Perinatal SARS-CoV-2 Infection and Neonatal COVID-19: A 2021 Update

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Practice Gap

Optimal management strategies are required for neonates born to mothers with SARS-CoV-2 in the immediate postpartum period to minimize chances of viral transmission.

Abstract

The coronavirus disease 2019 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has swept across the world like an indiscriminating wildfire. Pregnant women and neonates are particularly vulnerable to this infection compared with older children and healthy young adults, with unique challenges in their management. Unfamiliarity with the consequences of this novel virus and lack of high-quality data led to considerable heterogeneity in obstetrical and neonatal management early in the pandemic. The aim of the this review is to summarize the impact of SARS-CoV-2 infection on pregnancy and childbirth and to examine care and possible outcomes for neonates with Covid-19-positive mothers. A brief review of vaccines currently approved by the United States Food and Drug Administration for emergency use and their potential effects on pregnant and lactating women in included.

Objectives   After completing this article, readers should be able to:

1. Describe perinatal management approaches for pregnant women to improve the outcomes in mothers and neonates.

2. Summarize the clinical presentation and management of neonatal SARS-CoV-2 infection.

3. Describe the neonatal multisystem inflammatory syndrome in children.

4. Review the mechanism of action of the vaccine against SARS-CoV-2.

ABBREVIATIONS

AAP	American Academy of Pediatrics
ACE	angiotensin-converting enzyme
COVID-19	coronavirus disease 2019
CPAP	continuous positive airway pressure
DR	delivery room
ECMO	extracorporeal membrane oxygenation
Ig	immunoglobulin
MIS-C	multisystem inflammatory syndrome in children
MIS-N	multisystem inflammatory syndrome in neonates
mRNA	messenger RNA
NPC-19 registry	National Registry for Surveillance and Epidemiology of Perinatal COVID-19 Infection
OR	operating room
PCR	polymerase chain reaction
PPE	personal protective equipment
PPHN	persistent pulmonary hypertension of the newborn
RT-PCR	reverse transcriptase–polymerase chain reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization

INTRODUCTION

Coronaviruses are positive sense–enveloped, single-stranded RNA viruses. Serotypes from the α- and β-coronavirus genera can cause human disease. The novel

severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a β-coronavirus, with ∼80% homology to SARS-CoV-1 (the agent causing severe acute respiratory syndrome, or SARS) and even greater homology to some bat coronaviruses, suggesting a zoonotic origin. (1) Like other coronaviruses, SARS-CoV-2 has a "crown" appearance on electron microscopy caused by projections of the spike (S) glycoprotein from the envelope (Fig 1). The S protein mediates attachment to human epithelial cells via the angiotensin-converting enzyme (ACE)-2 receptor, which is distributed widely throughout the human respiratory tract epithelium and is also the target of SARS-CoV-1.

SARS-CoV-2 is more transmissible than SARS-CoV-1, which may be the result of stronger binding to the ACE-2 receptor (2) and more effective transmission of virus from asymptomatic and presymptomatic hosts. (3) Transmission primarily occurs via respiratory droplets, though airborne and contact transmission may occur to a lesser extent. (4) Disease caused by SARS-CoV-2 tends to occur in a biphasic manner, with the initial illness thought to be the result of direct viral infection and the subsequent phase being immune-mediated. (5) In addition, SARS-CoV-2 infection is known to cause coagulopathy, which may contribute to organ dysfunction as well.

COVID-19 IMPACT ON PREGNANT WOMEN

In the United States, pregnant women with coronavirus disease 2019 (COVID-19) are significantly more likely to be admitted to an intensive care unit and receive invasive ventilation and extracorporeal membrane oxygenation (EC-MO) (Fig 2) compared with nonpregnant women who have
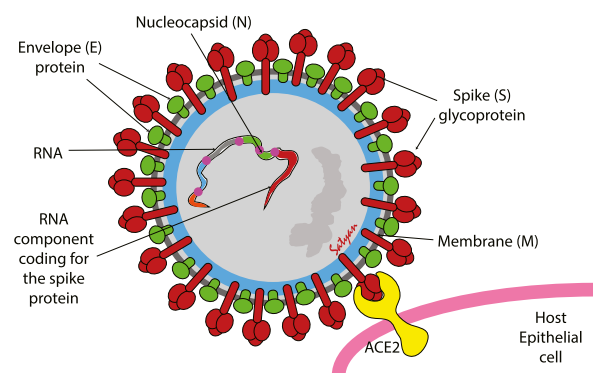
COVID-19. (6) Mortality is also higher among pregnant women infected with COVID-19. (6) These findings may be related to physiologic changes of pregnancy, such as increased heart rate and oxygen consumption, shift in cell-mediated immunity, reduced lung capacity secondary to upward diaphragmatic shift, and increased risk for thromboembolism.

Similar to nonpregnant women, pregnant women with COVID-19 present with cough (50%), fever (32%), myalgia (37%), and shortness of breath. In addition to respiratory symptoms, the placenta may be affected in COVID-19. (7) The possibility of vertical transmission appears low but placental infection can potentially affect the fetus. (8)(9)

Measures to prevent COVID-19 during pregnancy include wearing a proper mask, frequent handwashing, and most importantly, avoiding crowded areas and parties (including baby showers). Vaccination during pregnancy is a controversial topic as to date, pregnant and lactating women have been excluded from vaccine studies. However, the American College of Obstetricians and Gynecologists and

