

Review

Malika D. Shah, Nicolas Miller and Ola D. Saugstad*

Newborns at risk of COVID-19, the story continues

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Abstract: After more than 4 years of the SARS-CoV-2 pandemic, a great deal of knowledge on how this virus affects pregnant women, the fetus and the newborn has accumulated. Guidelines for mode of delivery, cord clamping, skin to skin, breastfeeding, and rooming-in have become uniform across the world. Vaccination has considerably improved outcomes, but hesitancy amongst pregnant patients and the emergence of variants remain challenged and SARS-CoV-2 positivity during pregnancy continues to be associated with an increased risk of maternal complications, premature delivery and higher neonatal mortality and morbidity. An emerging body of data now exists on the effect of SARS-CoV-2 in pregnancy on early neonatal outcomes, medical education in obstetrics and pediatrics, and longer-term developmental outcomes. In this article, we review the development in this field since our last review.

Introduction

In 2020, we summarized recommendations from different communities related to mothers and newborns with suspected or laboratory confirmed SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection [1]. The Chinese employed a very strict regime, encouraging cesarean section, avoiding contact between mother and child, and withholding both breastfeeding and expressed breast milk [2].

***Corresponding author: Ola D. Saugstad**, MD, PhD, Northwestern University Feinberg School of Medicine, 420 E. Superior St. Chicago, Chicago, IL 60611, USA; Division of Neonatology, Ann and Robert H. Lurie Children's Hospital of Chicago, 225 E Chicago Ave, Chicago, IL 60611, USA; and Department of Pediatric Research, University of Oslo, 0424 Oslo, Norway, E-mail: o.d.saugstad@medisin.uio.no. <https://orcid.org/0000-0002-3166-5254>

Malika D. Shah, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; and Division of Neonatology, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA. <https://orcid.org/0000-0001-8347-9587>

Nicolas Miller, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. <https://orcid.org/0009-0000-7201-9227>

The guidelines from the American Academy of Pediatrics (AAP) and the USA Centers for Disease Control and Prevention (CDC) advocated routine delivery, separation between mother and child and encouraged use of expressed breast milk fed by alternate caregiver [3, 4]. By contrast, the World Health Organization (WHO) and European organizations as Union of European Neonatal and Perinatal Societies (UENPS) recommended keeping mothers and infants together and allowing direct breastfeeding with careful breast hygiene [5].

Knowledge accumulated and many studies reported on outcomes of diverse approaches to handling of the mother and newborn during the COVID-19 pandemic. In 2021, we published an update on revised recommendations highlighting that the AAP had changed their position to resemble the WHO and UENPS recommendations, and that breastfeeding and rooming-in were now encouraged [6]. Both vertical and horizontal transmission appeared rare, and it became known that antibodies passed from mothers to infants through both the placenta and breast milk. Affected infants appeared to have mild infections. Alterations for delayed cord clamping, mode of delivery, and timing of discharge were no longer recommended based on SARS-CoV-2 diagnosis alone. Vaccination for pregnant women had not yet been recommended as data were lacking.

An enormous amount of research on SARS-CoV-2 has since emerged on vaccination and its safety in pregnancy and lactation. In addition, concern for the emergence of a multisystem inflammatory syndrome and delayed developmental outcomes in neonates exposed to SARS-CoV-2 *in utero* have been published. Finally, effects on pediatric and obstetric medical education, and repercussions for healthcare workers have been reported. We review the development in this field since our last review [6].

Vaccination and pregnancy

Numerous studies throughout the world have shown improved pregnancy outcomes with vaccination. Vaccination is now the most effective intervention for improving neonatal morbidity due to SARS-CoV-2 and can be given at any time during pregnancy. In a population-based cohort study of 142,006 live births in Ontario, Canada, maternal mRNA COVID-19 vaccination during pregnancy was associated with

lower risks of severe neonatal morbidity, neonatal death, and neonatal intensive care unit admission and no increase in neonatal readmission or hospital admission up to age 6 months, compared with no maternal COVID-19 vaccination before delivery [7].

