Coronavirus Disease 2019 Infection in Newborns

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KEYWORDS

• SARS-CoV-2 • COVID-19 • Vertical transmission • Maternal vaccination
• Preterm birth • Breast milk • Syncytiotrophoblast

KEY POINTS

- Newborns with positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test results appear to have minimal burden of illness that is directly associated with a viral infection.
- A symptomatic SARS-CoV-2–infected mother increases the risk for preterm and medically induced preterm birth.
- There is an important association of societal and health disparity and positive SARS-CoV-2 infection.
- In population studies, there is a consistent association of SARS-CoV-2 infection and a reduction in preterm birth rates.
- Messenger RNA-based coronavirus disease 2019 vaccines in pregnant women lead to maternal antibody production and transplacental transfer of passive immunity to the neonate.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic owing to the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide with serious consequences on global public health during the past 1.5 years. During this time, it has become apparent that adults with comorbidities have the highest risk for severe disease and death; meanwhile, it became clearer that children, even though not immune from acquiring the infection, had a less severe presentation and outcome compared with adults. Seroprevalence from some reports seems similar to adults, but the observed cases are less, indicating most likely that children are asymptomatic or very mildly ill to draw medical attention and to be tested.[1–4]

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As of April 2021, the American Academy of Pediatrics (AAP) reported that the cumulative percentage of children positive for SARS-CoV-2 was 13.6% of total cases, but only 0.1% to 1.9% needed hospitalization, with a death rate of 0% to 0.03% depending on the reporting state.[5] Although the natural course is uneventful in most pediatric cases, a very small percentage can develop, about 2 to 4 weeks after the acute COVID-19 infection, a hyperinflammatory state, which is now known as multisystem inflammatory syndrome in children.[6]

In March 2020, little was known about the possible consequences of SARS-CoV-2 infection in pregnant women and fetuses, and there was scant information regarding vertical transmission, neonatal outcomes, and optimal management of the mother-newborn dyad. Respiratory viruses uncommonly result in intrauterine transmission of infection to fetuses, and because SARS-CoV-2 is a respiratory virus, intrauterine transmission was anticipated to be low. On the other hand, the most appropriate perinatal management of the newborns was unknown. Many worldwide societies initially advised, as preferred management to decrease the risk of perinatal transmission, isolation of the newborns immediately after delivery, formula or expressed breastmilk feeding, and no contact, if possible, with the mother for 14 days or at least 7 days from symptoms onset.[7–9] Over the months, several studies showed that the proportion of newborns who tested positive for COVID-19 in the perinatal period was low, from 0% to 6.9% depending on the study.[10–13] Two studies from New York City demonstrated that transmission of COVID-19 appears unlikely to occur despite newborns rooming-in with the mother immediately after birth and breastfeeding, if associated with adequate parental education of safe infection control practices, such as surgical mask wearing at all times and frequent hand and breast hygiene.[10,14] Nevertheless, there are still open questions about newborns when exposed to COVID-19, as they are a particularly vulnerable population with unique challenges in their management.

POSSIBLE METHODS OF MATERNAL TRANSMISSION TO NEWBORNS

There are 3 potential methods of transmission:

- Intrauterine transmission through occult maternal viremia and hematogenous spread to the fetus through the placenta or through ingestion of viral particles present in the amniotic fluid (AF). The extent of this mechanism appears to be rare with only a few case reports in literature.
- Intrapartum transmission through contact with maternal-infected secretions, either respiratory droplets or vaginal secretions, at time of birth.
- Postnatal transmission through contact with infected secretions from any infected caregiver, who could be parents, medical staff, or other household member. As SARS-CoV-2 is a respiratory virus, this seems to be the most prevalent mechanism of transmission to newborns.[15,16]

Most neonates born to asymptomatic COVID-positive mothers are triaged to a regular nursery.[10,14,17] Neonates born to symptomatic mothers are more likely to be admitted to a neonatal intensive care unit (NICU) perhaps as a consequence of premature delivery secondary to the severity of maternal symptoms (see later discussion). For in utero transmission to occur, the virus must be present in maternal blood and be able to cross the placenta to infect the fetus.[18] The presence of angiotensin-converting enzyme 2 (ACE2), the SARS-CoV-2 receptor, in maternal-fetal interface cells, including stromal cells and perivascular cells of decidua, cytotrophoblast, and syncytiotrophoblast (ST) in placenta, as well as specific cell types of human fetal heart, liver, and lung suggests transplacental passage and fetal infection may be possible.[19]

Intrapartum infection can occur through exposure of the infant to infectious virus in maternal blood or secretions during the birth process. Evaluation of a newborn at risk for SARS-CoV-2 particularly with maternal symptoms and/or positive maternal nasopharyngeal (NP) swab should include detection of virus by polymerase chain reaction (PCR) in umbilical cord blood, AF, neonatal blood, NP swab within 24 hours, repeated at 48 hours and 7 days, and from stool and urine. In addition, a placental swab from the fetal side for viral detection should be obtained. In addition, where appropriate, cord blood should be obtained for immunoglobulin G (IgG) and IgM antibodies. In this regard, a classification defining confirmed, probable, or possible infection has been proposed by Shah and colleagues[20] (**Box 1**).