Figure 1. An illustration of the enveloped single-stranded RNA virus, severe acute respiratory syndrome coronavirus 2. The various proteins in the virus are labeled as S (spike glycoprotein), E (envelope glycoprotein), M (membrane protein), and N (nucleocapsid protein). Angiotensin-converting enzyme 2 (ACE-2) is the receptor for the virus in the host cell that facilitates attachment of the virus by the S protein and its subsequent entry into the host cell. The portion of the RNA that encodes the S protein is also shown in the figure. (Copyright Satyan Lakshminrusimha used with permission.)
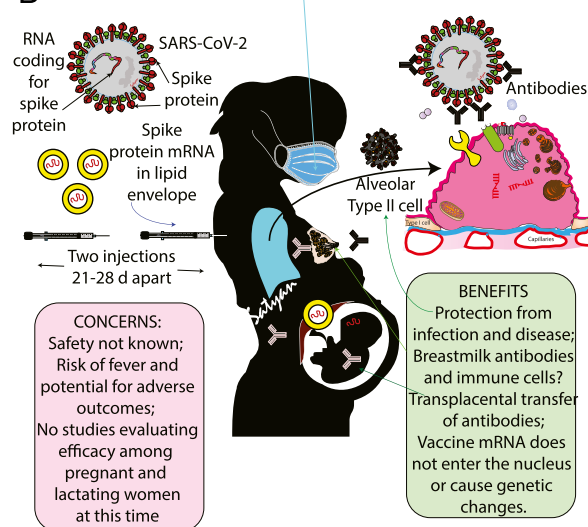
Figure 2. Strategies to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy (A), and benefits and risks of vaccination during pregnancy (B) are illustrated. Currently Food and Drug Administration–approved vaccines (as of January 1, 2021) consist of messenger RNA (mRNA) of the spike protein in the lipid envelope. The possible benefits and concerns of vaccination during pregnancy are shown in the green and pink boxes, respectively. (Copyright Satyan Lakshminrusimha, used with permission.)

the Society of Maternal-Fetal Medicine have issued statements suggesting that pregnant and lactating women should be given a choice to receive the vaccine after discussing individual risks (including the possibility of fever following vaccination) (Fig 3).

The American Academy of Pediatrics (AAP) Section on Neonatal Perinatal Medicine has issued a statement recommending shared decision-making regarding vaccination during pregnancy and lactation. The risk of transmission of the vaccine (ie, COVID-19 messenger RNA [mRNA]) across the placenta is unlikely but maternal immunoglobulin (Ig) G antibodies in response to the vaccine are likely to be transmitted. Antibodies to COVID-19 are found in infants born to mothers with COVID-19 and in the breast milk of mothers with COVID-19. (10)(11) Active immunization with other vaccines has been shown to increase specific IgA levels in breast milk. (12)

MATERNAL TRANSMISSION TO THE NEWBORN

There are 3 potential mechanisms of maternal transfer of SARS CoV-2 to the infant (Fig 4). (13)

1. Intrauterine transmission through transplacental hematogenous spread or viral particles in amniotic fluid that are ingested or inhaled by the fetus. This mode appears less likely but there are anecdotal reports suggesting that this is possible. (9)(14)(15)(16)(17)(18)
2. Intrapartum transmission after exposure to maternal infected secretions or feces around the time of birth.

3. Postpartum transmission from an infected mother, family member, or health care worker (probably the most likely mode of prevaccine transmission). Transmission from an infected mother is more likely from respiratory secretions and less likely from breast milk.

DELIVERY OF A NEWBORN OF A MOTHER WITH COVID-19

Pregnant women with suspected COVID-19 (symptomatic or recent positive household contact) must be prioritized for SARS-CoV-2 testing, while universal screening may be used in areas with high prevalence. (19) The timing and mode of delivery and anesthesia in pregnant women with suspected/confirmed SARS-CoV-2 infection are dependent on obstetrical indications. A cesarean section rate of 24% to 41% has been reported in pregnant women infected with COVID-19 from hospitals in the United States. (20)(21)(22) Antenatal steroids may be administered to infected pregnant women at risk for preterm delivery (including 34–36 6/7 weeks) until more evidence is available because of the potential benefits of promoting fetal lung maturity and decreasing maternal mortality. (23)(24) The delivery room (DR)/operating room (OR) should be equipped to function as a negative pressure isolation room with the door remaining closed. Personnel inside the DR should be limited to essential health care workers (1–3 obstetric and 1–2 pediatric clinicians) caring for the mother-infant dyad. Additional personnel should wait outside the DR/OR and be given a
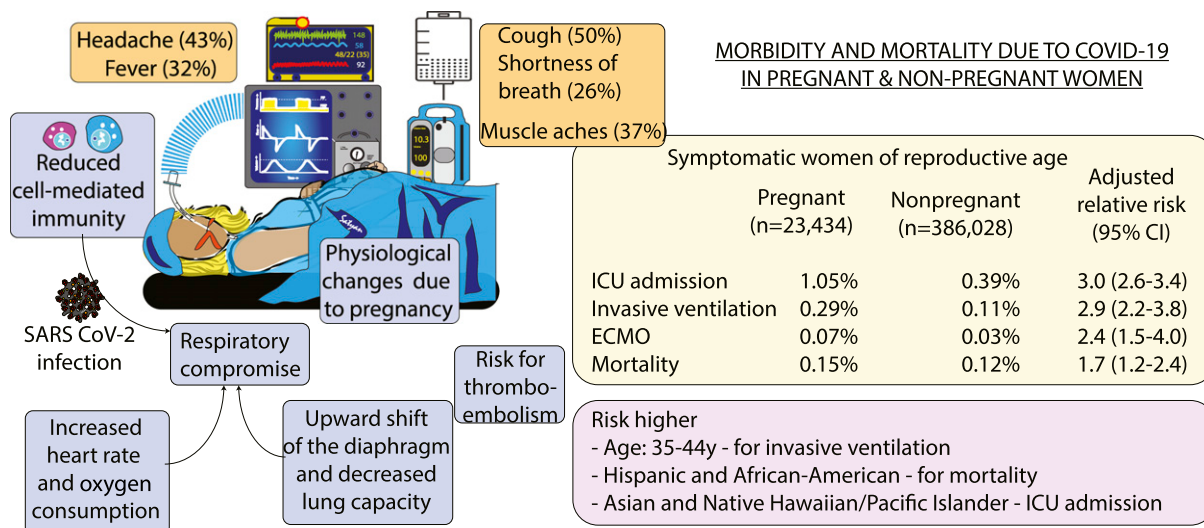

