

Review

Malika D. Shah and Ola Didrik Saugstad*

Newborns at risk of Covid-19 – lessons from the last year

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Abstract: After more than 1 year 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. The gap between different guidelines how to handle newborn infants during this pandemic has been minimized, and the American Academy of Pediatrics (AAP)'s recommendations are now more in accordance with those of the World Health Organization (WHO). In this article we summarize present knowledge regarding transmission from mother to the fetus/newborn. Although both vertical and horizontal transmission are rare, SARS-CoV-2 positivity is associated with an increased risk of premature delivery and higher neonatal mortality and morbidity. Mode of delivery and cord clamping routines should not be affected by the mother's SARS-CoV-2 status. Skin to skin contact, rooming in and breastfeeding are recommended with necessary hygiene precautions. Antibodies of infected or vaccinated women seem to cross both the placenta and into breast milk and likely provide protection for the newborn.

Keywords: COVID-19; guidelines; newborn.

Introduction

As the Covid-19 pandemic comes to age the medical community has actively collected and gained information regarding this disease. A year ago, we summarized

recommendations from different communities related to mothers and newborns with suspected or laboratory confirmed SARS-CoV-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, 3]. The guidelines from the 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 [4, 5]. By contrast, WHO recommended keeping mothers and infants together, and allowing direct breastfeeding with careful breast hygiene [6]. Guidelines similar to the WHO were issued by European organizations as Union of European Neonatal and Perinatal Societies (UENPS) [7]. Guidelines from 17 countries were recently summarized by Yeo et al. [8].

At that early stage of the pandemic, the possibility of vertical or horizontal transmission was unknown, and it was not fully known how newborns would be affected. However, as knowledge accumulated over the last year, many studies have reported on outcomes and approaches to handling of the mother and newborn during the COVID-19 pandemic. Subsequently recommendations have been revised. Most notably, AAP has gradually changed their position to more closely resemble the WHO recommendations [4, 6]. In this article, we review the development in this field over this past year and summarize the evolution of guidelines for caring of newborns and mothers with suspected or laboratory confirmed SARS-CoV-2 infection. While data on long term outcomes continue to be lacking, there is greater consensus on delivery room practices and early management of newborns.

Transmission to the newborn

Although maternal morbidity can be severe, vertical transmission has been reported to be rare. Huntely et al. reviewed 99 articles and found no confirmed vertical transmission [9]. Horizontal transmission of SARS-CoV-2 to the newborn seems to occur primarily through respiratory droplets when neonates are exposed to mothers or other caregivers with SARS-CoV-2 infection. Neonatal infection is uncommon,

*Corresponding author: Ola Didrik Saugstad, MD, PhD, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; and Department of Pediatric Research, University of Oslo, 0424 Oslo, Norway, E-mail: o.d.saugstad@medisin.uio.no

Malika D. Shah, Prentice Newborn Nursery, Northwestern Memorial Hospital, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA; and Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

although neonates born to newly infected symptomatic women are more likely to be infected and some studies have found correlations with other maternal characteristics. Out of 1,200 pregnant women from the USA, the PRIORITY study prospectively followed 179 newborns of SARS-CoV-2 positive and 84 newborns of SARS-CoV-2 negative pregnant mothers. During the follow-up period of 6–8 weeks an estimated incidence of a positive test for SARS-CoV-2 among infants of mothers with positive testing for SARS-CoV-2 was 1.1% (95% CI 0.1%, 4.0%). No infant required re-hospitalization in the follow-up period [10].

A more recent multicenter cohort from 11 institutions in Massachusetts included 255 neonates born to mothers with SARS-CoV-2 infection, and only five (2.2%) had positive results during the birth hospitalization. High maternal social vulnerability was associated with higher likelihood of neonatal test result positivity (adjusted odds ratio, 4.95; 95% CI, 1.53–16.01; $p=0.008$), adjusted for maternal COVID-19 symptoms, delivery mode, and rooming-in practice. Of the 151 newborns with follow-up data in the first month of life, seven underwent SARS-CoV-2 testing, and only one had a positive result [11].

In an international multicenter study, a total of 706 pregnant women with COVID-19 diagnosis and 1,424 pregnant women without COVID-19 diagnosis were enrolled. Among women who tested positive (98.1% by real-time polymerase chain reaction), 54 (13%) of their neonates tested positive. Cesarean delivery (RR, 2.15; 95% CI, 1.18–3.91) but not breastfeeding (RR, 1.10; 95% CI, 0.66–1.85) was associated with increased risk for neonatal test positivity [12].

