



The effect of coronavirus disease 2019 on newborns

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Purpose of review

To evaluate the available literature regarding effects of coronavirus disease 2019 (COVID-19) on newborns, ranging from effects related to *in utero* and perinatal exposure to maternal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, to pandemic-related stress and socioeconomic changes.

Recent findings

Several large studies and national registries have shown that the risk of vertical transmission from SARS-CoV-2-infected mothers to newborns is rare and does not appear to be related to postnatal care policies such as mother–newborn separation and breastfeeding. Newborns exposed to SARS-CoV-2 *in utero* are at higher risk for preterm delivery for reasons still under investigation. When newborns do acquire SARS-CoV-2 infection, their disease course is usually mild. Long-term follow-up data are lacking, but preliminary reports indicate that, similarly to prior natural disasters, being born during the pandemic may be associated with developmental risk.

Summary

Although risk of vertical or perinatal transmission is low across a range of postnatal care practices, early indicators suggest developmental risk to the generation born during the pandemic. Long-term follow-up data are critically needed to determine the developmental impact of *in utero* and early life exposure to SARS-CoV-2 and the COVID-19 pandemic.

Keywords

coronavirus disease 2019, development, newborn, pregnancy

INTRODUCTION

As of this writing, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected over 200 million people worldwide, more than 2% of the world's population. In some countries, like the United States and Sweden, the proportion of infections has reached over 10% of the population. Much emphasis has been placed on protecting populations most vulnerable to severe coronavirus disease 2019 (COVID-19) disease. Early in the pandemic, pregnant women and newborns were considered two potentially high-risk groups based on the epidemiology of other viral illnesses. Initial reports of potential vertical transmission [1] and severe newborn illness [2^{*}] fueled fear and contributed to conservative postnatal care policies that included mother–newborn separation and recommendations against direct and/or indirect breastfeeding [3–5]. Mounting data have since demonstrated that newborns rarely acquire SARS-CoV-2 from infected mothers, and newborns who do become infected perinatally

commonly show a mild or asymptomatic disease course. However, numerous reports on other *in utero* exposures to microbial infections and/or maternal immune activation (MIA) have shown that long-term effects on development may appear later in life [6,7]. In addition, pre and postnatal stress itself, abundant during world events like pandemics, is known to impact development [8,9]. Here, we review major pieces of evidence that have been published since early 2020 regarding the effect of COVID-19 on newborns, and suggest that the real

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KEY POINTS

- Risk of vertical and/or perinatal transmission of SARS-CoV-2 from infected mothers to newborns is low.
- Maternal SARS-CoV-2 seropositivity via infection or vaccination might protect against infant infection.
- Newborns exposed to SARS-CoV-2 *in utero* are at increased risk of premature birth.
- Newborns infected with SARS-CoV-2 have a generally mild disease course.
- The long-term health and developmental impact of *in utero* and early-life exposure to SARS-CoV-2 and/or stressors associated with the COVID-19 pandemic are currently unknown and prospective follow-up studies are urgently needed.

risk of the pandemic for most newborns may not be the virus itself, but its effect on the world (Table 1).

LOW RISK OF VERTICAL AND PERINATAL TRANSMISSION OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 FROM INFECTED MOTHERS TO NEWBORNS

At the onset of the COVID-19 pandemic in early 2020, unknown risk of vertical and perinatal transmission from SARS-CoV-2-infected mothers to their newborns led to varying, often overly conservative postnatal care recommendations [3–5]. Although rates of vertical transmission with other coronaviruses, including

SARS-CoV and Middle East respiratory syndrome coronavirus, are reportedly low [10,11], limited data and comparatively high case rates of SARS-CoV-2 infection in pregnant women resulted in reasonable fear regarding transmission and clinical outcomes in newborns born to infected mothers. In the last 18 months, a considerable body of literature has assuaged these concerns, with systematic reviews and studies on large cohorts demonstrating that a low proportion, between 0–5%, of infants with *in utero* exposure to maternal SARS-CoV-2 infection have tested positive neonatally via reverse transcription-PCR [12,13,14[■], 15[■],16[■],17[■],18,19[■]].