EPIDEMIOLOGIC STUDIES AND POTENTIAL TRANSPLACENTAL VERTICAL TRANSMISSION

Edlow and colleagues[21] undertook a cohort study among pregnant women to quantify SARS-CoV-2 viral load in maternal and neonatal biofluids and incidence of fetoplacental infection. Participants included 127 pregnant women of whom 64 tested positive for SARS-CoV-2 and 63 tested negative. Of the 64 positive women, 23 (36%) were asymptomatic, 22 (34%) had mild disease, 7 (11%) had moderate disease, 10 (16%) had severe disease, and 2 (3%) had critical disease. Among 107 women, there was no detectable viremia in maternal or cord blood and no evidence of vertical transmission. Among 77 neonates tested in whom SARS-CoV-2 antibodies were quantified in cord blood, one had detectable IgM to nucleocapsid. Among 88 placentas tested, SARS-CoV-2 RNA was not detected in any. In antibody analyses, among 37 women with SARS-CoV-2 infection, antireceptor binding domain IgG was detected in 24 women (65%) and antinucleocapsid was detected in 26 women (7%). Nonoverlapping placental expression of SARS-CoV-2 receptors ACE2 and transmembrane

Box 1
Classification of confirmed, , probable and possible infection in symptomatic and asymptomatic newborns[20]

Symptomatic newborns

1. For confirmed infection in symptomatic newborns, there should be detection of the virus by PCR in umbilical cord blood or neonatal blood collected within first 12 hours of birth or AF collected before rupture of membrane.
2. For probable infection, there should be detection of the virus by PCR in NP swab at birth (collected after cleaning baby) and placental swab from fetal side of placenta in a newborn born via CS before rupture of membrane.
3. Possible infection would include no detection of the virus by PCR in NP swab at birth (collected after cleaning baby) but the presence of anti–SARS-CoV-2 IgM antibodies in umbilical cord blood or neonatal blood collected within first 12 hours of birth.

Asymptomatic newborns

4. Confirmed infection would include detection of the virus by PCR in cord blood, or neonatal blood collected within first 12 hours of birth.
5. Probable infection would include detection of the virus by PCR in AF collected before rupture of membrane but no detection in umbilical cord blood or neonatal blood collected within first 12 hours of birth.
6. Possible infection would include the presence of anti–SARS-CoV-2 IgM in umbilical cord blood or detection of the virus by PCR in placental tissue but no detection of the virus by PCR in umbilical cord blood or neonatal blood collected within first 12 hours of birth or AF.

serine protease 2 (TMPRSS2) was noted. In summary, there was no evidence of placental infection or definitive vertical transmission of SARS-CoV-2. Transplacental transfer of anti–SARS-CoV-2 antibodies was inefficient.

Bahadur and colleagues[22] questioned whether there was antenatal or intrapartum vertical transmission from mother to baby after SAR-SCoV-2 infection during pregnancy. From 75 studies, 18 newborns were SARS-CoV-2–positive. A first reverse transcriptase (RT) -PCR diagnostic test was done in 449 babies, and a second diagnostic test was done in 82 babies. Positive results in the first RT-PCR were seen in 14 (3.1%) newborns. Three babies with negative first RT-PCR became positive on the second RT-PCR on days 6 or 7. Testing of AF for SARS-CoV-2 was observed in a few cases. These findings indicate a strong likelihood that intrapartum vertical transmission of SARS-CoV-2 from mother to baby, although rare, is possible.

Single case reports highlighting the transplacental vertical passage of SARS-CoV-2 from maternal to the fetal compartment are as described in **Table 1**.

The authors describe a series of cases (n = 15) that highlight the potential small risk for the transplacental passage of the virus (see **Table 1**). There were 4 confirmed cases of transplacental passage of SARS-CoV-2,[23–26] one case of probable infection 27[27–32] 7 possible cases 28-33[33] and 2 cases of infection proximal to delivery.[34,35]

These few cases of early-onset neonatal SARS-CoV-2 infection indicate that intrapartum vertical transmission of SARS-CoV-2 from mother to baby, although rare, occurs. Infected infants with SARS-CoV-2 may be symptomatic or asymptomatic. Signs include early fever as well as respiratory and neurologic symptoms. Improving access to molecular testing of AF, cord blood, urine, stool, and breast milk, as well as cord blood antibody testing should be a priority to enable investigators to further describe the epidemiology of congenital and neonatal disease in the setting of maternal SARS-CoV-2 infection.

CORONAVIRUS DISEASE 2019 DIAGNOSIS AND IMPACT ON MOTHER AND NEWBORN

Villar and colleagues[36] reported on the extent of SARS-CoV-2 (COVID-19) in pregnancy and the risk of adverse maternal and neonatal outcomes compared with pregnant individuals without COVID-19. Seven hundred six pregnant women with COVID-19 and 1424 pregnant women without COVID-19 were enrolled in a multinational cohort study. Women with a COVID-19 diagnosis were at significantly higher risk for (a) preeclampsia (PEC)/eclampsia (relative risk [RR] 1.76), (b) intensive care unit admission (RR, 5.04), (c) maternal mortality (RR, 22.3), (d) preterm birth (PTB; RR, 1.59), (e) medically indicated PTB (RR, 1.97), (f) severe neonatal morbidity index (RR, 2.66), and (h) severe perinatal morbidity and mortality index (RR, 2.14). Fever and shortness of breath for any duration were associated with increased risk of severe maternal complications (RR, 2.56) and neonatal complications (RR, 4.97). Asymptomatic women remained at higher risk only for maternal morbidity (RR, 1.24) and PEC (RR, 1.63). Among positively tested women, 13% of their neonates tested positive. Cesarean section (CS) delivery (RR, 2.15) but not breastfeeding (RR, 1.10) was associated with increased risk for neonatal test positivity.

Angelidou and colleagues[37] identified 255 neonates born to 250 mothers with positive SARS-CoV-2 test results. This included 79 (32%) symptomatic and 170 (68%) asymptomatic mothers. Worsening COVID-19 illness prompted delivery in 23 mothers (9%), of which 20 (87.0%) were via CS. Six neonates (2.2%) presented with positive SARS-CoV-2 test results within the first week of life. Of the 6 neonates, 2 neonates presented with respiratory distress and were delivered preterm, 1 neonate had nasal

Table 1
Case series describing transplacental (vertical) severe acute respiratory syndrome coronavirus 2 infection