Flannery et al. showed that maternally derived IgG but not IgM antibodies were detected in cord blood in 72 of 83 pregnant women who were seropositive. Transfer ratios were associated with time elapsed from maternal infection to delivery and not associated with severity of maternal infection [13]. Maternally derived antibodies to provide neonatal protection from SARS-CoV-2 infection seems therefore possible.

Delivery and cord clamping

The first consensus guidelines from China recommended cesarean delivery for SARS-CoV-2 affected mothers. We now know that there is no indication to prefer one mode of delivery over another. Induction of labor and caesarean section should only be undertaken when medically justified and based on maternal and fetal condition. While symptomatic COVID in mother may necessitate early delivery of the infant, COVID-19 positive status alone is not an indication for caesarean section. AAP emphasizes the use of gown, gloves, 95 respiratory mask, and eye protection or

an air-purifying respirator that provides eye protection for personnel involved. The goal is to protect against both maternal virus and potential newborn virus aerosols during resuscitation procedures such as bag mask ventilation. Delayed cord clamping should be practiced per usual center practice. The risk of transmission of COVID-19 through blood is likely to be minimal. There is no evidence that delaying cord clamping increases the possibility of viral transmission from the mother to the newborn [14]. Table 1 summarizes appropriate IPC (infection prevention and control) measures needed.

Newborn resuscitation

Suspected or confirmed COVID-19 alone in an otherwise uncomplicated pregnancy is not an indication for the resuscitation team. However, delivery room preparation and management should include consideration for prompt donning of appropriate personal protective equipment (PPE).

It is unclear if a woman can disseminate the SARS-CoV-2 virus through droplets, aerosols, body fluids, and fomites during labor and delivery. Where respiratory support is required at delivery, spread through aerosolization may be increased. Providers involved in aerosol generating procedures (AGP) such as intubation, open airway suctioning, surfactant administration, and application of nasal cannula interface at flow of >2 L/min are at higher risk of exposure to the SARS-CoV-2 virus. Hence, in many units, all personnel attending neonatal resuscitation should according to Perlman et al. don N95 particulate respirator masks, goggles or face shield, full-length water-resistant gowns and gloves [15]. Personnel assigned with AGP should consider wearing a powered air purifying respirator (PAPR). All providers should undergo training in donning and doffing of PPE, and

Table 1: Infection prevention and control (IPC).

- Frequent hand hygiene with soap and water or alcohol-based hand rub.
- Respiratory hygiene: sneeze or cough into a tissue and immediately dispose of the tissue. Hands should immediately be washed with soap and water or alcohol-based hand rub.
- Clean and disinfect surfaces with which the mother has been in contact.
- Wear a medical mask until symptom resolution and criteria for release from isolation have been met.
- If an infected mother chooses not to nurse her newborn, she may express breast milk after appropriate hand hygiene, and this may be fed to the infant by other uninfected caregivers.
- Mothers of NICU infants may express breast milk for their infants during any time that their infection status prohibits their presence in the NICU. Centers should make arrangements to receive this milk from mothers until they are able to enter the NICU.

simulation of code situations with full PPE to familiarize with the facility, access, special precautions and communication. Pre-assigned facility for delivery, functional equipment, trained personnel and an established workflow are requisites for safe and effective resuscitation [15–18].

Women with suspected or confirmed COVID-19 infection in labor should be cared for in a negative pressure room or isolation room, if available. High-risk pregnancies should be referred to a tertiary facility. Where dedicated space is unavailable, door to labor room should be closed at all times and compliance to infection control measures enforced. Donning of mask by the patient is recommended. The resuscitation area should be placed at least 2 m away from the mother if an adjacent room for neonatal resuscitation is unavailable [16–19].

Where high-risk delivery is expected, a designated team, limited to three personnel should be in attendance—a neonatal nurse and two medical personnel, one of whom is experienced in advanced resuscitation. Additional help may be waiting outside the delivery room. For low-risk delivery where the need for resuscitation is not anticipated, a single neonatal responder may remain available outside the delivery area fully donned and ready to be activated [16, 17, 19].

Skin to skin care

At this time, there are insufficient data on the routine practice of immediate skin-to-skin care for the purpose of preventing SARS-CoV-2 transmission to the neonate. The World Health Organization recommends mother and infant to remain together throughout the day and night and practice skin-to-skin contact, including kangaroo care, regardless of suspected or confirmed COVID-19 virus infection. The AAP recommends that mothers with COVID-19 should use a mask while holding their baby [4, 6].

Breast milk and breastfeeding

Transmission in general of viruses through breastfeeding varies being high for CMV, and low for hepatitis B and C. For SARS-CoV-2 the transmission rate was initially unknown and data has been accumulated over the last year. Pace et al. collected repeated milk samples from 18 women following COVID-19 diagnosis. None contained SARS-CoV-2 RNA; however, risk of transmission via breast skin should according to these authors be further evaluated [18].