Headache (43%)
Fever (32%)

Cough (50%)
Shortness of breath (26%)

Muscle aches (37%)

Reduced cell-mediated immunity

SARS CoV-2 infection

Respiratory compromise

Physiological changes due to pregnancy

Risk for thrombo-embolism

Increased heart rate and oxygen consumption

Upward shift of the diaphragm and decreased lung capacity

MORBIDITY AND MORTALITY DUE TO COVID-19 IN PREGNANT & NON-PREGNANT WOMEN

	Symptomatic women of reproductive age		
	Pregnant (n=23,434)	Nonpregnant (n=386,028)	Adjusted relative risk (95% CI)
ICU admission	1.05%	0.39%	3.0 (2.6-3.4)
Invasive ventilation	0.29%	0.11%	2.9 (2.2-3.8)
ECMO	0.07%	0.03%	2.4 (1.5-4.0)
Mortality	0.15%	0.12%	1.7 (1.2-2.4)

Risk higher
- Age: 35-44y - for invasive ventilation
- Hispanic and African-American - for mortality
- Asian and Native Hawaiian/Pacific Islander - ICU admission

Figure 3. Clinical presentation of coronavirus disease 2019 (COVID-19) during pregnancy. (6)(93) Infected pregnant women have reduced cell-mediated immunity, upward shift of the diaphragm leading to decreased lung capacity, increased risk for thromboembolism, and an increase in heart rate and oxygen consumption. The yellow box compares the risk of intensive care unit (ICU) admission, invasive ventilation, extracorporeal membrane oxygenation (ECMO), and mortality between pregnant and nonpregnant women with symptomatic COVID-19. The purple box lists the demographic characteristics with higher risk for invasive ventilation, mortality, and ICU admission. SARS CoV-2=severe acute respiratory syndrome coronavirus 2. (Copyright Satyan Lakshminrusimha, used with permission.)
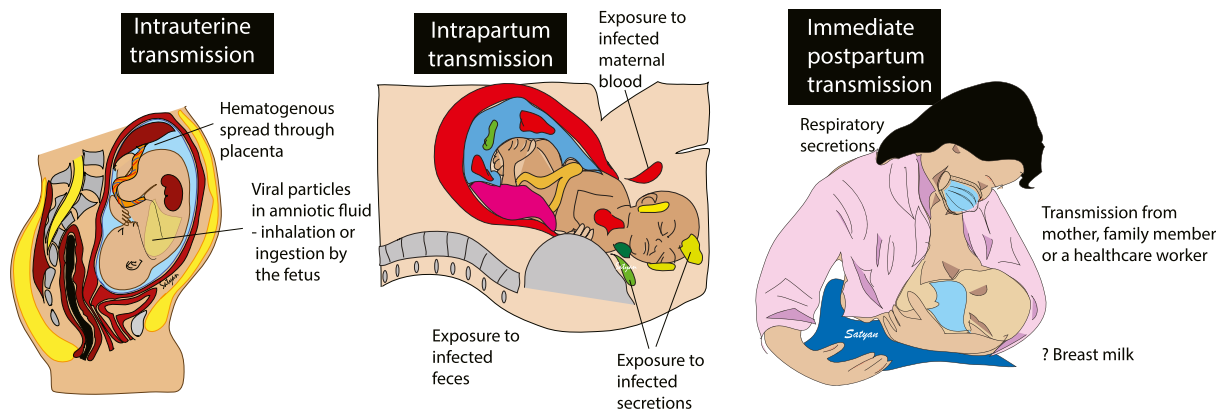
Figure 4. Potential modes of transmission of the severe acute respiratory syndrome coronavirus 2 infection from the pregnant woman to the fetus/newborn. The 3 potential modes include vertical/maternal-fetal transmission, intrapartum transmission, and postnatal transmission. (13) (Copyright Satyan Lakshminrusimha, used with permission.)

cue to enter if needed (Fig 5). Careful hand hygiene must be performed by clinicians before donning and doffing personal protective equipment (PPE), which include N95 mask/higher respirator (preferred) or surgical mask (acceptable) with face-shield/goggles, isolation gown, and gloves. (19) The pregnant woman should wear a surgical mask. Visitors may be limited to only the necessary support person for the woman; telemedicine/video-based interactions with visitors may be valuable, if available.

The World Health Organization (WHO) endorses deferring cord clamping and early skin-to-skin contact in neonates born to mothers with COVID-19. (25)(26)(27) After discussion of the pros and cons of these interventions based on the available evidence, shared decision-making with the parents is encouraged. (28)

If a pregnant woman has significant COVID-19–related illness and requires invasive mechanical ventilation, delivery may need to be conducted in the intensive care unit setting. Cesarean section has been reported in a pregnant woman with COVID-19 who was receiving ECMO. (29)