Case No.	Author	Description
1	Vivanti et al,[23] 2020	A 23-yr-old gravida 1, para 0 mother who presented with respiratory symptoms and was SARS-CoV-2–positive. Delivery was via CS with SARS-CoV-2–positive AF. The placenta demonstrated a very high viral load as well as histologic and immune histochemical findings consistent with placental inflammation. A male neonate was delivered at 35 5/7 wk GA with a birth weight (BW) of 2540 g. Apgar scores were 4, 2, and 7 at 1, 5, and 10 min, respectively. Delivery room resuscitation included bag mask positive pressure ventilation and intubation. The baby was extubated after ~6 h. NP and rectal swabs obtained on DOL 1, 3, and 18 were all positive for the S and E SARS-CoV-2 genes. In addition, blood and bronchial lavage fluid obtained before extubation was positive for SARS-CoV-2. On DOL 3, the neonate suddenly presented with irritability, poor feeding, axial hypertonia, and opisthotonos. Cerebrospinal fluid (CSF) was negative for SARS-CoV-2, bacteria, fungi, herpes simplex virus 1 and 2. The infant gradually improved over subsequent days and was discharged on DOL 18. MRI on DOL 11 demonstrated bilateral gliosis of the deep periventricular and subcortical white matter.
2	Kirtsman et al,[24] 2020	A 40-yr-old gravida 2, para 1 mother who presented with myalgia, decreased appetite, fatigue, dry cough, and temperature of 39°C in the 24 h before delivery. An NP swab was positive for SARS-CoV-2. Delivery was via CS with artificial rupture of membranes at delivery with clear AF. A male neonate of BW 2930 g was delivered vigorous. The Apgar scores were 9 and 9 at 1 and 5 min, respectively. Placental tissue was positive from the maternal and fetal side, the parenchyma and chorion for SARS-CoV-2 gene targets. Vaginal secretions and NP swabs obtained on DOL 1, 2, and 7 were all positive for SARS-CoV-2 gene targets. Neonatal plasma tested positive on day 4, and stool tested positive on day 7. Breast milk was also positive on DOL 2 but not on DOL 7. The neonate was discharge on DOL 4.
3	Von Kohorn et al,[25] 2020	A 34-wk GA 2414-g male neonate was born to a mother with a history of cough for a week; diagnosed 14 h before delivery with positive NP swab for SARS-CoV-2 infection. Delivery was via CS. AF was clear. Apgar scores were 7 and 9 at 1 and 5 min, respectively. The physical examination was normal. The infant continued to be asymptomatic and was discharged on DOL 8 and

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Table 1
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Case No.	Author	Description
		remained healthy through the first months of life. The cord blood, NP swabs on DOL 2, 4, 7, and urine were positive for SARS-CoV-2. Placental tissue was negative SARS-CoV-2 gene targets and cord serum, and plasma was seronegative for IgM and IgG antibodies.
4	Lorenz et al,[26] 2020	A healthy 40 3/7-wk GA female newborn born to a mother who an elevated temperature (maximum 38.1°C) during labor coupled with a history of mild respiratory infection and loss of smell and taste. She tested positive for SARS-CoV-2. Apgar scores were 9 and 9 at 1 and 5 min, respectively. At 24 h, the newborn developed refractory fever (38.6°C), appeared lethargic, and progressed to encephalitic symptoms (ie, hyperexcitable, high-pitched crying) over the next 30 h. She was transferred to a tertiary center NICU. The newborn's NP and rectal swabs tested positive for SARS-CoV-2. Bacterial cultures of CSF and blood were sterile. CSF tested negative for SARS-CoV-2. A cranial ultrasound scan was unremarkable. The initial chest radiograph was normal; however, the newborn developed respiratory distress at about 80 h of life and needed continuous positive airway pressure and oxygen therapy until DOL 6. At DOL 10, severe staccato-like coughing emerged, and another chest radiograph was consistent with bilateral pneumonia. The newborn's NP and rectal swaps remained positive for SARS-CoV-2 through 14 d after birth. The patient was discharged free of symptoms on DOL 14.
5	Sisman et al,[27] 2020	A 34-wk gestation 3280-g female infant born to a 37-yr-old gravida 4, para 3 woman. She was admitted for evaluation of preterm labor. Her NP swab was positive for SARS-CoV-2. Labor was augmented with oxytocin on the third day after hospitalization following premature preterm rupture of membranes 8 h before delivery. The AF was clear. Delivery was vaginal. Apgar scores were 7 and 9 at 1 and 5 min of life, respectively. There was no respiratory distress. The infant's NP swab was positive by RT-PCR for SARS-CoV-2 at 24 and 48 h of life. The infant developed fever and respiratory distress, that is, mild subcostal retractions, tachypnea on DOL 2. Blood and CSF bacterial cultures, and surface, blood, and CSF for herpes simplex virus DNA PCR were obtained. All cultures were negative. Respiratory signs resolved within 3 d, and the infant was weaned to room air by DOL 5. NP RT-PCR for SARS-CoV-2 remained

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Table 1
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Case No.	Author	Description
		positive on DOL 14. SARS-CoV-2 virus was detected in the placental tissue. The infant was discharged home on DOL 21.
6	Patanè et al,[28] 2020	Two cases. The first represents a mother who presented at 37 6/7 wk GA who presented with a fever and a cough and had a positive NP swab for COVID. Delivery was vaginal. The BW was 2660 g. Apgar scores were 9 and 10 at 1 and 5 min, respectively. No skin-to-skin contact was permitted; however, rooming-in and breastfeeding with a mask were allowed. The newborn had a positive result for COVID-19 from NP swabs obtained immediately after birth, and at DOL 1 and 7. The neonate remained asymptomatic and was discharged from the hospital at 10 DOL after being hospitalized for observation. The second case represents a mother who presented at 35 1/7 wk of gestation with a fever, cough, and a positive COVID-19 NP swab test. Delivery was via CS secondary to a non-reassuring fetal status. The newborn was female with a BW of 2686 g. Apgar scores were 9 and 10 at 1 and 5 min, respectively. She was admitted to the NICU. A neonatal NP swab obtained at birth was negative for SARS-CoV-2, but a follow-up NP swab obtained on DOL 7 was positive. No contact between the mother and the neonate during that period occurred. The neonate was discharged on DOL 20 after hospitalization for routine late preterm care. The placentas of these 2 women demonstrated SARS-CoV-2 antigens seen in the villous ST on the fetal side of the placenta in both cases.
7	Alamar et al,[29] 2020	A 32-yr-old gravida 2, para 0 female who presented at 35 6/7 wk GA with vaginal bleeding. She reported fever, mild chills, fatigue, dysgeusia, and anosmia beginning 1 d before arrival. A 2630-g female neonate was delivered via emergent CS due to bleeding. The Apgar scores were 9 and 9 at 1 and 5 min, respectively. The newborn was asymptomatic. The maternal pharyngeal screen for SARS-CoV-2 was positive on postpartum day 1. The infant's NP PCR for SARS-CoV-2 was positive on DOL 1, 2, and 7. The mother and infant remained afebrile, asymptomatic, and hemodynamically stable throughout the hospitalization. In situ hybridization for SARS-CoV-2 RNA revealed a strong signal in the villous ST but not in villous stromal cells, Hofbauer cells, or villous endothelium.

