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REVIEW ARTICLE

COVID-19: neonatal–perinatal perspectives

Alejandra Barrero-Castillero[1,2] · Kristyn S. Beam[1,2] · Laura B. Bernardini[2] · Erika G. Cordova Ramos[2,3] · Patricia E. Davenport[2] · Anna R. Duncan[2] · Yarden S. Fraiman[2] · Lauren C. Frazer[2] · Helen Healy[2] · Emily M. Herzberg[2,4] · Madeline L. Keyes[2] · Kristen T. Leeman[2] · Kristin Leone[2] · Jonathan C. Levin[5] · Matthew Lin[2] · Ravikiran M. Raju[2] · Anne Sullivan[2] · On behalf of the Harvard Neonatal-Perinatal Fellowship COVID-19 Working Group

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Abstract
The coronavirus disease 2019 (COVID-19) pandemic, resulting from infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused severe and widespread illness in adults, including pregnant women, while rarely infecting neonates. An incomplete understanding of disease pathogenesis and viral spread has resulted in evolving guidelines to reduce transmission from infected mothers to neonates. Fortunately, the risk of neonatal infection via perinatal/postnatal transmission is low when recommended precautions are followed. However, the psychosocial implications of these practices and racial/ethnic disparities highlighted by this pandemic must also be addressed when caring for mothers and their newborns. This review provides a comprehensive overview of neonatal–perinatal perspectives of COVID-19, ranging from the basic science of infection and recommendations for care of pregnant women and neonates to important psychosocial, ethical, and racial/ethnic topics emerging as a result of both the pandemic and the response of the healthcare community to the care of infected individuals.

Introduction

The COVID-19 pandemic has led to significant changes in healthcare delivery and clinical management of pregnant women and their newborns as the availability of healthcare resources, rates of infection, and scientific data continue to evolve. This review provides a summary of the current global literature and professional society recommendations for the management of pregnant women and neonates. Critical gaps in the literature remain, and important areas for future research are identified. The authors performed an extensive literature review of peer-reviewed publications within PubMed and also included published professional society recommendations (last updated on 7/31/20). The topics covered include the virology of SARS-CoV-2 infection, a summary of the current data on the epidemiology, diagnosis, outcomes, and management recommendations of SARS-CoV-2 related to pregnant women and newborns, as well as emerging psychosocial, ethical, and racial/ethnic considerations. This review discusses pertinent topics across numerous disciplines to provide a broad understanding critical to tackling the complex landscape of the COVID-19 pandemic from a neonatal–perinatal perspective.

✉ Kristen T. Leeman
Kristen.Leeman@childrens.harvard.edu

[1] Department of Neonatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

[2] Division of Newborn Medicine, Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

[3] Department of Pediatrics, Boston Medical Center, Boston University School of Medicine, Boston, MA, USA

[4] Division of Neonatology and Newborn Medicine, Department of Pediatrics, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

[5] Divisions of Newborn Medicine and Pulmonary Medicine, Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Basic science of SARS-CoV-2 infection

Origins of SARS-CoV-2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of the global coronavirus

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disease 2019 (COVID-19) pandemic, is a member of the *Coronaviridae* family, initially discovered in the 1960s as the agent responsible for the common cold [1–3]. Since their initial discovery, seven unique coronaviruses have been implicated in clinically relevant infections, with three of the seven (severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus, and SARS-CoV-2) having the capacity to cause severe respiratory illness with significant morbidity and mortality. The *Coronaviridae* family consists of hundreds of additional viruses that utilize bats as a central reservoir of infection [4, 5]. Zoonotic transmission occurs after the virus undergoes genetic mutations that enable it to infect human cells. In the case of SARS-CoV-2, the receptor-binding domain (RBD) of the coronavirus spike protein located on the viral capsid evolved to enable binding to the human cell-surface protein angiotensin-converting enzyme 2 (ACE2) and initiate viral entry [2, 6]. Phylogenetic analysis of the RBDs of different coronaviruses suggests that SARS-CoV-2 likely originated in bats and that the pangolin was possibly an intermediate host, although further studies are needed to determine the definitive origin [2, 7, 8].

Viral cell entry

The expression of ACE2 on the epithelial surface of the upper and lower airways permits viral entry into these cells and underlies the ability of SARS-CoV-2 to cause respiratory illness [9–11]. Upon binding to ACE2, the SARS-CoV-2 life cycle requires the proteolytic activity of a host serine protease, Transmembrane protease, serine 2 (TMPRSS2), for viral entry (Fig. 1) [12, 13]. SARS-CoV-2 then gains access to the cytoplasm of the cell either through endocytosis or direct fusion with the host cell membrane [13]. Given that coronaviruses are positive, single-stranded RNA viruses, the viral RNA that enters the cytoplasm can directly be translated by the host protein-synthesis machinery. Translation results in the creation of a large polyprotein that is cleaved by a virally encoded protease to yield individual viral proteins [14]. Subsequent viral replication also requires a virally encoded protein, the RNA-dependent RNA polymerase, to synthesize the RNA intermediaries needed to make more SARS-CoV-2-positive-stranded RNA. Finally, viral proteins and newly synthesized viral RNA are packaged into a complete nucleocapsid that can be released from the cell to propagate infection [15]. The synthesized viral proteins and the host proteins that