NEONATAL RESUSCITATION

Neonatal clinicians should attend deliveries based on their hospital/center-specific policies. Maternal COVID-19 alone is not a specific indication for attending a delivery. Current data suggest that only 1.6% to 2% of infants born to women who test positive for SARS-CoV-2 near the time of delivery test positive in the first 1 to 3 days after birth (AAP National Registry for Surveillance and Epidemiology of Perinatal
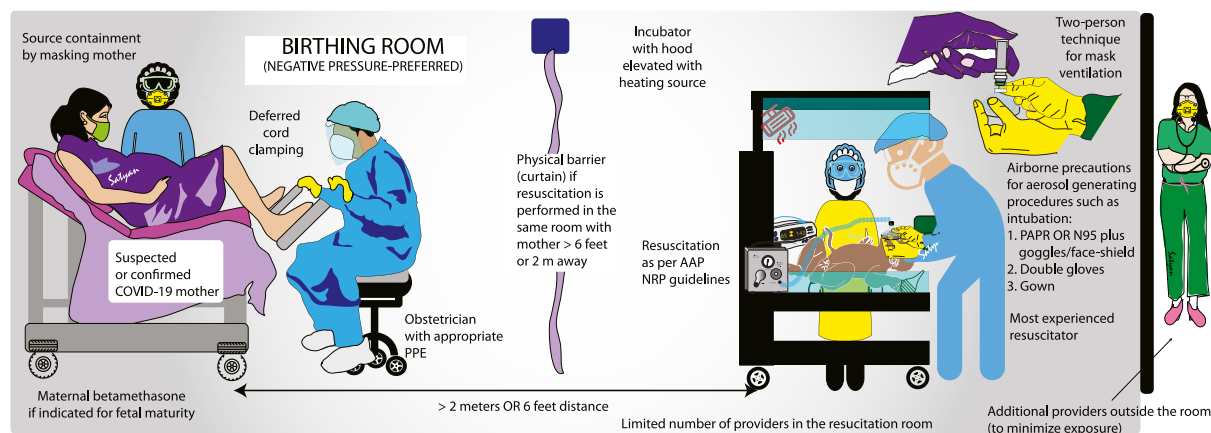

Figure 5. Delivery room management of a severe acute respiratory syndrome coronavirus 2–positive pregnant woman and resuscitation of her newborn. Maternal masking for source containment and complete personal protective equipment (PPE) use by the health care clinician inside the birthing room (negative pressure room) are recommended. A distance of 6 feet and curtain as a physical barrier should be kept between the mother and the newborn requiring resuscitation. When positive pressure ventilation (PPV) with a mask is required, the 2-person technique with 1 clinician maintaining an appropriate seal with a facemask and a second clinician providing PPV could minimize leak and risk of viral transmission. Airborne precautions should be used for aerosol-generating procedures. AAP=American Academy of Pediatrics, COVID-19=coronavirus disease 2019, NRP=Neonatal Resuscitation Program; PAPR=powered air purifying respirator. (Copyright Satyan Lakshminrusimha, used with permission.)

COVID-19 Infection/NPC-19 registry accessed on December 14, 2020). All neonatal clinicians should don a gown and gloves and use an N95 respirator mask and a face shield or eye-protection goggles or an air-purifying respirator (with eye protection). (30) Because it is not known if a newborn might require an aerosol-generating procedure soon after birth, adequate precautions must be taken to minimize the risk of infection (Fig 5). Aerosol-generating procedures in the DR include T-piece and mask ventilation, bag-mask ventilation, intubation, suctioning, high-flow oxygen therapy at more than 2 L/min, continuous positive airway pressure (CPAP), and mechanical ventilation. (31)

During mask ventilation, it is better to use the 2-person technique with 1 provider holding the mask with both hands to ensure a good seal and reduce air-leak and the second person performing bag-mask ventilation or managing the T-piece resuscitator (Fig 5). The use of videolaryngoscopy may be considered to reduce risk to the clinician during intubation.

Transport of an infant born to a COVID-19–positive woman from the DR to the NICU or newborn nursery should take a predetermined path in a closed incubator with minimal exposure to other personnel.

BREASTFEEDING IN TERM INFANTS BORN TO MOTHERS WITH COVID-19

There is no current compelling evidence suggesting that SARS-CoV-2 can be transmitted from an infected mother to her neonate via breast milk; rather, breast milk may be beneficial by providing protective antibodies against SARS-CoV-2 infection. (31)(32) The nutritional, immunologic, and developmental benefits of breastfeeding, if permitted by the mother's health, outweigh the potential transmission risk, given that infants typically have mild illness. (33)(34) Newborns are more likely to acquire infection via horizontal transmission from an infected mother or another care provider; thus, the importance of maintaining appropriate respiratory hygiene when an infected person is in contact with a newborn cannot be overemphasized. An infected mother should wear a surgical mask, wash her hands and breasts with soap and water before feedings, and breastfeed the infant. Alternatively, the infant can be fed expressed breast milk by a healthy care provider. Between feedings, the infant's crib (or incubator) should be placed at least 6 feet from an infected mother's bed, preferably behind a physical barrier (such as a curtain). (29) Both international and national societies, including the WHO and AAP, support protecting breastfeeding during this pandemic. (35)

It is worth mentioning that although passage of remdesivir (an antiviral medication used for the treatment of moderate to severe SARS-CoV-2 disease) to an infant via breast milk is unknown, no adverse events were reported in a newborn whose mother received remdesivir therapy for Ebola infection. (36) The Academy of Breastfeeding Medicine does not recommend cessation of breastfeeding when lactating mothers receive an mRNA-based liposomal vaccine (see later section on vaccines).