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Case No.	Author	Description
8	Alzamora et al,[30] 2020	A 41-yr-old gravida 3, para 2 who presented with a 4-d history of malaise, low-grade fever, and progressive shortness of breath. An NP swab was positive for COVID-19. The patient progressed to respiratory failure requiring mechanical ventilation on day 5 of disease onset. Delivery was via CS. The neonatal NP RT-PCR swab on DOL 1 was positive for SARS-CoV-2. Maternal IgM and IgG were positive on postpartum day 4 (day 9 after symptom onset); neonatal immunoglobulins were negative.
9	Parsa et al,[31] 2020	A 41-yr-old mother who presented with signs and symptoms of acute respiratory illness, including shortness of breath and cough. RT-PCR on the mother was positive, and she was diagnosed with COVID-19 pneumonia. Delivery was via emergency CS. A term 3500-g female infant was delivered with Apgar scores of 9 and 10 at 1 and 5 min, respectively. The RT-PCR results of the AF and neonate (<24 h after birth) were positive for COVID-19. She was admitted to the NICU and received routine care. She developed a fever on DOL 10; all tests were negative. NP swabs were negative on DOL 11 and 14. She was discharged on DOL 28 in good condition.
10	Lima-Rogel et al,[32] 2021	A term 3450-g male infant born to a 19-yr-old asymptomatic mother via CS secondary to fetal bradycardia. The mother roomed in with another mother-baby pair, both positive for SARS-CoV-2. On DOL 2, the neonate developed tachypnea with distress, and a chest radiograph suggested pneumonia. On DOL 3, both the mother and the newborn RT-PCR were positive for SARS-CoV-2; the mother remained asymptomatic. The neonate required mechanical ventilation and was transferred to a tertiary level neonatal unit on day 5. He was extubated on DOL 8. An RT-PCR test for SARS-CoV-2 was negative on DOL 8, and he was discharged DOL 21.
11	Zamaniyan et al,[33] 2020	A 22-y-old mother who presented with respiratory symptoms, myalgia, and fever with positive testing for SARS-CoV-2. After 3 d, she underwent a CS and delivered a 30 5/7-wk 2350-g female infant with Apgar scores of 9 and 9 at 1 and 5 min, respectively. The infant exhibited initial fever and was treated with antibiotics. She recovered and was without issues by DOL 8. Cultures from the AF and from the NP at DOL 1 and 7 were positive for SARS-CoV-2.

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Case No.	Author	Description
12	Dong et al,[57] 2020	A 29-yr-old gravida 1, para 0 mother who presented 1 mo before delivery at 34 2/7 wk gestation suspected of being exposed to SARS-CoV-2. Over the next month, her NP swabs were repeatedly SARS-CoV-2–positive. Vaginal swab 1 day before delivery was negative for SARS-CoV-2. Delivery was via CS. Apgar scores were 9 and 10 at 1 and 5 min, respectively. The BW was 3120 g. The neonate was asymptomatic. At 2 h of age, both IgG and IgM levels as well as cytokines, interleukin-6 (IL-6), and IL-10 were elevated. Five NP RT-PCR swabs from 2 h to 16 d of age were negative. Her IgM and IgG levels were still elevated a month later. Discharge was on DOL 30.
13	Hascoët et al,[34] 2020	A mother presented with COVID-19 infection with positive RT-PCR results 6 wk before delivery. She exhibited fever and profound asthenia for 10 d. The mother was considered cleared with negative NP and stool SARS-CoV-2 RT-PCR before delivery. Labor was uncomplicated, and delivery was vaginal. A 39-wk healthy-appearing female infant was delivered. The baby was initially fed with expressed milk and then directly breastfed. RT-PCR testing of the breast milk yielded negative results. NP swabs yielded negative results on DOL 3; however, testing of the baby's stool yielded positive results on day 1. IgG antibodies were detected in the mother and newborn, and IgM antibodies in the mother only. The infant was seen in clinic 45 d following delivery and 12 wk from maternal symptoms and positive PCR. Physical examination was normal. IgG antibodies detection remained positive; however, IgM antibodies were negative.
14	Bandyopadhyay et al,[35] 2021	A 37 2/7 wk female newborn born to a 24-yr-old mother who developed a low-grade fever. Her RT-PCR pharyngeal swab for SARS-CoV-2 at the time was positive. Repeat RT-PCR pharyngeal swab 2 wk later was again positive. A repeat RT-PCR test done 2 d before delivery was negative. Delivery was vaginal. The BW was 2590 g. Apgar scores were 8 and 9 at 1 and 5 min, respectively. The newborn was formula fed. An NP swab specimen collected immediately from the newborn (16 h) after birth was positive; qualitative infant serum IgG antibody test was positive for SARS-CoV-2 infection with a concurrent negative qualitative IgM antibody test. Repeat NP swabs obtained on DOL 2 and 3 were negative. The newborn remained in the NICU for 9 d.

congestion, and 3 neonates were asymptomatic. Adjusting for maternal symptoms, delivery mode, and rooming-in practice, mothers with high social vulnerability index (≥90th percentile) were more likely to have neonates with positive SARS-CoV-2 test results (adjusted odds ratio [OR], 4.95) (P = .008). Newborns with positive SARS-CoV-2 test results appeared to have minimal burden of illness that was directly associated with a viral infection. Those born in the context of delivery prompted by worsening maternal COVID-19 symptoms were more likely to be PTB, which led to a need for resuscitation in the delivery room, more respiratory morbidity, and longer length of stay.