In another multicenter review of nine observational studies involving 81,349 vaccinated and 255,346 unvaccinated individuals during pregnancy, Watanabe et al. found COVID-19 vaccination during pregnancy to be associated with lower risk of NICU admission and intrauterine fetal death with no statistically significant association with preterm birth, small for gestational age status, or low Apgar score. COVID-19 vaccination during pregnancy was associated with a lower risk of postpartum hemorrhage, and chorioamnionitis [8].

Studies show that boosters appear to confer additional protection for pregnant patients. In a retrospective multicenter cohort study on the impact of COVID-19 vaccination on outcomes for 106,428 birthing parents across 7 western USA States from January 2021 to October 2022, vaccinated pregnant women had lower rates of COVID-19 compared with unvaccinated matched women [9]. COVID-19 rates were even lower in boosted. Vaccinated women were also less likely to have a preterm birth, stillbirth, or very low birthweight neonate compared with unvaccinated matched women. Boosted women were even less likely to have a stillbirth and showed no differences in rates of preterm birth or very low birthweight neonates compared with vaccinated, unboosted matched women. The study concluded that COVID-19 vaccination protects against adverse maternal–fetal outcomes, with booster doses conferring additional protection.

Vaccination during pregnancy, in addition to being safe and effective, may also protect infants after delivery. Goh et al. showed that vaccination during pregnancy provided some protection against COVID-19–related hospitalizations among infants, particularly those aged <3 months [10]. Simeone et al. showed that maternal mRNA vaccination was associated with a lower risk of Omicron SARS-CoV-2 infection among infants up to 6 months of age only if the vaccine was given during the antenatal period [11].

Vaccine hesitancy

Despite the abundance of studies on safety and improved outcomes, many pregnant women remain unvaccinated, often due to vaccine hesitancy. In February 2022, Engjom et al. voiced that severe covid-19 in pregnancy was almost entirely limited to unvaccinated pregnant women [12]. Through study of six European countries, they found widely

differing uptake rates from 22 % in England to 80 % in Norway despite multiple initiatives to promote uptake of COVID-vaccination in pregnancy. After evaluating combined surveillance data of the most critically ill pregnant and postpartum women in these countries, they found almost none were vaccinated. Additional studies from South Africa, Brazil, India, the United Kingdom, and Jordan show similar results [13–15]. In a systematic literature review that included 30 studies of pregnant women, determinants of hesitancy included religious concerns, socioeconomic factors, inadequate information regarding the vaccine and lack of trust towards medical professionals [16].

Healthcare workers, including those in maternity settings can also be resistant to vaccine [17]. Due to the combination of vaccine hesitancy and emergence of variants, we need to remain vigilant in our care of pregnant women with SARS-CoV-2 and their newborns and in ensuring that staff and trainees are educated and protected.

Delivery, cord clamping, and neonatal resuscitation

Delivery, cord clamping, and neonatal resuscitation recommendations have not changed since our previous review. Newborns and caregivers should be protected from acquiring the infection during the delivery by using transmission-based precautions including gown, gloves, and either an N95 respirator and eye protection (goggles or face shield) or an air-purifying respirator that provides eye protection [18]. NRP (Neonatal Resuscitation Program) is per usual practice and not to be changed due to COVID-19 [19]. Delayed cord clamping is recommended even if mother is infected; a systematic review and meta-analysis by Berg et al. summarized 48 studies including 1,476 neonates. Neonatal SARS-CoV-2 positivity rates were similarly low following both delayed and early cord clamping, <1.5 % [20].

Rooming-in care, breast milk and breastfeeding

Rooming-in continues to be recommended for well newborns and birthing parents well enough to care for their newborns. The AAP recommends mask usage, but WHO clarifies that if a mask is not available, rooming-in, skin to skin and breastfeeding should be continued, and other infection prevention measures including washing hands and cleaning surfaces should be prioritized [3, 21].