CARE OF TERM AND PRETERM INFANTS BORN TO MOTHERS WITH COVID-19

Vertical transmission of SARS-CoV-2 appears to be uncommon because of lack of viremia and nonoverlapping expression of ACE-2 and transmembrane serine protease 2. (37)(38) Neonatal infection was reported in 1% to 3% of births to US mothers with COVID-19, with lower chances of infection if the mother tested positive more than 14 days before delivery. (22)(39)(40) Preterm birth (12.9%, compared to the national average of 10.2% in 2019), low birthweight, cesarean section, and NICU admissions were frequently observed among COVID-19 deliveries. (20)(41) Contrary to initial beliefs, the rate of neonatal infection was not increased with vaginal delivery, rooming-in, or breastfeeding. (42)(43)

Mother-infant separation and NICU admission may be required for preterm infants (<34 weeks' gestation) and for underlying medical conditions or symptomatic illness requiring higher level of care for either the infant or mother. Preterm and term infants admitted to the NICU with respiratory distress could potentially require respiratory support and aerosol-generating procedures (such as CPAP, endotracheal intubation, and surfactant). (30) Intubation should be performed by the most experienced neonatal clinician using appropriate PPE. Infants should be monitored closely for symptoms and signs of SARS-CoV-2 infection, which may include fever, cough, rhinorrhea, respiratory distress, poor feeding, lethargy, vomiting, diarrhea, rash, and edema (Fig 6). (39)(44)(45)(46)(47)

Testing for SARS-CoV-2 RNA with reverse transcriptase–polymerase chain reaction (RT-PCR) is recommended for all neonates born to mothers with suspected or confirmed COVID-19 at 24 and 48 hours after birth (or a single test at 24–48 h) using a nasopharyngeal, oropharyngeal, or nasal swab. (26) Asymptomatic SARS-CoV-2–positive neonates can be discharged from the hospital after ensuring close follow-up. An infected mother who has been afebrile for 24 hours without antipyretics and is improving is not likely to be contagious 10 days after the onset of symptoms and can safely care for her infant. (26)

NEONATES WITH SARS-COV-2 INFECTION

The immature immune system, passive transfer of maternal IgG antibodies, and lower ACE-2 expression may result in

EARLY ONSET NEONATAL COVID:
Often asymptomatic with positive SARS CoV-2 PCR before hospital discharge (1.6% of infants born to positive mothers)

Common: Asymptomatic - detected by routine testing

Perinatal transmission (? vertical - uncommon)

Typical onset 2 to 7 days after birth

Temperature instability or low-grade fever

Loss of interest in feeds

Nasal congestion Flaring

Blue discoloration

Lethargy Diarrhea Irregular breathing

LATE-ONSET NEONATAL COVID:
Readmission at 5 - 35 days after birth

Temperature instability

Lethargy

Non-specific opacities on chest X-ray

Respiratory distress Apnea Feeding intolerance

Postnatal transmission

Leukocytosis Lymphopenia Thrombocytopenia

MULTI-SYSTEM INFLAMMATORY SYNDROME IN NEONATES (MIS-N)

Maternal lympho-cytes

Myocarditis, ↑Troponin, ↑BNP, Coronary aneurysms

Plasma cell

Antibodies

Neonatal hyperimmune response

DIC, ↓Fibrinogen, ↑D-dimers, Thrombocytopenia Neutropenia Lymphopenia

Maternal COVID-19 (past or present infection)

Hyponatremia Oliguria Renal failure Anasarca

Feeding intolerance vomiting "NEC" like presentation

Hypoxemia Pulmonary infiltrates PPHN
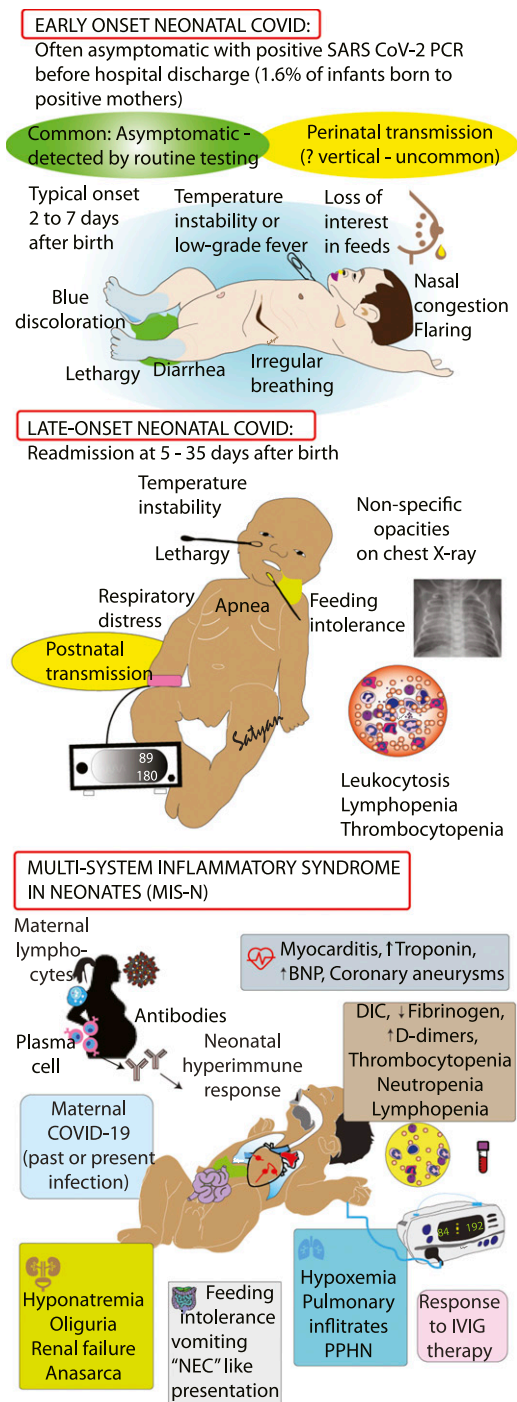
Response to IVIG therapy

Figure 6. A schematic describing the clinical presentation of early-onset and late-onset neonatal coronavirus disease 2019 (COVID-19) and multisystem inflammatory syndrome in neonates (MIS-N). The mechanism of MIS-N is thought to be a neonatal hyperimmune response to maternal antibodies against severe acute respiratory syndrome coronavirus 2 and has not been clearly described in the literature. Neonates with MIS-N could be critically ill with myocarditis, myocardial dysfunction, coronary aneurysms, disseminated intravascular coagulation (DIC), necrotizing enterocolitis (NEC)–like illness, hypoxemia, and renal failure. BNP=brain natriuretic peptide, IVIG=intravenous immunoglobulin, PPHN=persistent pulmonary hypertension of the newborn. (Copyright Satyan Lakshminrusimha, used with permission.)