Gale and colleagues[38] carried out a prospective UK population-based cohort study of 66 inpatient newborns with confirmed SARS-CoV-2 infection in the first 28 days of life (DOL; incidence 5.6 [95% confidence interval [CI], 4.3–7.1] per 10,000 live births), of whom 28 (42%) had severe neonatal SARS-CoV-2 infection (incidence 2.4 [1.6–3.4] per 10,000 live births). Of these newborns, 16 (24%) were born preterm. (a) Thirty-six (55%) babies were from white ethnic groups (SARS-CoV-2 infection incidence 4.6 [3.2–6.4] per 10,000 live births), (b) 14 (21%) babies were from Asian ethnic groups (15.2 [8.3–25.5] per 10,000 live births), (c) 8 (12%) babies were from black ethnic groups (18.0 [7.8–35.5] per 10,000 live births), and (d) 7 (11%) babies were from mixed or other ethnic groups (5.6 [2.2–11.5] per 10,000 live births). One (2%) newborn died of a cause unrelated to SARS-CoV-2 infection.

Norman and colleagues[39] evaluated neonatal outcomes in relation to maternal SARS-CoV-2 test positivity during pregnancy in Sweden. Of 88,159 infants, 2323 (2.6%) were delivered by mothers who tested positive for SARS-CoV-2. There was an association of maternal SARS-CoV-2 infection with newborns' admission for neonatal care (11.7% versus 8.4%; OR, 1.47; 95% CI, 1.26–1.70) and any neonatal respiratory disorder (2.8% vs 2.0%; OR, 1.42; 95% CI, 1.07–1.90). There was a higher rate of preterm delivery (near term) among infected mothers: 8.8% versus 5.5% in the SARS-CoV-2–positive group versus the comparison group, respectively. There were no differences in neonatal mortality, length of hospital stay, or breastfeeding rates.

Mullins and colleagues[40] reported the outcome of SARS-CoV-2–infected pregnancies from a collaboration between investigators of 2 registries, the UK and Global Pregnancy and Neonatal outcomes in COVID-19 (PAN-COVID) study and the AAP Section on Neonatal-Perinatal Medicine (SONPM) National Perinatal COVID-19 Registry. Analysis of data from the PAN-COVID registry included pregnancies with suspected or confirmed maternal SARS-CoV-2 infection at any stage in pregnancy, and the AAP-SONPM National Perinatal COVID-19 registry included pregnancies with positive maternal testing for SARS-CoV-2 from 14 days before delivery to 3 days after delivery. The outcome on 4005 pregnant women with suspected or confirmed SARS-CoV-2 infection (n = 1606 from PAN-COVID and n = 2399 from AAP-SONPM) was available. For obstetric outcomes in those with confirmed infection in PAN-COVID and AAP-SONPM, respectively, maternal death occurred in 0.5% and 0.2% of cases, early neonatal death occurred in 0.3% and 0.3% of cases, and stillbirth occurred in 0.6% and 0.4% of cases, respectively. Preterm delivery (<37 weeks' gestation) was noted in 16.1% of women with confirmed infection in PAN-COVID and in 15.7% of women in AAP-SONPM. The rates of a small-for-gestational-age (SGA) neonate were 9.7% in those with confirmed infection and 9.6% in AAP-SONPM. The findings from the UK and US registries of pregnancies with SARS-CoV-2 infection were remarkably concordant.

The above studies indicate that a symptomatic SARS-CoV-2–infected mother increases the risk for preterm and medically induced PTB.[36] An asymptomatic COVID-19–positive mother was not associated with an increased risk of neonatal

morbidity. Two studies in this section highlight an important association of societal and health disparity and positive SARS-CoV-2 infection. Thus, mothers with a high social vulnerability index (≥90th percentile) were more likely to have neonates with positive SARS-CoV-2 test results.[37] In a second study, a high proportion of newborns from black, Asian, or minority ethnic groups was more likely to have newborns with positive SARS-CoV-2 infection.[38] Newborns with positive SARS-CoV-2 test results appear to have minimal burden of illness that is directly associated with a viral infection but rather through the impact of preterm delivery, undertaken because of the mother's worsening illness.[37] Preterm delivery affected a higher proportion of women than expected based on historical and contemporaneous national data.[40] The proportions of pregnancies affected by stillbirth, SGA infant, or early neonatal death were comparable to those in historical and contemporaneous UK and US data. The reported incidence of positive neonatal SARS-CoV-2 PCR test ranges from 0.56% to 2%.[37–40] Finally, neonatal mortality as a result of SARS-CoV-2 is extremely rare.

FURTHER EVIDENCE TO SUPPORT A RELATIONSHIP BETWEEN SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 AND PREMATURE BIRTHS

The question of whether SARS-CoV-2 infection is associated with increased or decreased likelihood of premature births is important to delineate. From the preceding section, the evidence suggests that premature birth is more likely to occur in the setting of symptomatic mothers. Conversely, a reduction in premature birth rates has been suggested from population studies that may reflect a change in social behavior that occurred during the pandemic.

In the below discussion, the authors present several population studies that have addressed this very relevant question.

Simpson and colleagues[41] evaluated 67,747 births during the pandemic period (March to September 2020) and compared the outcomes to 348,633 births delivered during a comparable historical period (2015–2019) in Canada. No differences in the overall risk of PTB, stillbirth, or other perinatal outcomes during the first 6 months of the COVID-19 pandemic were noted. However, a small reduction in PTB less than 32 weeks' gestational age (GA) in the 2 groups (1.3% versus 1.2%; OR, 0.89; 95% CI, 0.80–0.99), which persisted after multivariable adjustment (OR, 0.91; 95% CI, 0.85–0.98) was observed.

Philip and colleagues[42] evaluated regional trends of very low birth weight (VLBW) (<1500 g) and extremely low birth weight (ELBW) infants (<1000 g) in 1 designated health area of Ireland over 2 decades (January to April 2001–2019) versus a similar time period in 2020. The regional historical VLBW rate per 1000 live births was 8.18 (95% CI, 7.21–9.29), which was reduced to 2.17 per 1000 live births during the first 4 months of 2020, reflecting a rate ratio of 3.77 (95% CI, 1.21–11.75) ($P = .02$), representing a 73% reduction of VLBW. There were no ELBW infants admitted to the regional NICU during the 4 months in 2020. When the data were extended through June 30, these observations persisted.