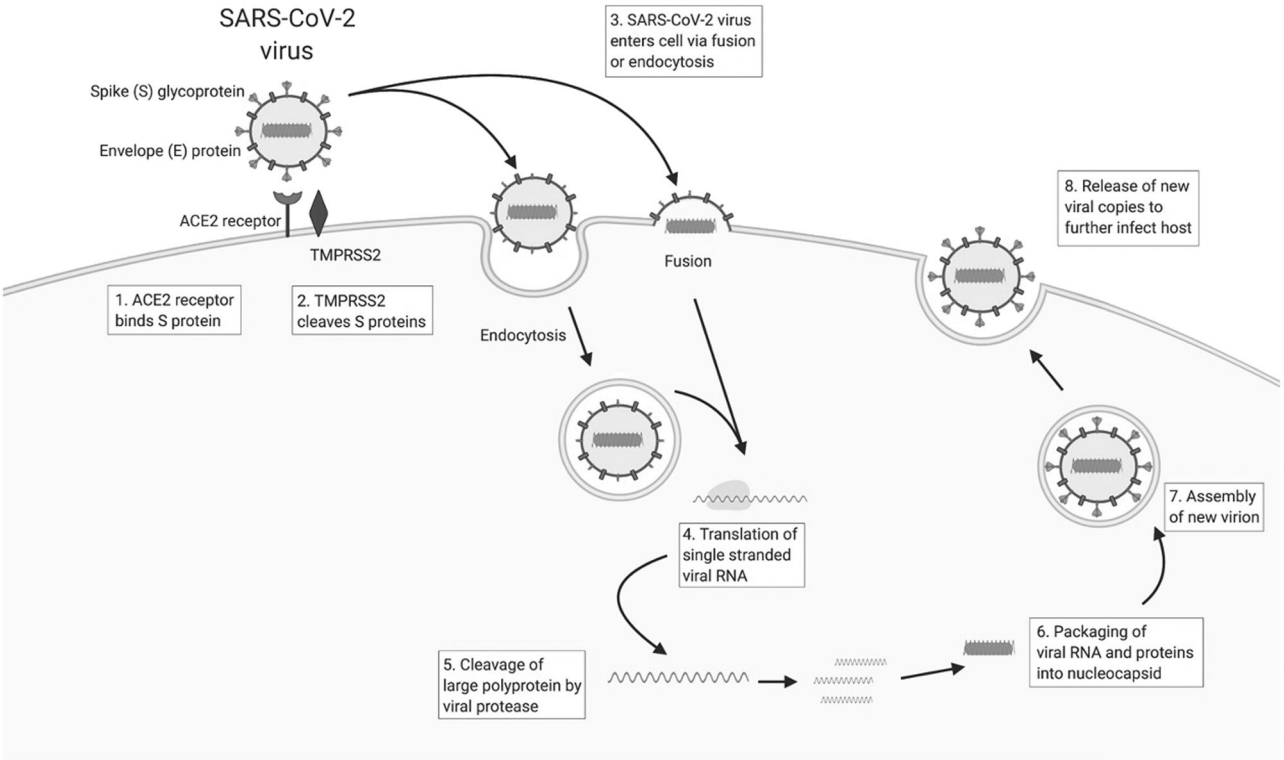


Fig. 1 SARS-CoV-2 viral entry and replication in host. The spike (S) glycoproteins of the SARS-CoV-2 virus bind to the ACE2 receptor on the host cell. (2) The TMPRSS2 protein cleaves the S proteins off the viral envelope, (3) allowing for viral entry either by endocytosis or fusion. (4) Single-stranded viral RNA is replicated by host machinery into a large polyprotein. (5) The polyprotein is then cleaved by a viral protease. (6) Viral protein and RNA is then packaged into a nucleocapsid. (7) New virions are assembled and (8) released to further infect the host [12–15].

enable entry into the host cell (ACE2 and TMPRSS2), have been suggested as possible pharmacologic targets.

Immune response and pathogenesis in neonates, children, and nonpregnant adults

After viral entry into the host cell, it is hypothesized that initial viral recognition and immune activation occurs via Toll-like receptors, Retinoic acid-inducible gene I-like receptors, and inflammasome activation [16, 17]. The host immune response to viral infection has been implicated in causing the pathology and clinical illness seen in SARS-CoV-2 infection, with an overly robust immune response causing more severe illness. A comparison of the inflammatory response between adult survivors and non-survivors of SARS-CoV-2 infection from Wuhan, China, demonstrated significantly higher levels of IL-6, ferritin, and lactate dehydrogenase, as well as significantly lower lymphocyte counts both on admission and throughout hospitalization [18]. Similarly, another study of adults with SARS-CoV-2 from Wuhan, China found higher levels of an array of plasma proinflammatory cytokines (IL-2, IL-7, IL-10, GSCF, IP10, MCP1, MIP1A, and TNFα) in SARS-CoV-2 infected patients who required admission to the intensive care unit (ICU) compared to those who did not need the ICU [19].

The etiology of reduced infection rates and the dampened immune response to infection seen in neonates and older children has been the subject of much debate and currently remains unclear [20–22]. Possible explanations include variations in the expression pattern of ACE2 with aging and the evolution of the immune system and response to infection that occurs with development [23, 24].

Obstetrical considerations in the era of COVID-19

Epidemiology in pregnant women

Pregnancy increases the risk of certain infections, particularly respiratory infections [25, 26].