less inflammation, milder illness, and hastened recovery in infants and children compared to adults. (11)(48) Neonates, however, have been reported to have more severe illness (in 12% of infected neonates) compared to older children (3% of older children required intensive care unit care) in a systematic review. (47)(49) SARS-CoV-2–positive neonates should be clinically monitored and isolated. Complete PPE should be used by clinicians while caring for these neonates, as described earlier. Early-onset neonatal COVID-19 (onset of illness between 2 and 7 days after birth) is likely caused by perinatal transmission (intrapartum or more commonly, immediately after birth). Most infected neonates are either asymptomatic (20%)(22)(47)(50) or have mild symptoms such as rhinorrhea and cough (40%–50%)(39)(45)(47) and fever (15%–45%) (Fig 6). (45)(50)(51) Moderate to severe symptoms such as respiratory distress (12%–40%), poor feeding, lethargy, vomiting and diarrhea (30%), and clinical evidence of multiorgan failure have been observed as well (Fig 6). (39)(45)(46) Laboratory evidence of COVID-19 infection in a neonate may include leukocytosis, lymphopenia, thrombocytopenia, and nonspecific findings of elevated inflammatory markers. (52)

Management for symptomatic COVID-19–positive neonates is mostly supportive. Appropriate respiratory support, such as CPAP, is recommended for respiratory distress. Endotracheal intubation is more likely to be indicated if there is neonate-specific lung pathology (such as surfactant deficiency and meconium aspiration syndrome) rather than COVID-19 lung disease. (53) A viral filter could be placed in the expiratory limb of the ventilator circuit to minimize risk of infection to health care workers by aerosolization. (30)

LATE-ONSET NEONATAL COVID-19 INFECTION

The majority of symptomatic SARS-CoV-2 infections in neonates are diagnosed beyond 5 to 7 days after birth (late-onset neonatal COVID-19). (39) Postnatal transmission by neonatal exposure to maternal respiratory secretions or exposure to infected health care workers or household contacts probably plays a major role in late-onset neonatal COVID-19 infection, though intrapartum exposure to maternal secretions and body fluids may contribute as well. (13) Many affected neonates had negative initial RT-PCR test results (at 24 and 48 hours after birth) before initial discharge from the hospital and were readmitted with symptoms suggestive of COVID-19. (54) In a cohort study of 61 neonates with SARS-CoV-2 infection requiring in-patient management, hyperthermia, coryza, mild respiratory symptoms, apnea, poor feeding or vomiting, and lethargy were commonly reported. (39) Chest radiographs were abnormal,

with nonspecific opacities in 56% and ground-glass changes in 28% (half of those were preterm). (39) A third of the infected neonates required respiratory support and supplemental oxygen. Mothers of infected neonates tested positive for SARS-CoV-2 in 26% of cases, and 52% of the infected neonates had close contact with an infected individual. (39) Lethargy, apnea, fever or hypothermia, tachycardia, tachypnea, hypoxemia, hypotension, and radiographic findings of ground-glass opacities have been reported with worsening illness. (50)(55)(56) Age less than 1 month has been associated with a 3-fold higher risk of critical care admission. (57) Leukocytosis, thrombocytopenia, elevated lactate (55%), raised C-reactive protein (29%), and lymphopenia (9%) have been observed. (39)(58) Disseminated intravascular coagulation may also occur. (46)

For neonates infected with COVID-19, management remains supportive and includes supplemental oxygen, respiratory support, fluid resuscitation, and temperature control. Currently, evidence for the use of antiviral medications and steroids in neonatal COVID-19 is lacking. Use of remdesivir has been reported in 2 newborns: a 22 day old with severe late-onset COVID-19 who clinically improved and tolerated the treatment well (59) and a 4 day old who continued to deteriorate and received dexamethasone and convalescent plasma, required invasive ventilation until 13 days of age and ultimately improved. (60)

NEONATAL MIS-C

Multisystem inflammatory syndrome in children (MIS-C) is a novel condition following COVID-19 infection in children, and is characterized by fever, elevated inflammatory markers, and high levels of both pro- and anti-inflammatory cytokines. (61) Children with MIS-C frequently present with symptoms related to the cardiovascular system (shock, left ventricular dysfunction, elevated cardiac enzymes, coronary artery abnormalities), gastrointestinal system (nausea, vomiting and diarrhea mimicking gastroenteritis, or inflammatory bowel disease), or with mucocutaneous symptoms resembling Kawasaki disease. (62)(63) The median age of children with MIS-C has been reported to be 5 to 9 years, as opposed to Kawasaki disease which is typically seen between 6 months and 5 years of age. MIS-C is infrequent in infants, with the Centers for Disease Control and Prevention reporting only 4% of MIS-C cases occurring in children younger than 1 year. (64)