The American Academy of Pediatrics Section on Neonatal-Perinatal Medicine (AAP-SONPM) National Perinatal COVID-19 Registry and the UK and Global Pregnancy and Neonatal outcomes in COVID-19 (PAN-COVID) Registry collect data on maternal and neonatal outcomes in SARS-CoV-2 infected pregnant women and their newborns [19[■],20]. Mullins *et al.* [19[■]] coreported on data from 4005 pregnant women included in the AAP-SONPM registry or the PAN-COVID registry and found vertical transmission rates of 1.8% and 2.0% in the US-based and UK-based registries, respectively. Although postnatal care practices differ between the centers included in each registry, both the US Centers for Disease Control (CDC) and the UK Royal College of Obstetricians and Gynaecologists recommended continued breastfeeding and skin-to-skin care and discouraged separation of infected mothers from newborns for much of the period reported on in the study [21,22], suggesting that rates of vertical transmission remain low in large

Table 1. Summary of major current findings related to coronavirus disease 2019 and newborns

Exposure	Associations	Nonassociations	Areas in need of additional research
<i>In utero</i> exposure to maternal SARS-CoV-2 infection	↑ Prematurity [16 [■] ,17 [■] ,19 [■] ,25 [■]]	↔/↓ Newborn SARS-CoV-2 infection [12,13,14 [■] ,15 [■] ,16 [■] ,17 [■] ,18,19 [■] ,46 [■] ,47 [■] ,48 [■] ,49] ↔ Newborn development at 6 months [52]	Newborn immunity and transfer of maternal antibodies Long-term child health and development
Neonatal SARS-CoV-2 infection	Conflicting findings on risk of severe respiratory disease: some studies indicate ↑risk [2 [■] ,35 [■] ,36 [■]], other studies indicate ↔risk [16 [■] ,37,38 [■] ,39,40]		Long-term child health and development
COVID-19 pandemic (e.g., maternal pre/postnatal stress, mask-wearing, social distancing)	↓ Newborn development at 6 months [52] ↑ Infant serotonin transporter gene methylation [51]		Mother–child bonding Early language and social development Long-term child health and development

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

cohorts in which many mothers breastfeed and are not separated from newborns. Similarly, our group reported no clinical evidence of vertical transmission in our large medical center in New York City during the peak of the pandemic, despite mother–newborn rooming-in and encouraging breastfeeding for all women [12]. Furthermore, national cohorts of pregnant women and neonates in Sweden [16[■]] and Spain [17[■]], where rooming-in, breastfeeding, and skin-to-skin care were also encouraged, showed newborn positivity rates of 0.9% and 0.4–3.0%, respectively.

In contrast to the rapid updating of guidelines in Western countries, Chinese authorities have continued to recommend postnatal mother–newborn separation and withholding of breastfeeding in infected mothers in the most recent published guidelines [23] and on the Chinese National Health Commission website [24]. Although it is difficult to measure the effects of postnatal care practices on vertical and perinatal transmission, a systematic review enriched with mothers from China (43.4% of 564) found an overall vertical transmission rate of 3.3% [25[■]] – a rate in line with, and possibly higher than, the US and European reports. This strongly suggests a lack of evidence for continued mother–infant separation and withholding of breastfeeding.

IN UTERO EXPOSED INFANTS HAVE AN INCREASED RISK OF PREMATURITY

Although vertical and perinatal transmission of SARS-CoV-2 from mother to newborn seems to be rare across a range of postnatal clinical care practices, clinical characteristics of *in utero* exposed newborns must be considered regardless of neonatal infection status. In a cornerstone study comparing neonatal outcomes in exposed versus unexposed newborns representing 92% of all births in Sweden from March 2020 through January 2021, Norman *et al.* [16[■]] reported significantly lower birth weight and gestational age at delivery in 2323 newborns born to SARS-CoV-2-infected mothers compared with 9275 case-matched infants born to uninfected women. The study was particularly well powered to detect differences in outcomes specifically related to *in utero* exposure, as the authors matched SARS-CoV-2-infected and uninfected pregnant women based on maternal characteristics known to affect a variety of neonatal outcomes, including age, BMI, smoking status, prepregnancy comorbidity, and multiple pregnancy status [16[■]]. Increased prevalence of preterm birth in exposed newborns was found to mediate increased rates of neonatal respiratory disorders as compared with unexposed newborns, but there was no significant direct relationship between maternal SARS-CoV-2 infection and neonatal respiratory

disorders [16[■]]. Sánchez-Luna *et al.* [17[■]] also found increased rates of preterm delivery (15.7%) in *in utero* SARS-CoV-2 exposed newborns compared with the general Spanish population (7.5%), and 19.9% of *in utero* SARS-CoV-2 exposed newborns reported on in Yuan *et al.* [25[■]] were delivered preterm. Similarly, the AAP-SONPM and PAN-COVID registries reported that 15.7% and 12.0% of newborns were delivered preterm [19[■]], respectively, rates that are also higher than the US and UK national averages of 10% [26] and 7.5% [27], respectively. Fortunately, although preterm birth does appear to be more prevalent in *in utero* SARS-CoV-2 exposed than in unexposed newborns, these studies do not show any indication that exposed newborns are at increased risk for severe morbidity or mortality above and beyond the risk conferred by prematurity itself [13,14[■],17[■],18].