Rates of infection with SARS-CoV-2 in pregnant women vary geographically and likely reflect the prevalence of the virus in the overall population. For example, data from a single center in New York City show that 20% of 161 pregnant women tested positive for SARS-CoV-2 with an asymptomatic carrier rate of 13% [27]. In contrast, a similar study performed in Connecticut found that 3.9% of pregnant women were positive for SARS-CoV-2 with an asymptomatic carrier rate of 2.9% at time of admission to labor and delivery (in addition to the 1.5% of known infections at time of admission) [28]. Regarding illness severity, data from the Centers for Disease Control (CDC) suggest that pregnant women with COVID-19 are at increased risk for hospitalization and admission to the ICU compared to nonpregnant women of reproductive age [29].

Several studies have demonstrated fetal complications of maternal SARS-CoV-2 infection including medically indicated preterm birth, growth restriction, and miscarriage [26, 30]. Given the hypercoagulability seen in patients with COVID-19, these fetal complications are hypothesized to be due to compromised perfusion in the maternal and/or fetal placental vasculature and possible thrombotic changes [31, 32]. More studies are needed to clarify the impact of SARS-CoV-2 infection on the physiology of pregnancy, the placenta, and resultant fetal complications.

Antenatal management

Based on recommendations from The American College of Obstetricians and Gynecologists (ACOG), prenatal care does not require significant modification based on the presence of SARS-CoV-2 infection alone and should be based on the clinical condition of the pregnant woman [33–35]. In the event that there is a suspected or confirmed SARS-CoV-2 infection in the first trimester, ACOG suggests an additional mid-trimester ultrasound be considered to evaluate fetal anatomy [33]. If infection occurs in the second or third trimester, ACOG guidelines recommend that an additional third-trimester growth assessment can be performed [33]. These recommendations will likely continue to evolve as the impact of SAR-CoV-2 on the developing fetus is better understood.

Use of antenatal corticosteroids in COVID-19

ACOG guidelines currently recommend a course of antenatal steroids for all pregnant women at risk for preterm delivery within 7 days with fetuses <33 6/7 weeks' gestational age, as well as for late preterm pregnancies 34 0/7 to 36 6/7 weeks' gestational age with no prior course of steroids administered [36]. Earlier in the pandemic, ACOG recommended against the use of antenatal corticosteroids at or beyond 34 weeks' gestation, given concerns at the time about the safety of corticosteroids in patients with SARS-CoV-2. These recommendations have since changed in response to new data supporting the possible benefit of treatment with corticosteroids in patients with COVID-19 [33, 37–39]. Specifically, a recent report showed that use of dexamethasone led to a lower 28-day mortality rate in hospitalized patients with COVID-19 who were mechanically ventilated or receiving oxygen [37]. At this time, ACOG guidance recommends that SARS-CoV-2 status should not alter decision-making regarding antenatal corticosteroid administration [33, 36].

Delivery considerations

The experience of labor and delivery has undoubtedly been altered by COVID-19 with numerous measures in place to protect the safety of pregnant women, caregivers, and newborns. ACOG currently recommends prioritization of testing for pregnant women admitted to labor and delivery units with suspected COVID-19 or who develop symptoms of COVID-19 during admission. Additionally, they suggest consideration of universal screening, utilizing rapid polymerase chain reaction (PCR) testing, in high prevalence areas, given concern for asymptomatic infection and transmission [33]. Other general precautions include limiting visitors and isolating persons under investigation (PUIs) or SARS-CoV-2-positive patients in negative pressure rooms, or at least rooms with high-efficiency particulate absorbing units, if negative pressure rooms are unavailable [33, 40].

ACOG recommendations state that SARS-CoV-2 infection alone is not an indication for preterm delivery or cesarean section, and timing of delivery should be informed by disease severity, maternal comorbidities, gestational age, and maternal and fetal status, as the majority of SARS-CoV-2 infections are asymptomatic or mild (defined as symptomatic with stable vital signs) and most individuals make a complete recovery [33, 34, 41]. For pregnant women who require inpatient management, regular monitoring of maternal vitals, and fetal heart rate for assessment of illness severity and fetal distress can assist in determination of delivery timing [41]. In severe illness (respiratory rate ≥30/min, resting SaO2 ≤ 93%, arterial blood oxygen partial pressure (PaO2)/oxygen concentration (FiO2) ≤300 mmHg), or critical illness (respiratory failure requiring mechanical ventilation, shock with organ failure, or refractory hypoxemia necessitating extracorporeal membrane oxygenation), delivery of the premature infant or termination of a nonviable pregnancy may need to be considered to reduce risk of maternal and fetal death [41].

Early delivery may also be warranted in refractory cases of maternal hypoxemia and increased maternal oxygen consumption due to the resultant critical fetal hypoxemia and acidemia. In these cases, the risks of prematurity are balanced against the risk of continued fetal compromise if the pregnancy were to continue [40], similar to the routine management of other conditions during pregnancy that improve after delivery. A review of 51 cases of SARS-CoV-2 infection in pregnant women reported an increase in medically indicated preterm birth and cesarean delivery. In this study, 96% of deliveries occurred by cesarean delivery and the median gestational age was 36.5 weeks' gestation with delivery indications (available in 34 cases) reported as COVID-19 pneumonia (55.9%), premature rupture of membranes (26.5%), and fetal distress (17.6%). The authors hypothesized that provider and patient anxiety may have influenced this high cesarean delivery rate [42]. More data are needed to determine the impact of COVID-19 on medically indicated preterm birth and delivery.