If the birthing parent has not had an opportunity to receive a covid vaccine or has declined vaccination during

pregnancy, vaccination should be encouraged in the postpartum period. Numerous studies have not only shown safety in breastfeeding, but also the presence of antibodies in the breast milk of vaccine recipients [22]. With clear data demonstrating efficacy and safety and no data demonstrating harm during lactation, recommendations to avoid vaccination while breastfeeding or to withhold breast milk from the infant for any period of time after vaccination are not supported by available evidence.

Mothers of infants in the NICU should express breast milk for their infants during any time that their infection status prohibits their presence in the NICU. Centers should arrange to receive this milk until visitation is allowed. Health care workers should use transmission-based precautions when caring for well infants when this care is provided in the same room as a person with COVID-19.

Transmission to newborns

Recent studies confirm our previous report that the risk of *in utero* transmission of SARS-CoV-2 is limited (between 0.8 and 3 %). Mand et al. used data from a German Covid-19 registry of 8,540 pregnant women who tested positive to SARS-CoV-2 infection between April 2020 and February 2023 and found a possible rate of vertical transmission of 2.1 %. Severe maternal COVID-19 and maternal infection with the Delta virus were associated with neonatal SARS-CoV-2 infection [23].

It appears vertical transmission of SARS-CoV-2 occurs through 2 mechanisms: The virus may enter the placenta with aid of transmembrane serine protease 2 by binding to ACE2. Crossing of the placenta by macrophages and monocytes infected by SARS-CoV-2 represents another route of viral transmission [24].

Celik et al. also summarizes several fetal conditions which may have been attributed to COVID-19 during pregnancy including myocarditis, tachycardia, calcification of fetal bowel and bladder, periventricular leukomalacia, cerebral venous thrombosis, cerebral ischemic lesions, neonatal necrotizing enterocolitis and infantile immune thrombocytopenia.

Horizontal transmission is also relatively rare. In a study of over 1 million neonatal encounters from March 2020 to February 2021 extracted from the Cerner Real World Database, COVID-19 diagnosis was assessed using SARS-CoV-2 laboratory tests and diagnosis codes [25]. COVID-19 was diagnosed in 918 (0.1 %) neonates. Most neonates infected with SARS-CoV-2 were asymptomatic or developed mild illness without need for respiratory support and <8 % had severe infection. Common signs of infection were tachypnea

and fever and those with severe infection were more likely to receive respiratory support.

Although neonatal morbidity from vertical and horizontal transmission is low, neonates born to mothers with SARS-CoV-2 may still be at risk of adverse outcomes from the newly characterized condition called multisystem inflammatory syndrome (MIS-N). In 2021, Pawar et al. described outcomes of 20 neonates who appeared to have a MIS-N in Kolhapur, India, from September 2020 to April 2021 [26]. Nineteen were positive for anti-SARS-CoV-2 IgG and all were negative for IgM antibodies. Eighteen neonates (90 %) had cardiac involvement with prolonged QTc, 2:1 AV block, cardiogenic shock, or coronary dilatation. Other findings included respiratory failure (40 %), fever (10 %), feeding intolerance (30 %), melena (10 %), and renal failure (5 %). All infants had elevated inflammatory biomarkers and received steroids and IVIG. Two infants died. No mothers were tested at the time of delivery, as all were asymptomatic. The team speculated that maternal SARS-CoV-2 *in utero* and transplacental antibodies cause multisystem inflammatory syndrome in neonates (MIS-N) and that immunomodulation may be beneficial. They recommended the following diagnostic criteria (Table 1).

Since that time, numerous case studies describing similar inflammatory conditions have been published [27–29]. Mascarenhas et al. reviewed clinical characteristics, laboratory parameters, treatment, and outcomes of 104

Table 1: (Adapted from Pawar et al, 2021).