The cause of the increased rate of preterm birth for *in utero* SARS-CoV-2 exposed newborns remains unclear. Maternal disease course, particularly in severely or critically ill women, likely plays a key role in accelerating delivery, as the severity of other acute respiratory diseases in pregnant women has been shown to correlate with rates of preterm delivery [28,29]. Although reports early in the pandemic suggested that pregnant women present with asymptomatic or mild COVID-19 disease more frequently than the general population [12,30,31], several large studies have since shown that pregnant women are more likely to experience severe illness than nonpregnant women. A CDC analysis on 400 000 women found that pregnant women with symptomatic COVID-19 disease were more likely to require intensive care unit (ICU) admission, invasive ventilation, and extracorporeal membrane oxygenation, and were at higher risk for mortality, when compared with nonpregnant women with COVID-19 disease [32[■]]. A meta-analysis on over 67 000 women also showed increased rates of ICU admission and invasive ventilation in pregnant as compared with nonpregnant women with COVID-19 disease, and further demonstrated that pregnant women infected with SARS-CoV-2 have increased risk of mortality and ICU admission than uninfected pregnant women [33[■]]. Although these findings are compelling, they should be interpreted with caution, as it is difficult to decisively compare studies on pregnant versus nonpregnant women due to differences in COVID testing prevalence and healthcare utilization and practices. A related and potentially further driving factor behind increased preterm delivery rates is that research studies on newborn exposure are more likely to be published by tertiary medical centers with high levels of research activity, which already have higher than average rates of preterm delivery and are more likely to provide care to severely or critically ill women [17[■],34].

OUTCOMES IN NEWBORNS INFECTED WITH SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

Regardless of whether infection is acquired vertically or perinatally, newborns who do acquire COVID-19 disease generally fare well, although some reports are conflicting. Early in the pandemic, a study from China indicated that infants under 1-year old had a higher prevalence of severe COVID-19 disease compared with other pediatric age groups (10.6 versus 3.0–7.3%) [2[■]], and a multicenter report from 25 European countries found that age under 1 month was a significant risk factor for ICU admission in SARS-CoV-2-infected infants and children [35[■]]. Although a report by Gale *et al.* [36[■]] found a population-level neonatal SARS-CoV-2 infection rate of just 5–6 per 10 000 newborns during the March–April 2020 peak in the UK, they also showed that of 66 newborns identified with confirmed infection, 36% received intensive care or respiratory support (although, of note, 24% of babies in the sample were born premature).

The above findings fueled initial concern that newborns would be a population more vulnerable to SARS-CoV-2 infection, but several recent reports have shown that, consistent with findings in older children, newborns have a mild COVID-19 disease course, primarily presenting with fever, cough, and congestion [16[■],37,38[■],39,40]. A study from New York compared clinical features and outcomes in febrile newborns under 57 days of age across March and April of 2018, 2019, and 2020 [38[■]], and found that febrile newborns seen in their medical center in 2020 were most frequently infected with SARS-CoV-2 (20 of 30 newborns). The authors showed that SARS-CoV-2-infected newborns more commonly exhibited lethargy or feeding difficulties and had lower white blood cell, neutrophil, and lymphocyte counts compared with febrile newborns that tested negative for SARS-CoV-2. However, with the exception of two of 20 newborns requiring supplemental oxygen, COVID-19 disease was generally mild with no newborn requiring intubation or other medical intervention [38[■]]. The report from Sweden similarly showed mild disease course: in the 21 infants who tested positive for SARS-CoV-2 neonatally, none had congenital pneumonia, and none had morbidities with a clear link to SARS-CoV-2 [16[■]]. Hassoun *et al.* [39] found that none of the 48 SARS-CoV-2-infected newborns reported on and seen in pediatric emergency departments in New York City required oxygen therapy or had respiratory distress, and Mithal *et al.* [37] also showed that no infected newborns required respiratory support or intensive care at a large medical center in Chicago. Further, several studies have reported asymptomatic disease course in newborns

[16[■],37,40]. Taken together, the available, albeit limited, literature on neonatal SARS-CoV-2-infection outcomes indicates that newborns are rarely infected and often present with mild symptoms.

IMMUNOLOGICAL CONSIDERATIONS FOR NEWBORNS EXPOSED TO SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

Concern for newborns as a population potentially more vulnerable to SARS-CoV-2 infection came, in part, from established knowledge on the immature neonatal immune system. A majority of global deaths in children under 5 years old occur due to infection, and 40.3% of deaths in this age group occur in neonates [41]. In general, newborns are particularly susceptible to respiratory infections, likely as a result of the neonatal immune system's inadequate B-cell response and preference for T-helper type 2 (Th2) over Th1 response to infection [42,43]. Significantly, this Th2-skewed immune response has been hypothesized to protect against severe SARS-CoV-2 infection in pediatric populations by preventing the systemic inflammation that is a hallmark of severe COVID-19 disease [44].