Hedermann and colleagues[43] explored the impact of COVID-19 lockdown on PTBs using a nationwide register conducted on all 31,180 live singleton newborns born between March 12 and April 14 during 2015 to 2020 in Denmark. There were 5162 singleton and 1566 premature births during the lockdown in 2020. The distribution of GA was significantly different ($P = .004$) during the lockdown period versus the previous 5 years. This reflected a significantly lower rate of extremely premature newborns (<28 weeks) delivered during the lockdown versus the corresponding mean rate for the same dates in the previous years (OR, 0.09; 95% CI, 0.01–0.40, $P<.001$) (90% reduction).

Harvey and colleagues[44] used Tennessee birth records from 2015 to 2020 and restricted analyses to March 22 to April 30 for each year to reduce the effect of seasonality. There were 49,845 births during the study period. The PTB rate (<37 weeks) during the 2020 stay-at-home order was lower than rates in previous years (10.2% vs 11.3%; $P = .003$). Specifically, late preterm (35–36 6/7 weeks' gestation) birth rates were also lower (5.8% vs 6.5%; $P = .03$). There was no difference in GA less than 32 weeks ($P = .27$). There was a higher rate of assisted ventilation during the pandemic versus the comparison period (4.5% vs 3.2%) ($P<.001$), respectively. This extended to premature infants less than 37 weeks, that is, 17.9 versus 12.3% ($P<.001$), respectively. After accounting for maternal age, education, race/ethnicity, diabetes, and hypertension, the ratio for PTB in 2020 compared with 2015 to 2019 was 0.86 (95% CI, 0.79–0.93).

Pasternak and colleagues[45] compared the risk for PTB and stillbirth among births from April 1 through May 31, 2020 with births from all April through May in the years 2015 to 2019 in Sweden. There was no association between being born in 2020 versus 2015 to 2019 and risk for extremely PTB (adjusted OR, 0.92; CI, 0.66–1.28), very PTB (adjusted OR, 1.09; CI, 0.85–1.40), or stillbirth (adjusted OR, 0.78; CI, 0.57–1.06). This nationwide study did not find any associations between being born during a period in 2020 and the risk for any of the PTB categories or stillbirth.

The authors reviewed data from their institution (New York Presbyterian Hospital) where PTB rates were compared for different GA categories for years 2017 to 2019 versus 2020. There was no difference in the number of births for the ELBW and VLBW infants but a significant reduction for the near term (34–36 6/7 week) newborn (**Table 2**).

There was a consistent association of SARS-CoV-2 infection and a reduction in PTB rates in 5 of the 6 studies reviewed. In 2 studies,[42,43] there was a striking reduction in VLBW infants less than 28 weeks and/or less than 1500 g ranging from 73% to 90%. A third study demonstrated a smaller reduction (11%) in the number of VLBW infants <32 weeks.[41] One study demonstrated a 14% reduction noted in the late preterm infant, an effect that was similar to the authors' observations.[44] Why the reduction in PTB delivery rates? The COVID-19 pandemic lockdown drastically changed lives in many ways, including a change in the working environment (work from home where possible), reducing physical interactions with a focus on hygiene (frequent hand washing, social distancing, and wearing a mask). These changes may have influenced the overall inflammatory state of pregnant women.

MATERNAL SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 INFECTION, MATERNAL VACCINATION, AND ANTIBODY PRODUCTION IN CORD BLOOD AND BREAST MILK

It remains unclear whether the maternal immune response to infection protects the fetus (**Table 3**). Moreover, the impact of maternal vaccination on maternal and

Table 2
Number of neonates admitted per year (2017–2020) as a function of gestational age

Gestational Age, wk	2017	2018	2019	2020
<27	16	9	18	18
≥27–30 6/7	41	41	32	44
31–33 6/7	68	77	84	70
34–36 6/7	174	173	195	127[a]

[a] $P<.05$ comparing 2020 to prior years.

Table 3
Studies that evaluated the impact of severe acute respiratory syndrome coronavirus 2 infection as well as maternal vaccination on immunoglobulin G , immunoglobulin M, and immunoglobulin A antibody concentrations and the impact of severe acute respiratory syndrome coronavirus 2 infection on breast milk

Author	Study Description
Flannery et al,[46] 2021	1471 mother/newborn dyads were studied to assess the association between maternal and neonatal SARS-CoV-2–specific antibody concentrations. SARS-CoV-2 IgG and/or IgM antibodies were detected in 83 of 1471 women (6%) at the time of delivery, and IgG was detected in cord blood from 72 of 83 newborns (87%). IgM was not detected in any cord blood specimen, and antibodies were not detected in any infant born to a seronegative mother. Placental transfer ratios >1.0 were observed among women with asymptomatic SARS-CoV-2 infections as well as those with mild, moderate, and severe COVID-19. Cord blood antibody concentrations correlated with maternal antibody concentrations and with duration between onset of infection and delivery. The findings indicate the potential for maternally derived SARS-CoV-2–specific antibodies to provide neonatal protection from coronavirus disease 2019.
Perl et al,[47] 2021	Study included 84 breastfeeding mothers who provided 504 breast milk samples in Israel. All participants received 2 doses of the Pfizer-BioNTech vaccine 21 d apart. Breast milk samples were collected before administration of the vaccine and then once weekly for 6 wk starting at week 2 after the first dose. Robust secretion of SARS-CoV-2–specific IgA and IgG antibodies was found in breast milk for 6 wk after vaccination. IgA secretion was evident as early as 2 wk after the first vaccine when 61.8% of samples tested positive, increasing to 86.1% at week 4 (1 wk after the second vaccine). Anti–SARS-CoV-2–specific IgG antibodies remained low for the first 3 wk, which increased to 91.7% of samples tested positive at week 4, increasing to 97% at weeks 5 and 6. Antibodies found in breast milk showed strong neutralizing effects, suggesting a potential protective effect against infection in the infant.
Collier et al,[48] 2021	This was an evaluation of the immunogenicity of COVID-19 mRNA vaccines in pregnant and lactating women, including against emerging SARS-CoV-2 variants of concern. This prospective cohort study enrolled 103 women (30 pregnant, 16 lactating, and 57 neither pregnant nor lactating) who received a COVID-19 vaccine and 28 women (22 pregnant and 6 nonpregnant unvaccinated) with confirmed SARS-CoV-2 infection. The women received either the mRNA-1273 (Moderna) or the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccines. After the second vaccine dose, fever was reported in 4 pregnant women (14%), 7 lactating women (44%), and 27 nonpregnant women (52%). Binding, neutralizing, and functional nonneutralizing antibody responses as well as CD4 and CD8 T-cell responses were present in all the women following vaccination. Binding and neutralizing antibodies were also observed in infant cord blood and breast milk. Binding and neutralizing antibody titers against the SARS-CoV-2 B.1.1.7 and B.1.351 variants of concern were reduced, but T-cell responses were preserved against viral variants. COVID-19 mRNA vaccine administration was immunogenic in pregnant women, and vaccine-elicited antibodies were transferred to infant cord blood and breast