Neonatal acquisition, outcomes, diagnosis, and management

Neonatal acquisition

Data indicate low rates of perinatal acquisition among neonates born to mothers positive for SARS-CoV-2. In a review of 27 studies, including data from the United States, China, Italy, Sweden, South Korea, and Honduras, only 4 out of 137 neonates (3%) born to SARS-CoV-2 infected mothers had positive viral PCR testing, and 3 neonates had equivocal testing (5% total prevalence including equivocal tests) [43]. Similar prevalence was reported in a large population-based cohort in the United Kingdom, which found 12/265 (5%) positive neonates born to SARS-CoV-2 infected mothers [44]. In a Spanish cohort, perinatal acquisition occurred in 5/72 (6.9%) of exposed newborns born to SARS-CoV-2-positive mothers, with no difference found between vaginal and Cesarean births [45]. In contrast, data from the National Registry for Surveillance and Epidemiology of Perinatal COVID-19 Infection (NPC-19) found 44/2287 (1.9%) of viral tests to be positive in neonates born to mothers with confirmed SARS-CoV-2 infection [46].

Perinatal transmission of SARS-CoV-2 from mothers to their offspring may occur via the transplacental route, or through environmental exposure to aerosolized droplets of viral particles after birth. Some reports of potential transplacental transmission have shown the presence of anti-SARS-CoV-2 IgG and IgM serum antibodies in neonates born to mothers with SARS-CoV-2 infection; however, all infants in these studies subsequently had negative viral PCR testing [47, 48]. SARS-CoV-2 specific IgM antibodies in neonates may indicate in utero infection given that IgM does not cross the placenta, and positive IgG titers in neonates may reflect maternal or neonatal infection [48, 49]. A recent case report provided virological and pathological evidence of likely transplacental transmission of SARS-CoV-2; the neonate was born to a viremic mother who presented after birth with neurological manifestations and was subsequently found to also have viremia. Histological analysis of the placenta found signs of acute and chronic intervillous inflammation and real-time reverse transcription polymerase chain reaction (RT-PCR) on the placental tissue was positive for SARS-CoV-2 [50]. In other studies, the SARS-CoV-2 virus has been found in the analysis of placental samples, providing evidence of possible

transplacental transmission, but contamination at time of delivery could not be excluded [51, 52].

Postnatal contact transmission via environmental contamination is also possible given that live SARS-CoV-2 virus has been isolated from urine and fecal samples [53]. The possibility of transmission via breastmilk is currently under investigation, as initial studies reported negative viral PCR results sent on breastmilk samples from infected mothers [48, 54–56]. Conversely, two recent studies of mother–newborn positive dyads have reported the presence of viral RNA in breastmilk, but it is unclear whether this was the route of transmission versus droplet or contact postnatal transmission [57, 58]. The implementation of infection control precautions in breastfeeding infants may reduce postnatal acquisition. Three New York City hospitals reported a series of 120 neonates born to SARS-CoV-2 infected mothers who all tested negative for the virus at 24 h of life, 5–7 days of life ($N = 82$ completed follow-up) and 14 days of life ($N = 72$ completed follow-up). In this cohort, 78% of infants were still breastfeeding at 5–7 days of life, and the study described use of precautions including hand hygiene, maternal use of a surgical mask during breastfeeding and skin-to-skin, and use of a closed isolette when infants were not being held or fed [59]. Risk factors for maternal transmission and neonatal acquisition are not fully elucidated, and it remains unclear if severity of maternal disease, timing of acquisition, gestational age at delivery, or delivery mode contribute to transmission and infection risk.

Neonatal presentations and outcomes

Clinical presentations of neonates infected with SARS-CoV-2 vary greatly, ranging from asymptomatic carriage to critical illness. A systematic review of SARS-CoV-2 infection in children and newborns included a total of 25 neonatal cases [60]. Neonates were most commonly tested due to a history of primary maternal infection (84%). Of the 25 cases, 20% were asymptomatic and a higher proportion of neonates were severely ill compared to children older than 1 month of age (12% vs. 2%). Among symptomatic neonates, the most common clinical presentation was respiratory distress (40%), with fever (32%) and feeding intolerance (24%) also described. Laboratory findings included elevated white blood cell count (20%), creatine phosphokinase (20%), liver enzymes (16%), and C-reactive protein and/or procalcitonin (12%) [60]. One case series included in this review [61] described two neonates who developed disseminated intravascular coagulation and one who suffered multi-organ dysfunction, the latter resulting in neonatal death. Both of these neonates tested negative after birth by nucleic acid amplification test [61].

There have also been reports of presumed postnatal acquisition of SARS-CoV-2 in term or late preterm infants who developed respiratory failure and were found to have ground glass opacities on chest radiography [62–64]. A case report of a 26-week preterm neonate described the new development of streaky infiltrates on chest radiography following acquisition of SARS-CoV-2 infection but had no changes in baseline respiratory support [65]. Additionally, the previously described neonate with confirmed transplacental transmission presented with neurological manifestations, including irritability, inflammatory findings in the cerebrospinal fluid, and white matter injury on brain MRI [50]. Together, these data suggest that neonates with SARS-CoV-2 infection range from asymptomatic to severely ill, with respiratory distress being the most common presentation. While studies are limited, neonates may be at higher risk of experiencing severe illness compared to older children, making them a vulnerable population.