Neonatal MIS-C (MIS-N) has rarely been reported (Fig 6). (65) A 49-day-old male infant, whose family member tested positive when the infant was 2 weeks old, presented with severe gastrointestinal manifestations (including diarrhea with colitis that was confirmed on biopsy), hypoalbuminemia, severe anemia, elevated serum D-dimer and ferritin, and thrombocytosis in the early phase, and subsequent thrombocytopenia. (66) Serum brain natriuretic peptide was elevated and echocardiography showed mitral regurgitation but normal coronary arteries. The infant was treated with intravenous immunoglobulin and pulse methylprednisolone therapy with subsequent improvement. Lima et al described a 33-week-gestation fetus with worsening pericardial effusion on ultrasonography in a pregnant woman with positive COVID serology (IgM and IgG) and recent febrile illness. (67) An emergency cesarean section was performed, and the infant's nasopharynx and oropharynx swabs and blood specimens at birth were positive for SARS-CoV-2 on PCR testing. Two days after birth, the infant developed hemodynamic instability, prompting pericardiocentesis with subsequent clinical improvement. Cardiac enzymes and plasma proinflammatory cytokines were elevated, consistent with a hyperinflammatory response. Of note, a fatal case of MIS-C in the NICU was reported in a 7-month-old infant born at 26 weeks' gestation who was hospitalized since birth and acquired acute SARS-CoV-2 infection from an unknown source. (68) The infant subsequently developed cardiovascular collapse with elevated inflammatory markers and echocardiographic evidence of myocarditis. (68) Recently a 4-hour-old term infant born to a mother without history of COVID-19 has been reported to have developed persistent pulmonary hypertension of the newborn (PPHN) and subsequently had multisystem involvement (fever, bilateral ground glass opacities, necrotizing enterocolitis–like illness, vasculitic rash, and elevated inflammatory markers and D-dimer). Both the mother and infant tested positive for IgG antibody against SARS-CoV-2, suggesting that transplacental exposure to maternal IgG could have contributed to the cytokine storm in the newborn. (69) This infant was treated with dexamethasone in addition to management of PPHN, which led to complete recovery. Further study in children younger than 1 year is needed to elucidate the risk factors for developing MIS-C and to clarify predictors of disease severity.

VACCINES AGAINST COVID-19

Recently 2 vaccines manufactured by Pfizer-BioNTech and Moderna were approved by the US Food and Drug Administration under Emergency Use Authorization. (70)(71) Both vaccines consist of a lipid nanoparticle encapsulated, nucleoside-modified mRNA that encodes the SARS-CoV-2 spike (S) glycoprotein (which mediates host cell attachment, a prerequisite for viral entry). The lipid nanoparticle preferentially
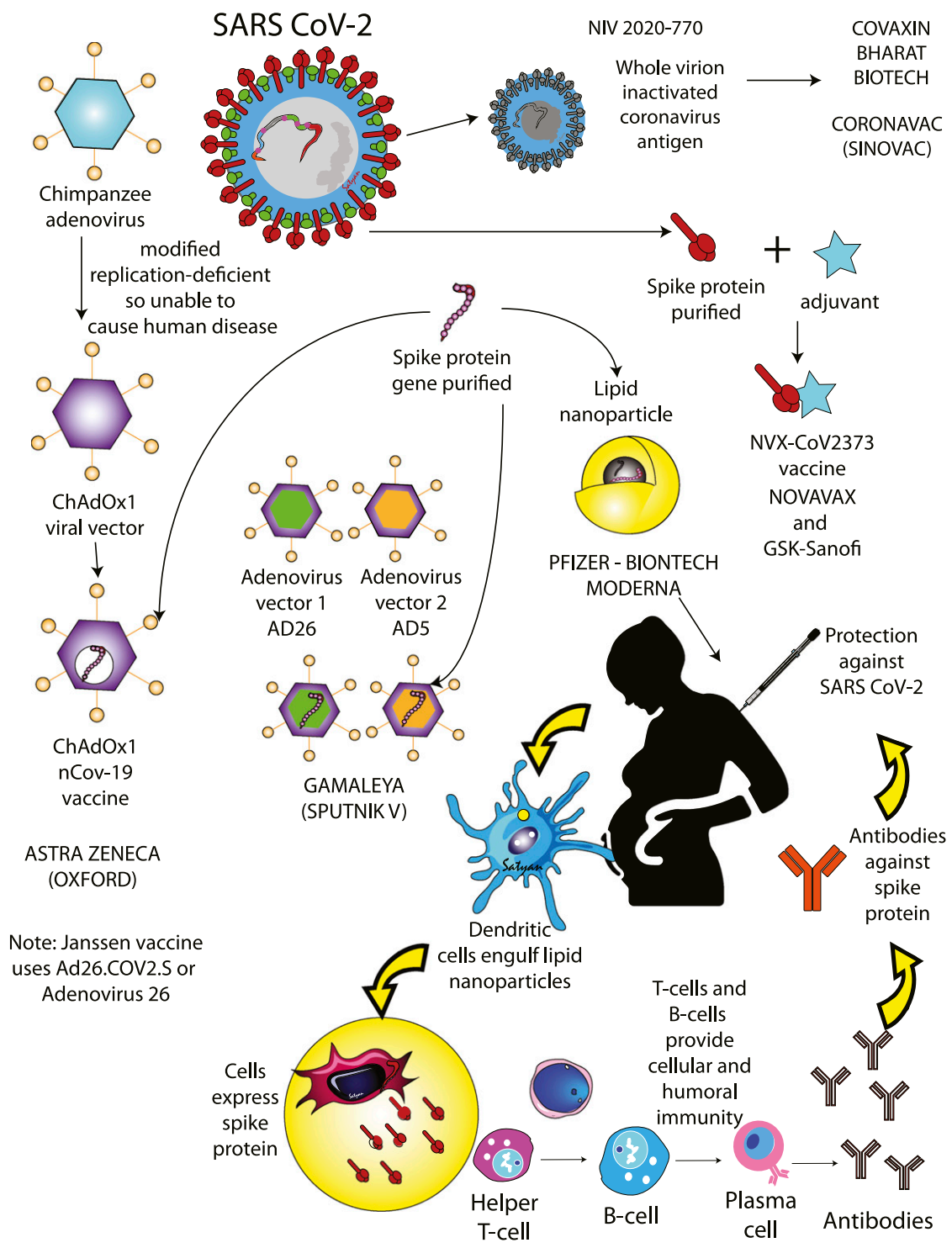
Figure 7. Active immunization against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral infection. Currently the US Food and Drug Administration–approved vaccines (Pfizer-BioNTech and Moderna) consist of spike (S) protein messenger RNA (mRNA) within a lipid nanoparticle. Other vaccines that are being evaluated at present include Covaxin (Bharat Biotech) and CoronaVac (Sinovac) (inactivated virion vaccines), AstraZeneca (Oxford), Gamaleya (Sputnik V), GSK-Sanofi, and NVX-CoV2373 (Novavax). AstraZeneca and Janssen vaccines involve a modified chimpanzee adenovirus acting as a vector for the viral S protein that is injected as a vaccine. Gamaleya has 2 different adenoviruses as vectors (Ad26 and Ad5 spike vaccines) for the initial and booster doses because of the concern that immune response to the same vector could lower immune response to the booster. Novavax consists of the combination of purified viral S protein with a saponin-based matric-M as an adjuvant. GSK-Sanofi COVID vaccine is also an S-protein mixed with an adjuvant. All vaccines cause active immunization by a) the dendritic cells engulfing lipid nanoparticles, b) host cells expressing S protein presenting to T- and B- lymphocytes inducing cellular and humoral immunity. (Copyright Satyan Lakshminrusimha, used with permission.)