(*continued on next page*)

Table 3
(*continued*)

Author	Study Description
	milk. Importantly, pregnant and nonpregnant women who were vaccinated developed cross-reactive antibody responses and T-cell responses against SARS-CoV-2 variants of concern.
Prabhu et al,[49] 2021	This was an evaluation of the impact of mRNA vaccine administered to 122 pregnant women of whom 55 had received one and 67 who received both vaccine doses. This included 85 who received the Pfizer-BioNTech vaccine, and 37 who received the Moderna vaccine. All women tested negative for SARS-CoV-2 infection using RT-PCR on NP swabs; all women and neonates were asymptomatic at birth and until time of discharge. Of the women tested at birth, 87 (71%) produced an IgG response, 19 (16%) produced both IgM and IgG response, and 16 (13%) had no detectable antibody response; the latter were within 4 wk of initial vaccine dose. The number of women who mounted an antibody response and conferred passive immunity to their neonates increased as a function of the number of weeks elapsed. All women and cord blood samples, except for one, had detectable IgG antibodies by 4 wk after the first vaccine dose. The earliest detection of antibodies in women occurred 5 d postvaccine dose 1, and the earliest detection of antibodies in cord blood occurred 16 d postvaccine dose 1. Forty-four percent of cord blood samples from women who received only 1 vaccine dose had detectable IgG, whereas 99% from women who received both vaccine doses had detectable IgG in cord blood. Maternal IgG levels increased significantly week by week, starting 2 wk after the first vaccine dose as well as between the first and second weeks after the second vaccine dose. Maternal IgG levels were linearly correlated with cord blood IgG levels ($r = 0.50$, $P<.0001$).
Chambers et al,[50] 2020	This was a study of women who tested positive by RT-PCR tests to determine whether there is transmission of infectious virus to the infant through breast milk. Breast milk samples were self-collected and mailed to the study center. In some cases, women also provided stored samples collected before enrollment. Only women who tested positive by RT-PCR tests were included. In addition, conditions of Holder pasteurization commonly used in human milk banks were mimicked by adding SARS-CoV-2 (200 $\times$ median tissue culture infectious dose 50%) to breast milk samples from 2 different control donors who provided milk samples before the onset of the pandemic. There were 18 women who provided between 1 and 12 samples, with a total of 64 samples collected at varying time points before and after the positive SARS-CoV-2 RT-PCR test result. All but 1 woman had symptomatic disease. One breast milk sample had detectable SARS-CoV-2 RNA. The positive sample was collected on the day of symptom onset; however, an additional sample taken 2 d before symptom onset and 2 samples collected 12 and 41 d later tested negative for viral RNA. The breastfed infant was not tested. No replication-competent virus was detectable in any sample, including the sample that tested positive for viral RNA. Following Holder pasteurization, viral RNA was not detected by RT-PCR in the 2 samples that had been spiked with replication-competent SARS-CoV-2, nor was culturable virus detected. However, virus was detected by culture in nonpasteurized aliquots of the same 2 milk-virus mixtures. These findings are reassuring given the known benefits of breastfeeding and human milk provided through milk banks.

neonatal antibody production remains unclear. Flannery and colleagues[46] studied 1471 mother/newborn dyads. SARS-CoV-2 IgG and/or IgM antibodies were detected in 83 of 1471 women (6%) at the time of delivery, and IgG was detected in cord blood from 72 of 83 newborns (87%). IgM was not detected in any cord blood specimen. Placental transfer ratios more than 1.0 were observed among all women whether asymptomatic or with severity of infection. Cord blood antibody concentrations correlated with maternal antibody concentrations and with duration between onset of infection and delivery.

Perl and colleagues[47] studied 84 breast-feeding mothers who had received 2 doses of the Pfizer-BioNTech vaccine 21 days apart. Robust secretion of SARS-CoV-2–specific IgA and IgG antibodies was found in breast milk for 6 weeks after vaccination. IgA secretion was evident as early as 2 weeks after the first vaccine, increasing to 86.1% at week 4. Specific IgG antibodies increased to 97% at weeks 5 and 6. In addition, antibodies found in breast milk showed strong neutralizing effects, suggesting a protective effect against infection in the infant.

Collier and colleagues[48] evaluated the immunogenicity of COVID-19 messenger RNA (mRNA) vaccines (either Moderna or Pfizer-BioNTech) in 30 pregnant women, 16 lactating women, 57 nonpregnant women, and 28 women (22 pregnant and 6 nonpregnant unvaccinated women) with confirmed SARS-CoV-2 infection. Binding, neutralizing, and functional nonneutralizing antibody responses as well as CD4 and CD8 T-cell responses were present in all the women following vaccination. Binding and neutralizing antibodies were also observed in infant cord blood and breast milk. T-cell responses were preserved against viral variants. COVID-19 mRNA vaccine administration was immunogenic in pregnant women, and vaccine-elicited antibodies were transferred to infant cord blood and breast milk. Importantly, pregnant and nonpregnant women who were vaccinated developed cross-reactive antibody responses and T-cell responses against SARS-CoV-2 variants of concern.