Diagnosis and management

The current gold standard to diagnose SARS-CoV-2 infection is RT-PCR on respiratory specimens. The reliability of this test has been established [66]. However, in asymptomatic or mildly symptomatic patients, as is often the case for newborns and infants, the sensitivity of the assay may be reduced by potential false negatives [61]. Diagnosis via serological testing in neonates is particularly challenging given the transplacental transmission of maternal IgG, and that IgM assays are prone to false-positives and false-negatives, and therefore, while their presence might suggest a fetal response to in utero infection, they are not the gold standard for diagnosis of congenital infections. The presence of IgG and/or IgM antibodies does not clearly define whether infection occurred transplacentally or postnatally, but a rising IgG antibody titer on serial testing may be helpful to identify active infection [49].

Management of SARS-CoV-2 infection in neonates is largely supportive, including respiratory support, oxygen, fluid and electrolyte therapy, and empiric antibiotics if there is suspected bacterial co-infection. Remdesivir, an RNA-dependent inhibitor of RNA polymerase in coronaviruses, is approved for use via an emergency drug authorization by the Food and Drug Administration with no minimum age [67]. Though data for remdesivir are lacking in neonates with COVID-19, remdesivir has safely and effectively been used in Ebola trials in infants under 5 days of age [68]. Additionally, oral absorption is poor, so there is likely limited absorption in neonates from breastmilk of mothers who may be on the agent [69].

During the respiratory management of a suspected or confirmed case of neonatal COVID-19, the risk of aerosol

Summary of Clinical Guidelines for Infants born to SARS-CoV-2 Positive Mothers

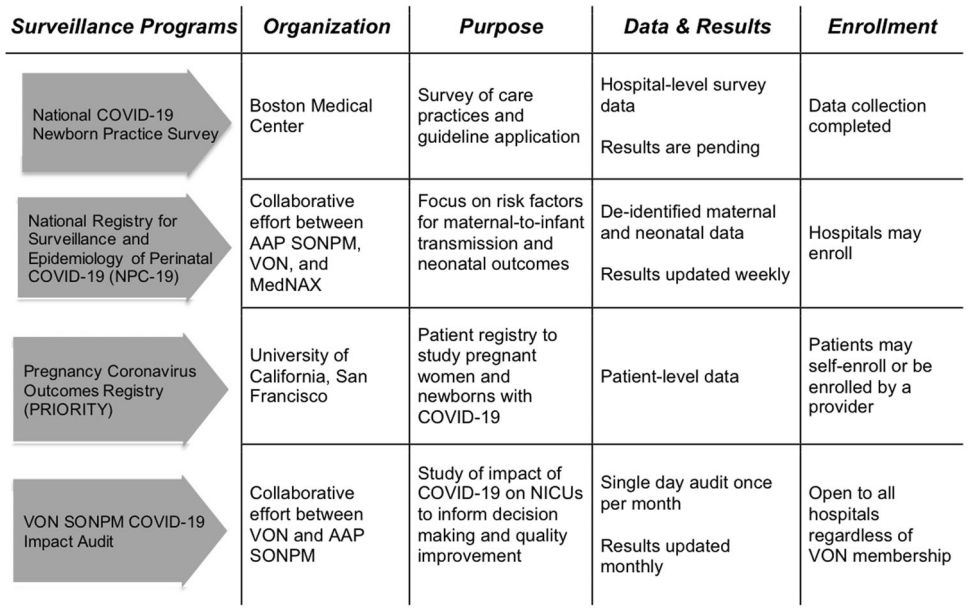
	Use of personal protective equipment	Establishing safe breastfeeding	Considerations for infant admission	Infant testing
AAP	• N-95 respirator, eye protection, gown, and gloves or an air-purifying respirator should be worn by providers attending the delivery and providers caring for infants of COVID-19 positive mothers that require positive pressure ventilation, mechanical ventilation, or supplemental oxygen >2 LPM. • COVID-19 positive mothers should wear masks & perform hand hygiene when providing care to infants.	• Mothers should perform hand hygiene before and wear a mask during breastfeeding. • An infected mother may express breast milk, and this may be fed to the infant by uninfected caregivers.	• Mothers and newborns may room-in according to usual center practice. • Mothers should wear a mask and perform hand-hygiene when performing hands-on care. Use of an isolette may facilitate distancing. • Symptomatic infants requiring NICU admission should be admitted in a single room with the potential for negative pressure air.	• Per institutional requirements, a single swab of the nasopharynx or oropharynx followed by nasopharynx, or two swabs of each site. • Testing at 24 hours and again at 48 hours of age. • Repeat tests on positive infants every 48-72 hours until two negative tests are obtained. • Infants that cannot be tested should be treated as positive for a 14-day period of observation.
CDC	• COVID-19 positive mothers should wear masks and perform hand hygiene when providing care to infants.	• Mothers should perform hand hygiene before and wear a mask during breastfeeding. • If possible, expressed breast milk should be fed to the infant by a healthy caregiver.	• Mothers and newborns may room-in, using shared decision-making. • Mothers should wear a mask and perform hand-hygiene when performing hands-on care. • Maintain a physical distance of ≥6 feet between mother and infant or use of an isolette when feasible. • Consider separation for neonates at higher risk for severe illness.	• RT-PCR testing on nasopharyngeal, oropharyngeal, or nasal swab samples. • Testing at 24 hours and again at 48 hours of age. • Infants without test results born to mothers with confirmed or suspected disease should be treated as positive.
WHO		• Infants should be breastfed within 1 hour of birth using appropriate infection prevention measures, including mothers performing hand hygiene before and wearing a mask.	• Mothers and infants should not be separated. • Support for skin-to-skin contact and kangaroo care regardless of SARS-CoV-2 status	
AAFP		• Mothers should perform hand hygiene before and wear a mask during breastfeeding. • Consider expressed breast milk fed to the infant by a healthy caregiver.	• Avoid parent-infant separation whenever possible. • Limit contact with the infant outside of breastfeeding.	