Several recent studies have found antibodies in human milk directed to specific SARS-CoV-2 antigens. Pace et al. found that milk produced by infected mothers is a

source of anti-SARS-CoV-2 IgA and IgG and neutralizes SARS-CoV-2 activity. Of the 70 swabs tested, eight had evidence of SARS-CoV-2 RNA. Of the milk samples tested, 76% contained SARS-CoV-2-specific IgA and 80% contained SARS-CoV-2-specific IgG. Concentrations of anti-SARS-CoV-2 IgA were consistently higher than those of IgG. 62% of collected samples from women with COVID-19 were found to neutralize SARS-CoV-2 infectivity in vitro, whereas none of the pre-pandemic samples were able to do so [18].

This is in accordance with data from milk samples studied by Fox et al. every 3–4th week from over 800 women who had recovered from COVID-19. 95% of milk samples contained anti SARS-CoV-2 sIgA. None of the milk contained detectable SARS-CoV-2 RNA [20]. One study demonstrated that pasteurization methods (such as those used to prepare donor milk) inactivate SARS-CoV-2 [21]. New data indicate that SARS-CoV-2 mRNA vaccinated pregnant women secrete antibodies into breast milk. Although adverse effects on the fetus require further study, vaccination of lactating women apparently seems safe [22].

Given these findings, direct breastfeeding is encouraged at this time by both the WHO and AAP. Recommendations are supported to continue breastfeeding during mild-to-moderate maternal COVID-19 illness as milk likely provides specific immunologic benefits to infants. If severe illness in a mother prevents her from continuing direct breastfeeding, mothers should be encouraged and supported to express milk to maintain supply.

Breastfeeding mothers should be helped to clean her chest with soap and water if she has been coughing on it before breastfeeding. She does not need to wash her breasts prior to every breastfeed. While mothers are recommended to wear medical masks, WHO underlines if the mother does not have a medical mask, she should still be encouraged to continue breastfeeding as the benefits of breastfeeding outweigh the potential risks of transmission of the virus when breastfeeding while applying other IPC measures.

Rooming in

Many recent studies have found no difference in transmission rates between infant who roomed in and those that did not. In New York, Dumitriu et al. found no transmission in 101 newborns of mothers positive for or with suspected SARS-CoV-2 infection, despite most newborns rooming-in and direct breastfeeding practices [23]. WHO and AAP now agree the mother and neonate in general should not be separated. Rooming-in is recommended including skin-to-skin contact. Mothers with suspected or confirmed SARS-CoV-2 infection may feel uncomfortable with the

potential risk and maternal autonomy in the medical decision whether she would like the neonate to be cared for in her room or a separate location should according to AAP be respected.

Measures to minimize risk of transmission

For infants who room-in with the mother, the AAP recommends measures to be taken to minimize the risk of transmission from a mother with suspected or confirmed COVID-19 to her neonate. Infants born to mothers with confirmed or suspected COVID-19 should be bathed after birth to remove virus potentially present on skin surfaces. According to AAP mothers should wear a mask and practice hand hygiene during all contact with their neonates. Masks should not be placed on neonates or children younger than 2 years of age. Maintaining a physical distance of ≥ 6 feet or 2 m between the mother and neonate may be used when feasible.

A healthy caregiver who is not at increased risk for severe illness, using appropriate infection prevention precautions (Table 1), should provide care for the neonate, if possible. If non-infected partners or other family members are present during the birth hospitalization, they should use masks and hand hygiene when providing hands-on care to the infant. When this care is provided in the same room as a mother with COVID-19, healthcare workers may use N95 respirators in place of standard procedural masks.

Clinical symptoms in the newborn

Maternal timing of infection and severity appear to affect NICU admission and prematurity as well. In the PRIORITY study, infants born to mothers who first tested positive 0–14 days prior to delivery were born earlier as compared to infants born to mothers who first tested positive more than 14 days prior to delivery (mean 37.5 vs. 39 week gestation, $p=0.0009$). Among infants born to mothers who first tested positive 0–14 days prior to delivery, 26.0% were admitted to the NICU compared to 12.2% born to mothers who first tested positive more than 14 days prior to delivery ($p=0.04$) [10]. In Dumitriu et al.'s study from New York, maternal severe/critical COVID-19 was associated with newborns born approximately 1 week earlier (median gestational age, 37.9 [IQR, 37.1–38.4] vs. 39.1 [IQR, 38.3–40.2] weeks; $p=0.02$) and at increased risk of requiring phototherapy (3 of 10 [30.0%] vs. 6 of 91 [7.0%]; $p=0.04$) compared with newborns of mothers with asymptomatic/mild COVID-19 [23].