(1)	Neonate aged <28 days at the time of presentation
(2)	Laboratory or epidemiologic evidence of SARS-CoV-2 infection in the mother <ol style="list-style-type: none"> Positive SARS-CoV-2 testing by RT-PCR, serology (IgG or IgM), or antigen during pregnancy Symptoms consistent with SARS CoV-2 infection during pregnancy COVID-19 exposure with confirmed SARS CoV-2 infection during pregnancy Serological evidence (positive IgG specific to SARS CoV-2 but not IgM) in the neonate
(3)	Clinical criteria <ol style="list-style-type: none"> Severe illness necessitating hospitalization AND Two or more organ systems affected [i.e., cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, neurological, temperature instability (fever or hypothermia)] OR Cardiac AV conduction abnormalities OR coronary dilation or aneurysms (without involvement of a second organ system)
(4)	Laboratory evidence of inflammation One or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6; elevated neutrophils or reduced lymphocytes; low albumin
(5)	No alternative diagnosis (such as birth asphyxia, viral or bacterial sepsis, maternal lupus).

neonates with MIS-N through conduction of a systematic review that included 27 case studies from January 1, 2020, through September 30, 2022, [30]. They found the median age of presentation was 2 days (range, 1–28 days). The cardiovascular system was the predominant system involved (83.7%) followed by respiratory (64.4%). Fever was noted in 20.2%. Evidence of SARS-CoV-2 antibodies (IgG or IgM) were seen in 95.9% neonates and evidence of maternal SARS-CoV-2 infection, either as history of COVID infection or positive antigen or antibody test, was noted in 100% of the cases. Anti-inflammatory agents were often used and included steroids 80.8% and IVIG. Outcomes were available for 98 cases, of whom 8 (8.2%) died during treatment in hospital and 90 (91.8%) were successfully discharged home. To date, there is no consensus definition for MIS-N. Many experts are calling for an internationally recognized consensus definition and international datasets to improve management and plan future clinical trials [31, 32].

NICU care

Separation in an ICU is only necessary for neonates requiring ICU care. If the infant is being tested for SARS-CoV-2 due to recent maternal infection, they should be admitted to a single patient room with the potential for negative room pressure (or other air filtration system). If this is not available, or if multiple SARS-CoV-2 exposed infants must be cohorted, there should be at least 6 feet (2 m) between infants. Use of air temperature-controlled isolettes can provide an additional barrier against droplet transmission. Providers should don a gown and gloves and use either an N95 respiratory mask and eye protection goggles or an air-purifying respirator that provides eye protection for care of infants requiring supplemental oxygen at a flow >2 L per minute, continuous positive airway pressure, or mechanical ventilation.

Supportive care is recommended for symptomatic infants with SARS-CoV-2 and in most symptomatic cases, oxygen and intravenous fluids are sufficient. Although remdesovir is only approved for patients >28 days and >3.0 kg, case reports have been published of its successful use in younger, smaller patients on mechanical ventilation [33]. With regards to MIS-N, a high threshold for consideration is required as there is neither consensus for diagnosis nor treatment. IVIG and other immune modulators may be beneficial, but data are only now emerging and are contradictory with some studies encouraging routine use and others suggesting restriction to severe cases due to the associated risk of infection and gastrointestinal issues [26, 32].

Visitation and testing

During the COVID-19 pandemic, most NICUs limited parent presence and nonparent visitation to minimize the likelihood that vulnerable infants in the NICU would acquire an infection and protect the health and integrity of the specialized NICU workforce. Regulations were adapted based on the region's infection risks.

The WHO does not provide specific guidance for visitation or testing of infants in the NICU but does assert that all efforts should be made to ensure that all pregnant and postpartum women and their newborns, including those with confirmed or suspected COVID-19 infections, have the right to high quality care where separation of mother and infant is avoided.

The AAP discusses several common scenarios and recommends the following [34]:

