoV-2 on days 2 and 4 of life (and negative on day 7). Thus, SARS-CoV-2 was not only transmitted vertically, but caused disease in the infected newborns. A third study [48] also demonstrated a positive IgM serology in a neonate born by Cesarean section to a mother with SARS-CoV-2 pneumonia. The infant was delivered in a negative-pressure isolation room, and her mother wore an N95 mask and did not hold the infant. The positive IgM titer in the newborn, along with an elevated cytokine profile, suggested vertical transmission had occurred, although nucleic acid studies were negative.

Thus, SARS-CoV-2 can likely be transmitted to the fetus pre-natally or to the newborn infant post-natally. Non-congenital routes of perinatal transmission could include aerosol and droplet transmission in the delivery room, or transmission in the birth canal. Another important possible route of post-natal transmission could be through breastfeeding. Studies reported to date do not find any evidence of COVID-19 in breast milk [38,49–51], although more studies are needed. Both intrapartum transmission during vaginal delivery and post-natal acquisition via breast milk are well-described for CMV infection [52]. These modes of transmission may complicate the analysis of whether an infant undergoing assessment for congenital CMV may have acquired infection *in utero* versus post-natally. Clinicians should learn lessons from these congenital/perinatal CMV infection considerations, and be mindful that these same issues may complicate the question of whether an infant with SARS-CoV-2 acquires infection by a pre-natal versus a post-natal route.

Although the studies performed to date leave us with mixed findings about whether SARS-CoV-2 can be acquired *in utero*, enough evidence exists of pre-natal acquisition that the transplacental route should be assumed to be a mechanism of transmission unless proven otherwise by future studies. The various studies reported to date are summarized in Table 1. It is also uncertain what measures should inform guidelines about the separation of a COVID-19 positive mother and her newborn infant, given inconsistent recommendations across expert groups [53]. At this time, the WHO advises that infected mothers can share a room with their infant and breastfeed but should practice “respiratory hygiene”, including washing their hands and wearing a mask, acknowledging that a mask might not be available. The CDC [54] advises that facilities should “consider temporarily” separating infected mothers and newborns after “discussing the risks and benefits with the mother and health care team.” Mothers may breastfeed while exercising respiratory hygiene, and separated infants must be isolated from other infants. The CDC also makes provisions for room sharing if “it is in accordance with the mother's wishes” or if it is unavoidable due to facility limitations. The American College of Obstetricians and Gynecologists (ACOG) defers to CDC guidelines; in addition, ACOG does not recommend routine COVID-19 testing for pregnant women [55]. The American Academy of Pediatrics, on the other hand, offers more stringent guidelines, including the recommendation that COVID-19 positive mothers be separated from their newborns until they are asymptomatic, and until they have two separate virological determinations demonstrating that they are free of infection [56]. These inconsistencies in expert recommendations underscore the knowledge gaps that exist regarding perinatal transmission of SARS-CoV-2 and highlight high priority areas for future studies.

3. Conclusions and priorities for future research

Although more knowledge is needed, we would submit that the SARS-CoV-2 virus is, in some cases, transmitted from mother-to-fetus, and that this virus should be included in our working list of TORCH infections. Animal models demonstrate the vertical transmission of related animal coronaviruses in pregnancy, and evidence of vertical transmission has been reported in parturient women with COVID-19 disease. Although more data about transplacental infections is needed [57], studies in women undergoing Cesarean delivery [47,48] are

Table 1
Summary of Case Series and Studies of Women with Proven COVID-19 Disease with Evaluation of Newborns for Evidence of Vertically-Transmitted SARS-CoV-2 Infection.

Study	Congenital Transmission	Assays Performed	Comments	Reference
Nine maternal-infant pairs; all were C-section births).	No	SARS-CoV-2 assayed in amniotic fluid, cord blood, and neonatal throat swab samples.	No positive results in infant samples; breast milk samples collected at first lactation, all negative.	[39]
Three maternal-infant pairs; 7 C-sections, 1 vaginal delivery.	No	SARS-CoV-2 assayed in placenta tissue, vaginal mucus, breast milk; infant oropharyngeal swabs, cord blood, serum.	Fetal distress and chorioamnionitis in one infant; hypotonia and decreased responsive in another infant.	[40]
Ten neonates (nine mothers); 7 C-sections, 2 vaginal deliveries.	No	Pharyngeal swabs from 9 of the 10 neonates, 1–9 days of age; all PCRs negative.	Shortness of breath, thrombocytopenia, abnormal liver function, tachycardia, vomiting, pneumothorax, fever; one infant death.	[41]
Two maternal-newborn pairs; both C-section deliveries.	No	Maternal serum, cord blood, placenta tissue, amniotic fluid, vaginal swab, breast milk, neonatal nasopharyngeal swab.	One infant had pneumonia and lymphopenia.	[44]
Four maternal-infant pairs; 3 C-sections, 1 vaginal delivery.	No	Three of 4 infants tested; all had negative throat swab by RT-PCR 72 h after birth.	Two infants had rashes; one infant required mechanical ventilation for 3 days.	[45]
Six maternal-infant pairs; all were C-sections.	Yes	COVID-19 PCR on neonatal serum, throat swabs; cytokines in neonatal serum; maternal neonatal IgG/IgM assays.	RNA not detected in infant serum or throat swab; specific IgM, detected in 2 infants; IL-6 elevated all infants.	[46]
Thirty-three maternal-infant pairs; 3 SARS-CoV-2 positive infants, all C-section births.	Yes	Infants tested by PCR of nasopharyngeal and anal swabs; all positive within 48 h of age.	3 of 33 infants with SARS-CoV-2 infection; all had pneumonia; 2/3 mechanical ventilated; one infant with lymphopenia.	[47]
Retrospective review of 43 women with SARS-CoV-2; data available for 18 infants.	No	All tested infants negative for SARS-CoV-2 by PCR; all infants reported to be negative by IgM and IgG testing.	32.6 % of pregnant women had no SARS-CoV-2 symptoms at presentation; one infant described with respiratory distress and sepsis syndrome.	[60]