If neonates become infected, the majority have either asymptomatic infections or mild disease not requiring respiratory support. Trevisanuto et al. reported 44 newborns from Italy with confirmed SARS-CoV-2 infection. Median age at diagnosis was five days. Twenty five percent of neonates were asymptomatic, and the remaining showed mild symptoms typical of acute respiratory infections and/or gastrointestinal symptoms. Median duration of hospitalization was 10 days [24].

Karabay et al. described the clinical characteristics of SARS-CoV-2 positive newborns. Respiratory difficulty (74%) and fever (63%) were most common. No term infant needed mechanical ventilation, by contrast to 50% of preterm. Gastrointestinal symptoms (diarrhea, feeding intolerance and abdominal distension) were present in 50%. Newborns neurologic symptoms were present in 53% in the form of irritability, hypertonia, lethargy, hyporeactivity, and hypotonia. Cough, vomiting and cyanosis were also described [25].

Norman et al. published a recent nationwide cohort of infants in Sweden, including 88,159 newborn infants regarding maternal SARS-CoV-2 infection in pregnancy. The mean gestational age of infants of SARS-CoV-2-positive mothers was 39.2 (SD, 2.2) weeks vs. 39.6 (SD, 1.8) weeks for comparator infants, and the proportions of preterm infants (gestational age <37 weeks) were 8.8% among infants of SARS-CoV-2-positive mothers and 5.5% among comparator infants. Mortality was significantly higher (0.30 vs. 0.12%) if mothers were SARS-CoV-2 positive compared to non-positive; (OR, 2.55; 95% CI, 0.99–6.57). Infants of SARS-CoV-2 positive mothers were also intubated more often, needed CPAP more, had more respiratory distress, more pulmonary hypertension and a higher incidence of several other morbidities [26].

It is important to note that respiratory distress in the newborn may be difficult to attribute to COVID as respiratory symptoms in newborns can be nonspecific and related to normal transitioning. The PRIORITY study did not see a difference in respiratory symptoms among neonates with and without laboratory confirmed SARS-CoV-2 [10].

Neonatal intensive care

Separation may be necessary for neonates at higher risk for severe illness (e.g., preterm infants, infants with underlying medical conditions, infants needing higher levels of care). Both WHO and AAP now recommend that isolating infants with suspected or confirmed SARS-CoV-2 infection in a Neonatal Intensive Care Unit (NICU) should be avoided unless the neonate's clinical condition or gestational age warrants NICU admission.

According to AAP infants requiring neonatal intensive care and respiratory support optimally 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 COVID-exposed infants must be cohorted, there should be at least 6 feet or 2 m between infants. In addition, 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. Mothers and partners who are COVID-19 persons under investigation (PUIs) should not enter the NICU until their status is resolved. If confirmed COVID-19, they should not visit NICU infants while able to transmit SARS-CoV-2. Because of the vulnerable health of NICU infants; and because of concerns around protecting personnel who support the critical infrastructure of NICUs, centers may choose to extend the period of time that should pass before parents with prior COVID-19 infection may safely enter the NICU. Extending that period to 14–20 days from onset of symptoms or first positive test (whichever comes first) is a reasonable option that will provide additional protection in the NICU environment. The open-bay structure of many NICUs may add to risk of viral transmission [4].

Testing of the newborn

For newborns 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 at approximately 24 and 48–72 h of age. This addresses risk if the infant has acquired the virus by vertical transmission. To address the risk of horizontal transmission testing on admission to the NICU, at 7 and 14 days after last maternal contact is recommended [4].

For newborns 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 14 days have passed since the last maternal-infant contact. Centers may determine testing based on their local resources. Testing well newborns will facilitate plans for care after hospital discharge and will determine the need for ongoing precautions and use of PPE for care of hospitalized infants. See Table 2 for a summary.

Table 2: Testing.