Fig. 2 Summary of clinical guidelines for care of infants born to SARS-CoV-2-positive mothers, updated as of July 22nd, 2020. We provide a summary of the clinical guidelines from the American Academy of Pediatrics (AAP), Centers for Disease Control (CDC), World Health Organization (WHO), and American Academy of Family Physicians (AAFP) for care of infants born to SARS-CoV-2-positive mothers, updated as of July 22nd, 2020.

generation and dispersion also depends on the proximity to the patient's airway and the risk of dispersion of aerosolized droplets through interface leaks or respiratory circuits [70]. Presumably, the lower tidal volumes of neonates and infants compared to adults decrease dispersion [43]. At some institutions, all neonates on respiratory support greater than 2 L/min nasal cannula or those that may require an aerosol-generating procedure are placed on airborne, contact, and eye-shield precautions, however the evidence directing which procedures require these increased precautions is unclear [71].

Recommendations for the management of neonates at risk for COVID-19 infection

At the time of this review, several organizations, including the CDC, the World Health Organization (WHO), the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN), have provided guidelines for the management of neonates at risk for COVID-19. These guidelines are summarized in Fig. 2. While initial AAP guidelines at the onset of the COVID-19 pandemic recommended temporary separation of the mother and newborn as the risk of perinatal and postnatal transmission were not completely understood, this guidance has since changed. Based on data suggesting that the risk of infection is the same for infants who are temporarily separated from their mothers compared to those that room-in with their mothers, the AAP now recommends that mothers and newborns may room-in according to usual center practice [72]. The CDC continues to recommend temporary separation between SARS-CoV-2-positive or suspected mothers and newborns, defined by maintaining separate rooms, a physical distance of 6 feet or greater between the mother and newborn, or by placing the neonate in a temperature-controlled isolette if the newborn remains in the mother's room [73]. With regard to rooming-in, both the AAP and CDC recommend barriers between mother and newborn to maintain 6 feet of distance when possible [72, 73]. The WHO does not currently recommend separation of mother and newborn, citing that physiological benefits of breastfeeding and skin-to-skin outweigh the likely limited risk of maternal to newborn transmission, especially in the context of the low virulence within the neonatal population [74]. The AAFP has similarly recommended promotion of breastfeeding and mother–newborn bonding and avoidance of separation of the mother and newborn whenever possible, although does suggest limiting contact between mothers infected with SARS-CoV-2 and their newborns when not directly breastfeeding [75].



Surveillance Programs	Organization	Purpose	Data & Results	Enrollment
National COVID-19 Newborn Practice Survey	Boston Medical Center	Survey of care practices and guideline application	Hospital-level survey data Results are pending	Data collection completed
National Registry for Surveillance and Epidemiology of Perinatal COVID-19 (NPC-19)	Collaborative effort between AAP SONPM, VON, and MedNAX	Focus on risk factors for maternal-to-infant transmission and neonatal outcomes	De-identified maternal and neonatal data Results updated weekly	Hospitals may enroll
Pregnancy Coronavirus Outcomes Registry (PRIORITY)	University of California, San Francisco	Patient registry to study pregnant women and newborns with COVID-19	Patient-level data	Patients may self-enroll or be enrolled by a provider
VON SONPM COVID-19 Impact Audit	Collaborative effort between VON and AAP SONPM	Study of impact of COVID-19 on NICUs to inform decision making and quality improvement	Single day audit once per month Results updated monthly	Open to all hospitals regardless of VON membership

Fig. 3 National surveillance programs of newborns exposed to SARS-CoV-2 in the United States, as of July 31, 2020. We provide a summary of national surveillance programs collecting data on newborns exposed to SARS-CoV-2 in the United States, as of July 2020.

Lastly, AWHONN has described the importance of shared decision-making as it relates to care of newborns born to SARS-CoV-2-positive mothers [76].

Practice surveillance and national registries

Extensive efforts are underway at hospital, state, and national levels to study the epidemiology and impact of SARS-CoV-2 infection on maternal and infant health and to fill gaps in the literature related to neonatal outcomes. National surveillance programs are summarized in Fig. 3. The National Registry for Surveillance and Epidemiology of Perinatal COVID-19 Infection (NPC-19) is a collaborative effort of the Section on Neonatal–Perinatal Medicine (SONPM) of the AAP, the Vermont Oxford Network (VON) and MedNAX, an organization of private neonatologists [46]. The NPC-19 is collecting data on mother–infant dyads with a goal to identify risk factors for neonatal transmission and outcomes. As of July 25, 2020 data have been collected from 231 centers and include 2067 mother–infant dyads [46, 77]. VON and the SONPM have also launched an audit with the goal of studying the impact of the pandemic on the neonatal community to inform decision-making and improve quality [77]. Additionally, the National COVID-19 Newborn Practice Survey, conducted by Boston Medical Center in May 2020, sought to ascertain the neonatal care practices related to COVID-19 at U.S. birth hospitals. Data collection from this survey has completed, and results are pending. Finally, the PRIORITY Study (Pregnancy Coronavirus Outcomes Registry) is being conducted by the University of California, San Francisco and is currently enrolling pregnant or recently pregnant women with known or suspected SARS-CoV-2 to study the impact of infection on pregnancy and newborns for 1 year following infection [78].