Table 2
High Priority Areas for Future SARS-CoV-2 Research in Pregnancy and Newborn Health.

Research Objective	Rationale/Unanswered Questions
Define correlates of maternal infection and immunity that impact on transmission.	Increased recognition that many pregnant patients shed SARS-CoV-2 asymptomatically; can a cytokine/immune profile/virologic profile (i.e., maternal RNAemia) be defined that predicts maternofetal transmission?
Resolve conflicting information about vertical transmission.	Some studies identify SARS-CoV-2 in newborn samples (C-section delivery, samples collected at < 48 h of age) but other studies do not. Are these discrepancies related to PCR testing differences? Does positive neonatal IgM alone stand as sufficiently sensitive/specific to define congenital transmission?
Investigate whether SARS-CoV-2 infects the placenta.	Preliminary reports are reassuring; however, transplacental transmission appears to clearly occur in other mammalian coronavirus systems; viremia occurs in human SARS-CoV-2 infection increasing plausibility of hematogenous seeding of placenta; we recommend placental histopathology for all cases of SARS-CoV-2 infection in parturition until more data is available.
Confirm that SARS-CoV-2 does not partition into breast milk and is not a risk to infect the nursing infant.	Preliminary evidence is reassuring about lactation and apparent lack of risk of transmission by this route; more confirmatory data is needed on breast milk and viral load.
Explore correlates of immunity.	Examine what level of IgG and/or neutralizing antibody protections mothers and infants. Are non-neutralizing functions of IgG (such as ADCC) involved in antiviral immunity?
Develop point-of-care testing for SARS-CoV-2 to improve management during labor and delivery.	Point-of-care immune assays and virologic assays can identify women with active infection who present in labor; particularly important in light of studies of high prevalence of asymptomatic infection upon presentation to labor and delivery suite; will enhance infection control protocols.
Develop vaccines, antivirals and immune based therapies.	Vaccines are of high priority, and should be tested, in pregnancy.

highly suggestive of *in utero* transmission. The fact that SARS-CoV-2 has been demonstrated to produce RNAemia [58] further suggests the biological plausibility of transplacental transmission by a mother-to-fetus hematogenous route. SARS-CoV-2 can also be found in fecal samples [59], suggesting that perineal colonization could lead to intrapartum infection of the newborn during labor and delivery. Reports from China suggest, based on limited assessment of IgM serology and virologic samples in neonates, that vertical transmission of virus does occur in some cases [46–48]. On the other hand, a recent report from Columbia University in New York found no evidence for vertical transmission in 43 COVID-19-positive pregnant women: moreover, this study also demonstrated that a high percentage (32.6 %) of infected women were, in fact, asymptomatic upon their original clinical presentation [60]. Increased availability of testing, including real-time "point-of-care" testing, should help clarify the risks of transmission to the fetus.

High-priority areas for future studies are highlighted in Table 2. Foremost among these will be the determination of potential modes of transmission in the newborn period – i.e., transplacental versus intrapartum versus postpartum. The finding of SARS-CoV-2 RNA in the first few days of life could represent *bona fide* congenital infection, acquired before birth; transient colonization acquired during labor and delivery; or post-natal acquisition via droplet spread from an infected mother. Strategies must be enhanced to differentiate among these possibilities. The issue of breastmilk transmission also requires further study. Examination of placentas from COVID-19 positive women for virologic and histologic markers of infection should be a high-priority area for investigation. Maternal and nenonatal biomarkers (possibly IL-6 [46]) that correlate with maternofetal transmission should also be studied. Optimal infection control procedures in the newborn period must be defined toward the goal of resolving the best strategies to prevent post-natal infection. Finally, the pregnant patient should be considered a top priority recipient of candidate vaccines and immunotherapies. It is premature to recommend antivirals or immune-based therapies (such as monoclonal or polyclonal anti-COVID 19 antibodies) aimed at interrupted perinatal transmission, but such strategies deserve consideration; in this context, efforts that have been considered and studied to block CMV transmission during pregnancy can be highly instructive [61]. Ultimately, an effective vaccine [62] is of the highest priority. A vaccine will not only protect maternal health during pregnancy and delivery, but also can likely minimize the risk of fetal and neonatal infection by potentially inducing transplacental antibodies that may help prevent infection from other household and community exposures. Vaccines stand the best chance for reducing the risk of both *in utero* transmission, and post-natal mother-to-infant transmission in the newborn period.

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Declaration of Competing Interest

None of the authors declares a competing interest.

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