targets dendritic cells, which interact with other cells in the lymphatic system (Fig 7). (72) Once injected, the lipid layer breaks down, releasing the mRNA. The mRNA is constructed so that the S protein code is inserted between the start and stop signals for translation, and additional code is included to increase protein translation. The host cell translates the mRNA to produce the S protein, which is then presented on the cell surface to T and B lymphocytes, which in turn produce an immune response to the protein, resulting in cell-mediated immunity and antibody production.

The Pfizer-BioNTech vaccine is given in 2 doses, 21 days apart, to individuals of age 16 years and older. (73) The Moderna vaccine is given in 2 doses, 28 days apart, to individuals of age 18 years and older. (74) Both vaccines are more than 90% effective in preventing symptomatic laboratory-confirmed COVID-19. (75)(76)(77) Both vaccines may cause local adverse reactions such as pain and swelling at the injection site, and/or systemic reactions such as fatigue, headache, or fever. Most reactions occur within the first 1 to 2 days, are mild, and resolve within 2 to 3 days. Blinded randomized placebo-controlled trials are currently recruiting (NCT04368728) or planning on recruiting (NCT04649151) 12- to 17-year-old children to study the safety, immunogenicity, and efficacy of these vaccines. (78)(79) Twelve women who were included in the Pfizer-BioNTech trial and received the vaccine subsequently became pregnant and did not experience any adverse effects. (70) More evidence is required on the safety of the vaccines in pregnant women and children, the effectiveness against the new and mutant strains of SARS-CoV-2, and the potential need for newer vaccines targeting the mutant strains of SARS-CoV-2. (80)(81)

LONG-TERM IMPACT OF NEONATAL COVID-19

Because of the uncertainty surrounding the virus, substantial heterogeneity was seen in perinatal management early in the pandemic. Practices such as mother-infant separation, cesarean section, early cord clamping, and avoidance of breastfeeding to err on the side of caution could alter neonatal colonization with maternal microbiota, hamper mother-infant bonding and breastfeeding, and predispose the infant to iron-deficiency anemia and increased frequency of respiratory and gastrointestinal infections in infancy. (82)

Long-lasting effects of SARS-CoV-2 infection have been noted in adults, with persistent cough and dyspnea and a potential for lingering lung inflammation, bronchiectasis, fibrosis, and pulmonary vascular disease. (83)(84) Infected neonates with no or mild symptoms may possibly remain hypoxemic for a variable period before becoming overtly symptomatic similar to what has been observed in infected adults. (85) Indeed, neonates may be silent carriers of the virus in their airway epithelia with prolonged asymptomatic shedding of the virus. (86) We speculate that chronic airway inflammation could result in airway remodeling and thickening, predisposing neonates to childhood asthma.

Vascular effects and thromboembolism have significantly contributed to COVID-19 mortality in adults and have been attributed to increased proinflammatory cytokines, (87) systemic inflammation, and endothelial injury from viral replication and attachment leading to a prothrombotic state. (46) In addition, there is lack of evidence on the consequences of early/first-trimester maternal SARS-CoV-2 infections on the fetus, and the incidence of early fetal losses, congenital defects, and teratogenicity is yet to be explored. (88)(89)(90) Long-term follow-up of exposed neonates to assess the respiratory, cardiovascular, and neurodevelopmental outcomes is warranted. Furthermore, the psychosocial impact on future generations remains to be understood.

CONCLUSION

Maternal and neonatal care during the COVID-19 pandemic has been a challenge to health care clinicians. This is because of the vulnerability of these populations, lack of high-quality evidence in management strategies and outcomes of infected patients, need for separation or isolation of parents from their infants, overwhelming of hospital systems during infection surges, and difficulty in ensuring adequate follow-up care. Pregnant women and neonates with SARS-CoV-2 infection should be monitored through the various available national registries (such as NPC-19). (91)

The advent of vaccines in the present scenario has offered a ray of hope toward nearing the end of this pandemic. Effects of vaccination on viral transmission remain unknown. If a large enough population were to be immunized by the vaccine, transmission may be reduced because of a decrease in symptomatic COVID-19. Vaccinated individuals could be asymptomatic carriers of the virus. It remains to be seen if asymptomatic viral carriage will be affected by widespread vaccination, though it is plausible that this will also decrease. (92) However, in the absence of strict masking and social distancing, viral transmission may continue in spite of vaccination.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Targeted prenatal, delivery room and postnatal care to optimize outcomes in perinatal SARS-CoV-2 infection.
- Understand the effects of SARS-CoV-2 infection on the mother and the newborn infant.
- Vaccine against SARS-CoV-2 virus mechanism of action and the effects of vaccination.

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