Psychosocial, ethical, and racial/ethnic considerations in the care of newborns and families during the COVID-19 pandemic

One of the major ethical concerns that has emerged from the COVID-19 pandemic is the separation of mothers with suspected or confirmed SARS-CoV-2 from their newborns after delivery. Professional society guidance on this issue has been conflicting, as described previously. Reports in the media of hospitals unilaterally separating mothers from their newborns without discussions of risks and benefits with families have exacerbated parental fear and concerns.

The medical and psychosocial implications of separation after birth are undoubtedly significant. Separation has been hypothesized to interfere with the establishment of breastfeeding and lead to decreased bonding between a mother and her newborn, which may have long-term consequences [79]. Separation without adequate parental involvement in decision-making may result in a loss of trust in the healthcare system. The combination of these concerns has led some women to change their birthing plan due to their fear of separation from their newborn at birth, inability to have a primary support person during delivery, and fear of being infected with SARS-CoV-2 in the hospital [80]. Current data are lacking and further research is needed on the impact of these changes, but there is the potential for an increase in home births and increased demand for midwives and other personnel to attend home deliveries, which may

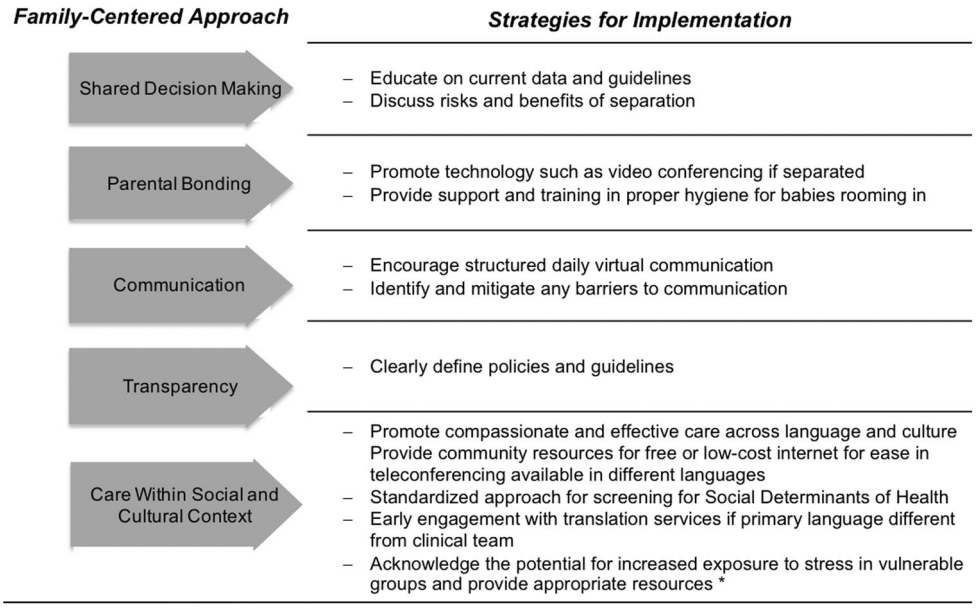


Fig. 4 Strategies for providing family-centered care for mothers and newborns during a pandemic [82, 85].

not be able to be met by the current out-of-hospital-birthing system.

Many of the neonatal/perinatal ethical concerns discussed above relate to balancing parental decision-making rights while mitigating risks to newborns, maintaining public trust in the healthcare system, and issues of equity and bias. Parents are generally given decision-making rights for their children, thus, in the absence of serious harm for the newborn, parents are allowed to consent or decline separation after appropriate counseling [81]. Transparency from hospitals about the guidelines they follow, and how they will implement policies aligned with those guidelines is key to maintaining public trust during the pandemic [82].

The long-term implications of COVID-19 in the neonatal and maternal populations are unknown, and stress and adversity experienced by families during the pandemic may have implications on health and well-being [83, 84]. Therefore, providers must continue to seek a balance for their patient's safety and wellbeing. Figure 4 details existing recommendations for providing family-centered care, in order to ease parental distress in the face of possible family separation and other issues created by COVID-19 [82, 85].