- **Pregnant persons who test positive for COVID-19 on routine obstetric testing but are asymptomatic** should be excluded from the NICU for 5 days from the positive test (enter on day 6) and wear a face mask on days 6 through 10 after positive test.
- **Pregnant persons and partners who test positive for COVID-19 by PCR-based or antigen-based testing following symptoms or a close exposure** should not visit NICU infants while able to transmit SARS-CoV-2. Immunocompetent people may be considered noninfectious if (a) afebrile for 24 h without use of antipyretics, (b) at least 10 days have passed since symptoms first appeared, and (c) symptoms have improved.
- **Birthing parents and partners who have a close exposure to another person with COVID-19** should not be excluded from the NICU if asymptomatic. Such people should wear a face mask for 10 full days following last close contact and have SARS-CoV-2 testing at least 5 days following last close contact. If such people develop symptoms consistent with COVID-19 infection, they should obtain testing as soon as possible and not enter the NICU until their status is clarified.
- **Newborn infants who have been separated from an infected mother shortly after birth and admitted directly to the NICU:** infection control precautions appropriate to the infant's required respiratory care should be used until the infant has negative testing within the first 72 h of age.
- **Newborn infants who have been rooming-in with an infected, presumed, or known contagious mother who subsequently require admission to the NICU:** infection control precautions appropriate to the infant's required respiratory care should be used until 10 days

have passed since the last maternal-infant contact. Centers may determine testing based on their local resources.

- **Well infant testing:** The AAP continues to recommend testing well newborn infants born to mothers with Covid-19 to help facilitate plans for care after hospital discharge. The test should be performed as close to the time of discharge as is practical to provide the most accurate family guidance.

Discharge and developmental outcomes

Discharge of newborns should be based on each center's routine criteria. If infant SARS-CoV-2 testing is positive, but the infant has no signs of COVID-19, frequent outpatient follow-up is recommended either by phone, telemedicine, or in-office through 14 days after birth. During this period, precautions should be taken to prevent spread from infant to caregivers by using masks, gloves, and hand hygiene in the home environment and by healthcare staff in the outpatient office practice. It is essential that providers responsible for the newborn in the hospital communicate with outpatient providers so that appropriate practices can be in place. Outpatient settings often do not have access to the same Personal Protection Equipment (PPE) as inpatient practices do and discussion with the follow-up physician prior to the appointment will allow for appropriate planning. In addition, MIS-N may appear after hospital discharge and has no clear consensus diagnostic criteria. A high index of suspicion is required. For infants with MIS-N, follow-up should be individualized with a low threshold for cardiology surveillance until more data are available.

Growth and developmental milestones should be followed closely with a low threshold for intervention or therapies as needed. Data are only now emerging on long-term neurodevelopmental outcomes of the COVID-19 pandemic with studies showing differing results. Goyal et al. recently studied follow-up data from India of 20 COVID-19 positive newborn infants. Thirty-five percent of infants had motor scores that suggested mild delay, 40 % had language scores that suggested mild delay and 10 % of infants had scores that suggested moderate language delay [35]. Similarly, In Turkey, Ergon et al. found SARS-CoV-2-positive neonates revealed lower psychomotor developmental index scores and greater mildly delayed performances at 18–24 months which were more noticeable with the Delta variant [36]. By contrast, studies from Kuwait showed no differences in cognitive outcomes at 18 months between infants diagnosed with COVID in

the neonatal period and those without [37]. A systematic review and meta-analysis examining the association between COVID-19 pandemic and the risk of neurodevelopmental impairment found birth during the first year of life during the COVID-19 pandemic, regardless of maternal or neonatal infection, to be significantly associated with the risk of communication delay among the offspring [38].

Although in-person post-discharge visits are the preferred means to provide timely newborn screening, bilirubin testing, and feeding and weight assessments, data on telemedicine and remote visits may show promise for visits outside the early neonatal period [39]. Remote visits have also shown promise for diagnosis of developmental delays [40, 41].

Medical education and staff wellness

The COVID-19 pandemic had profound impacts on medical education and staff wellness. Data on the impact on medical education is only now emerging. These effects were especially pronounced in pediatrics training, as patient load and procedural exposure significantly decreased. Hamid et al. found that the percentage of pediatrics trainees in Pakistan managing more than 30 patients and 5 procedures per week decreased from between 55 and 66 % to between 16 and 18 % during the pandemic [42]. In the United States, programs also experienced substantial decreases in pediatric resident patient exposure, most notably to non-COVID-19 respiratory illnesses in both the inpatient and outpatient settings [43, 44]. Silver et al. described the effects of the pandemic on pediatric critical care fellows, noting that program directors had less confidence in the procedural skills of fellows and fellows were less likely to feel that they were adequately trained [45]. COVID-19 also had an impact on pediatrics trainee well-being. Sanghavi et al. reported that 50 % of pediatric residents experienced increased anxiety as a direct result of the pandemic and that many residents were concerned about the pandemic's effect on their education [46]. In Argentina, over 60 % of pediatrics residents felt that the COVID-19 pandemic impaired their ability to become a pediatric specialist [47].