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- **How:** Obtain either a single swab of the nasopharynx; or a single swab of the throat followed by the nasopharynx; or two separate swabs from each of these sites, and submit for a single test. Some centers have transitioned to swabs of the anterior nares.
 - **When:** At approximately 24 h of age and again at approximately 48 h of age. Some infants could have had a negative test at 24 h only to have a positive test at a later time, particularly when rooming-in with a contagious mother. If it is planned that a healthy newborn will be discharged prior to 48 h of age, clinicians may choose to order a single test, optimally as close to discharge as possible.
 - **Follow-up of positive test:** While initial recommendations suggested repeating tests until two consecutive negative tests obtained, it is now well-known that viral particles can exist in both the respiratory tract and feces long after the patient is no longer infectious [27]. Healthy infants who test positive may be cleared with clinical criteria. Neonatal intensive care units should continue to individualize practices with regards to COVID positive infants requiring intensive care.
 - **Ongoing hospital care:** Regardless of whether infants exposed to SARS-CoV-2 test positive, health care providers caring for these infants should continue to use appropriate PPE until discharge, particularly as rooming in and having contact with mother have become standard of care.
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Suspected or confirmed SARS-CoV-2

There is general agreement that all neonates born to mothers with suspected or confirmed infection should be considered as having suspected SARS-CoV-2 infection when test results are not available. Mothers with suspected or confirmed SARS-CoV-2 infection and their neonates should be isolated from other healthy mothers and neonates and cared for according to recommended IPC practices for routine healthcare delivery. If a neonate does not remain in the mother's room, facilities should consider the institution's capacity and resources as well as the potential risk of SARS-CoV-2 transmission to other high-risk neonates when determining where the neonate should be isolated.

Discharge, transition to home, outpatient follow-up

Discharge of newborns should be based on each center's usual criteria. There is no specific benefit for infants born to mothers with COVID-19 that results from discharge earlier than usual center practice. If infant SARS-CoV-2 testing is positive, but the infant has no signs of COVID-19, plan for frequent outpatient follow-up (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 (as available) and hand hygiene in the home environment and by healthcare staff in the outpatient office practice (AAP) [4].

In most cases, the infant SARS-CoV-2 testing will be negative, and infants may be discharged to families where other caregivers may have been exposed to and may have acquired COVID infection. Every effort should be taken to provide infection-prevention education to all caregivers of the infant. While challenging in the home environment, mother should according to AAP use a mask and hand-hygiene when directly caring for the infant, until: 1) the mother has been afebrile for 24 h without use of antipyretics, 2) at least 10 days have passed since her symptoms first appeared (or, in the case of asymptomatic women identified only by obstetric screening tests, at least 10 days have passed since the positive test), 3) symptoms have improved. Other caregivers in the home should use masks and hand hygiene before and after contact with the infant until their status is resolved. If the infant cannot be tested, then caregivers should treat the infant as if virus-positive for the 14-day period of observation. Mother should still maintain precautions until she meets the criteria for non-infectivity as above [4].

There is a paucity of data on transitioning of SARS-CoV-2 exposed infants to home and outpatient follow-up. 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 PPE as inpatients practices do and discussion with the follow-up physician prior to the appointment will allow for appropriate planning.

In general, discharge prior to usual practice with the intent to reduce risk of COVID-19 infection provides no advantage to the newborn or family. Early discharge may in fact place additional burdens on families and on outpatient pediatric offices to provide recommended newborn care and screenings which can be more difficult to complete in the outpatient setting. In-person post-discharge visits are the preferred means to provide timely newborn screening and bilirubin testing, as well follow-up of feeding and weight assessments.

Discussion

After more than a year with the Covid-19 pandemic, more evidence based recommendations have been developed. Globally, 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 with the AAP joining the WHO in encouraging breastfeeding and rooming in.

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 and bonding outweigh potential negative effects of separation of mother and child in case of suspected or proven maternal infection. Further, SARS-CoV-2 seems not to be transmitted via breast milk. In fact, antibodies are detected in breast milk and likely provide protection to the newborn. Breast feeding reduces morbidity and mortality for both mothers and their infants and lactating women vaccinated with mRNA vaccines against SARS-CoV-2, secrete antibodies in the breast milk [22]. Rooming-in promotes family-centered care and can allow for parent education about newborn care and infection prevention and control practices. Rooming in and breast feeding therefore should be practiced in SARS-Cov-2 positive or suspected positive mothers. Discharge planning can be challenging for newborns of mothers newly diagnosed with SARS-CoV-2 who have not completed quarantine and communication with outpatient health care providers is essential for not only the safety of the newborn, but also for the safety of clinic staff. Most studies reporting on short term outcomes have been largely favorable.

While much has been learned about optimal maternity practices during the COVID-19 pandemic, less known is the psychosocial aspects and longer-term effects on neonates of infants born to mothers with SARS-CoV-2 infection and ongoing efforts to collect data should continue. Larger studies are needed on longitudinal outcomes and partnerships between hospitals, academic centers, and outpatient clinics should be formed to facilitate such research. Further, new and unknown mutations of the SARS-CoV-2 virus may have different effects than described in this article, on both the pregnant women and her newborn child.

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