Finally, consideration of the ethical implications of neonatal care during the COVID-19 pandemic must include a discussion of disparities. Despite being a racial/ethnic minority of the general U.S. population, the non-White population has been disproportionately impacted by infection, severe disease manifestations, and death [86–90]. Data collected from the CDC suggest this is true specifically for Hispanic and non-Hispanic Black pregnant women [29]. Multiple mechanisms are responsible for these disparities, including the disproportionate burden of chronic medical conditions among Black and non-White Hispanic/Latinx adults in America, disparities in living conditions, residential segregation, inequitable access to food and healthcare systems, and environmental particulate pollution [86, 91]. Furthermore, the disproportionate representation of Black and non-White Hispanic and Latinx adults in "essential" jobs places communities of color in America at a disproportionate risk of infection [91]. There is a need to understand how bias in the healthcare system, long known to a be driver of disparities, impacts neonatal and perinatal outcomes during the pandemic [92, 93]. Vulnerable groups, including individuals in prisons, individuals with disabilities, individuals experiencing homelessness, immigrants, refugees, and asylum seekers are also disproportionately affected by the pandemic and need attention and ethical considerations [94–97]. Further research and longitudinal studies will be useful in addressing current gaps in understanding the long-term implications of COVID-19 on all populations, across the life course.

Conclusion

In this comprehensive review, we have presented an up-to-date summary of the literature on the management of the COVID-19 pandemic, with a focus on the care of pregnant women and newborns. Current data suggest the risk of neonatal transmission is low and that neonatal disease most commonly ranges from asymptomatic to mildly symptomatic. This has informed existing recommendations from professional societies for the management of these populations. These recommendations

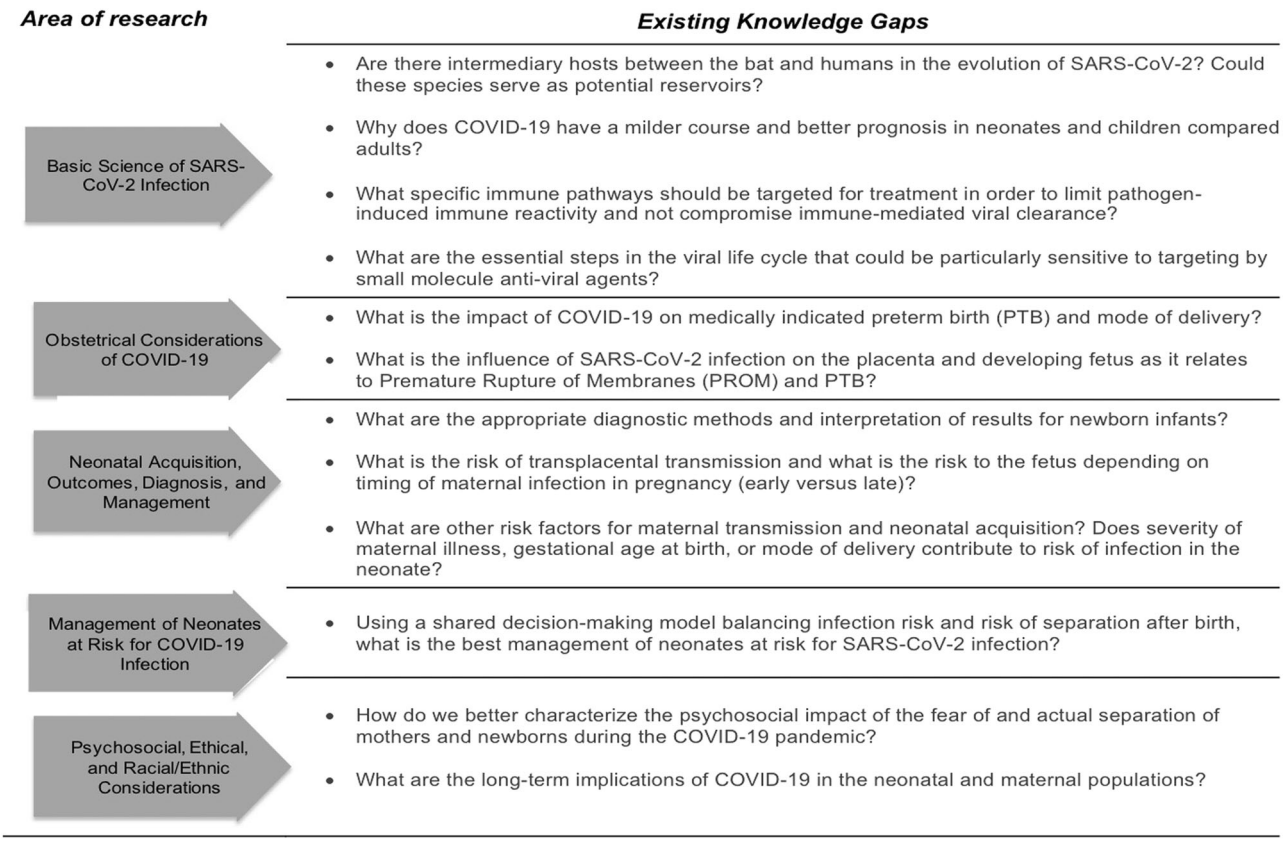


Fig. 5 Existing knowledge gaps related to neonatal–perinatal perspectives of COVID-19. Current knowledge gaps in the literature related to neonatal–perinatal perspectives of COVID-19.

represent different perspectives and prioritization, taking into consideration factors including the current understanding of disease transmission and pathology, local infection rates, and existing resources. The COVID-19 pandemic has created an unprecedented challenge for the global healthcare system. Research efforts have mobilized rapidly, but many questions and knowledge gaps remain in our understanding of basic disease pathophysiology, epidemiology, and clinical manifestations of illness in pregnant women and neonates (Fig. 5). There remains a critical need for the adaptation of the healthcare system, as information is changing rapidly and the knowledge informing best practices in the care of pregnant women and newborns continues to evolve.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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