Postgraduate medical educators were often forced to adopt new methods of teaching during and continuing after the pandemic. These adaptations were widespread in Neonatal-Perinatal Medicine (NPM). The COVID-19 pandemic greatly disrupted in-person simulation sessions which were commonplace for early year fellows in many neonatology programs. Lombardi et al. reviewed a relatively successful transformation of an NPM bootcamp into a hybrid model where most participants across 17 different programs agreed that the format was effective and course objectives were met

despite the change [48]. Similarly, methods were created for teaching the logistics of neonatal transport to fellows in a flipped classroom approach. NPM fellows showed increased knowledge of transports and increased confidence in their ability to perform a neonatal transport after the course [49]. Kim et al. investigated the use of video conferencing to teach antenatal counseling to NPM fellows, a skill that is traditionally taught with direct observation or simulated scenarios before the fellows counsel real patients. Fellows evaluated the course favorably and felt that their counseling skills improved despite not being in person [50].

While clinical and procedural exposure suffered for pediatric residents and fellows during the pandemic, many felt obstetrics training was overall less impacted. Less than half of obstetrics and gynecology trainees felt that COVID adversely affected their training and most of those effects were seen in benign gynecological training, not obstetrics care [51, 52]. In Europe, Boekhorst et al. found that despite widespread cancelled surgeries and reduced patient care in gynecology and family planning, obstetrics did not see the same effects. The survey found that 92% of trainee respondents across 25 European countries reported that necessary obstetrics care continued through the COVID-19 pandemic [53].

Both pediatric and obstetric staff have also experienced considerable stress during the past 4 years with numerous publications indicating discomfort with changing guidelines, enforcing visitation policies, providing lactation support, working increased hours, and being exposed to and/or exposing family members to COVID-19 [54–56].

Discussion

The world has now lived with COVID for more than four years. For newborns, we have come a long way from the first experience from China and the very conservative position of cesarean sections, isolating mothers from babies, and withholding breast milk. As more research on outcomes has become available, the world is more united in its approach towards prevention through vaccination. The evidence to date suggests that the risk of the newborn acquiring infection during the birth hospitalization is low when precautions are consistently taken to protect newborns from maternal infectious respiratory secretions and in-room care and breastfeeding have increasingly become standard of care. The benefits of maternal-infant attachment, breastfeeding, and bonding outweigh potential negative effects of separation of mother and child in case of suspected or proven maternal infection. Further, SARS-CoV-2 antibodies but not the virus itself seem to be transmitted via breast milk. Rooming-in promotes family-centered care and can allow

for parent education about newborn care and infection prevention and control practices.

Although transmission is low, infants born to mothers with SARS-CoV-2 may be at risk for MIS-N, and a high index of suspicion is required due to considerable overlap with conditions common in the neonatal period. Immune modulators may be of benefit. Data are only now emerging on short- and longer-term outcomes. Developmental data are difficult to discern as infants born during the pandemic may have developmental effects due to social isolation. Communication with outpatient health care providers is essential for not only the safety of the newborn, but also for the safety of clinic staff. Developmental and/or cardiac follow-up may be needed when available.

While much has been learned about optimal maternity practices during the COVID-19 pandemic, we are only now learning about longer-term effects on neonates, new families, pediatric and obstetric training, and healthcare worker wellness. Continued study is needed on longitudinal outcomes and the effectiveness of strategies to combat trainee and healthcare worker challenges. Partnerships between hospitals, academic centers, and outpatient clinics continue to be essential to facilitating this research.

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