Exposure to SARS-CoV-2 *in utero* may confer additional protection against COVID-19 disease for newborns, as trans-placentally transferred antibodies for several viruses have been shown to protect newborns for the first 3–6 months of life [45]. Consistent with this, initial reports on *in utero* exposure to maternal SARS-CoV-2 antibodies through maternal infection [46[■]] or vaccination [47[■]] show more than 90% seropositivity of newborns born to seropositive mothers. In addition, the breastmilk of mothers with a previous SARS-CoV-2 infection has been shown to contain antibodies against the virus, adding another potential layer of early postnatal protection [48[■],49].

NEED FOR LONG-TERM FOLLOW-UP TO ASSESS EFFECTS OF MATERNAL SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 INFECTION DURING PREGNANCY AND/OR THE CORONAVIRUS DISEASE 2019 PANDEMIC ACROSS THE LIFESPAN OF THE AFFECTED GENERATION

Even in the absence of newborn SARS-CoV-2 infection or *in utero* exposure, the virus and the unprecedented circumstances of the COVID-19 pandemic may impact long-term development. Although reports to-date have focused on immediate postnatal outcomes in newborns born to SARS-CoV-2-infected

mothers, long-term data are lacking, and studies from other *in utero* viral exposures, such as HIV, have shown that exposed, uninfected infants have higher risk for neurodevelopmental delay [6,7].

Potential pandemic-associated deficits may also extend beyond children exposed to SARS-CoV-2 *in utero*: population-level reports have shown that the generation born during the 1918 Spanish flu pandemic had lower educational attainment during childhood and lower socioeconomic status as adults [50]. Preliminary reports on early development in infants born during the COVID-19 pandemic suggest the potential for similar generation-wide effects [51,52]. Recently, our group found no differences between *in utero* SARS-CoV-2 exposed versus unexposed infants in scores on the *Ages and Stages Questionnaire, 3rd Edition (ASQ-3)* neurodevelopmental screening tool at 6 months of age, but significantly lower gross motor, fine motor, and personal-social scores in the overall pandemic-born cohort when compared with a prepandemic cohort born at the same medical center who completed the ASQ-3 at the same age [52]. These differences were most pronounced in infants whose mothers were in the first trimester of pregnancy during the peak of the pandemic in New York City, suggesting a potential role of COVID-19-related maternal stress early in gestation in mediating pandemic-associated effects on development, which is consistent with other studies on prenatal stress during natural disasters and child neurodevelopment [8,9]. Recent data from Italy further supports the possibility that *in utero* exposure to COVID-19-related stress alters infant development. The team found an association between maternal COVID-19-related prenatal stress and infant serotonin-transporter gene methylation, which predicted infant temperament at 3 months of age [51].

Beyond *in utero* exposure to maternal infection, MIA and/or stress, newborns born during the COVID-19 pandemic are born into a changed world. As highlighted in a recent review by Green *et al.* [53[■]], early experience of one such societal change, widespread mask-wearing, may have a profound impact on development. Several classic studies have shown that newborns are highly attuned to faces, particularly those of early caregivers, and likely rely on facial expression as an early means of communication [54,55]. This suggests that, for the generation born during the COVID-19 pandemic, reduced access to faces early in life may have long-term impact on bonding and social and language development [53[■]]. Many newborns are additionally cared for in more stressful home environments, due to COVID-19-related increases in unemployment, food insecurity, and housing insecurity [56[■]], and increased incidence and severity of intimate partner violence [57].

Exposure to early life stressors, including low socioeconomic status and household violence, is well established to have lasting impact on child health and development [58–60].

CONCLUSION

Large studies and national registries have conclusively shown that vertical and/or perinatal transmission of SARS-CoV-2 from infected mother to newborn is rare. Newborns with *in utero* exposure to maternal SARS-CoV-2 infection have a higher risk of premature birth but are otherwise healthy and possibly protected from neonatal SARS-CoV-2 infection. In addition, most newborns who do become infected with SARS-CoV-2 have a mild or asymptomatic disease course. However, long-term follow-up data are urgently needed to determine whether *in utero* exposure to SARS-CoV-2 and/or the COVID-19 pandemic, a global societal disruptor, will impact development in these children.

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Conflicts of interest

M.H.K. has none to report. D.D. has pending reimbursement for consulting for Medela Inc.

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