Prabhu and colleagues[49] evaluated the impact of mRNA vaccine administered to 122 SARS-CoV-2–negative pregnant women (85 who received the Pfizer-BioNTech and 37 who received the Moderna vaccine). Of the women tested at birth, 87 (71%) women produced an IgG response, 19 (16%) women produced both IgM and IgG response, and 16 (13%) women had no detectable antibody response. Women who mounted an antibody response and conferred passive immunity to their neonates increased as a function of the number of weeks since vaccination. The earliest detection of antibodies in women occurred 5 days post–initial vaccine dose, and the earliest detection of antibodies in cord blood was 16 days after the initial vaccine dose. Importantly, 99% of women who received both vaccine doses had detectable IgG in cord blood. Maternal IgG levels were linearly correlated with cord blood IgG levels.

A separate question is whether there is transmission of infectious virus to the newborn through breast milk. Chambers and colleagues[50] studied symptomatic women (n = 18) who tested positive by RT-PCR testing. In addition, conditions of Holder pasteurization commonly used in human milk banks were mimicked by adding SARS-CoV-2 to breast milk samples from 2 different control donors who provided milk samples before onset of the pandemic. No replication-competent virus was detectable in any of the 64 samples. Following Holder pasteurization, viral RNA was not detected by RT-PCR in the 2 samples that had been spiked with replication-competent SARS-CoV-2. However, virus was detected by culture in nonpasteurized aliquots of the same 2 milk-virus mixtures.

mRNA-based COVID-19 vaccines in pregnant women lead to maternal antibody production, and this can occur as early as 5 days after the first vaccination dose and transplacental transfer of passive immunity to the neonate as early as 16 days after the first

vaccination dose. The increasing levels of maternal IgG over time and the increasing placental IgG transfer ratio over time suggest that timing between vaccination and birth (as shown by Perl and colleagues[47] and Prabhu and colleagues[49]) is likely to be an important factor to consider in vaccination strategies of pregnant women. The variability in antibody transfer and lack of transfer in 13% of cases in the study[49] highlight the importance of additional studies to understand factors that influence transplacental transfer of IgG antibodies as well as the protective nature of these antibodies.

PLACENTA FINDINGS IN SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS2–POSITIVE MOTHERS

Several studies have evaluated the placentas of mothers who were SARS-CoV-2–positive. The pathologic findings appear to reflect whether the mother was asymptomatic or symptomatic.

Jaiswal and colleagues[51] described the histopathologic alterations in the placenta of 27 SARS-CoV-2–positive singleton pregnancies with no symptoms or mild COVID-19-related symptoms and an equal number of SARS-CoV-2–negative singleton pregnancies. Features of maternal vascular malperfusion were significantly higher in the placentas of COVID-19-positive pregnancies. The percentage of spontaneously delivered women was comparable in the 2 groups. Schwartz and Morotti[52] summarized the spectrum of pathology findings from pregnant women with COVID-19 based on the infection status of their infants. Placentas from infected maternal-neonatal dyads were characterized by the finding of mononuclear cell inflammation of the intervillous space (chronic histiocytic intervillositis), coupled with ST necrosis. Hecht and colleagues[53] examined 19 SARS-CoV-2–positive exposed placentas for histopathologic findings and for expression of ACE2 and TMPRSS2 by immunohistochemistry. ACE2 membranous expression was observed in the ST of the chorionic villi and was predominantly in a polarized pattern with expression highest on the stromal side of the ST. Cytotrophoblast and extravillous trophoblast expressed ACE2. TMPRSS2 expression was only present weakly in the villous endothelium and rarely in the ST.

Hosier and colleagues[54] analyzed the placenta for the presence of SARS-CoV-2. SARS-CoV-2, which localized predominantly to ST cells at the maternal-fetal interface of the placenta. Histologic examination of the placenta revealed a dense macrophage infiltrate. Argueta and colleagues[55] investigated the impact of SARS-CoV-2 infection on the placenta from a cohort of women who had tested positive for SARS-CoV-2 at delivery. Three placentas with high virus content were obtained from mothers who presented with severe COVID-19 and whose pregnancies resulted in adverse outcomes, including intrauterine fetal demise, stillbirth, and a preterm delivered baby admitted to the NICU. Infection was restricted to ST cells that envelope the fetal chorionic villi and are in direct contact with maternal blood. The infected placentas displayed massive infiltration of maternal immune cells, including macrophages into intervillous spaces, potentially contributing to inflammation of the tissue.

ST cells that envelope the fetal chorionic villi are in direct contact with maternal blood and are particularly vulnerable to SARS-CoV-2. Infection in many studies was restricted to the ST cell with subsequent necrosis. Placentas from infected maternal-neonatal dyads display massive infiltration of maternal immune cells, including macrophages into intervillous spaces. Massive infiltration of maternal immune cells coupled with ST necrosis appears to heighten the risk for maternal-fetal viral transmission. ACE2 membranous expression was observed in the ST of the chorionic villi predominantly in a polarized pattern with expression highest on the stromal side of the ST.

SUMMARY

Maternal SARS-CoV-2 infection can present with or without symptoms at the time of birth. The reported incidence of positive neonatal SARS-CoV-2 PCR test ranges from 0.56% to 6.9%. Symptomatic mothers are likely to be associated with PTB. By contrast, population studies demonstrate a consistent association of SARS-CoV-2 infection and a reduction in PTB rate. Newborns with positive SARS-CoV-2 test results appeared to have minimal burden of illness that is directly associated with a viral infection. Finally, maternal vaccination in pregnant women leads to maternal antibody production with passive transfer to their fetuses, which increases as a function of time.

CLINICS CARE POINTS

- Asymptomatic COVID 19 positive mothers need not be separated from their newborn baby after delivery.
- Breast-feeding is safe if associated with adequate parental education of safe infection control practices.
- COVID-19 vaccination is recommended for women who are pregnant or breastfeeding.
- Women who are pregnant may receive a booster vaccine shot.

DISCLOSURE

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