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Review Article

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Coronavirus Disease (COVID-19) in Neonates: Current Perspectives

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Abstract

Coronavirus disease (COVID-19) is a new respiratory disease that is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). First described in December 2019, in Wuhan, China, the virus rapidly spread across continents leading to an enormous global public health crisis. To date, it has infected more than 35.6 million people worldwide, with a case fatality rate of 2.9 percent. Although massive research has been published on this subject, the majority involve adults, and yet, neonates have not been spared by the disease. Currently, there are more questions than answers, and available evidence is changing rapidly. Compared to adults, infected neonates are more likely to be asymptomatic or to develop non-specific multisystemic features; and to have favorable outcomes. At present, no specific therapy or vaccine has been approved for use in neonates with COVID-19, and the current treatment protocols are informed by expert consensus, and extrapolation of adult recommendations. In this review, we conjugate the current evidence regarding transmission, diagnosis, management, outcome, and prevention of COVID-19 in neonates.

Key words: SARS-CoV-2 In Neonates, Vertical Transmission, Clinical Characteristics, Prevention.

Introduction

In December 2019, the Coronavirus Disease (COVID-19), a viral pneumonia known to be caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged from Wuhan, the capital of Hubei Province in China [1]. Subsequently, a global public health emergency was declared by the World Health Organisation (WHO) on January 30, 2020 [2], after which several countries implemented lockdown restrictions. To date, COVID-19 remains a significant global health crisis. As of October 7, 2020, the WHO had reported more than 35.6 million confirmed COVID-19 infections, and more than 1 million confirmed deaths worldwide, corresponding to a case fatality rate of 2.9% (https://covid19.who.int). Due to an immature immune system, neonates are considered a vulnerable group. So far, only a limited number of COVID-19 cases have been reported among neonates, predominantly informed by case reports, case series, and retrospective case reviews with small population samples [3,4,5]. Of course, due to limited testing capacity across many countries, several cases of neonatal COVID-19 remain undocumented. Due to the scarcity and inconclusiveness of currently available literature, a lot remains unknown about COVID-19 in neonates. However, these incongruences may be addressed as the pandemic evolves, and more robust evidence becomes available.

The SARS-Cov-2 virus is an enveloped positive-sense single-stranded RNA (+ssRNA) β-coronavirus with more than half of its genomic sequence identical to Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). In 2002–2003 and 2012, SARS-CoV and MERS-CoV caused major epidemics in China and the Middle East respectively [6,7].

Case definitions [8]

Suspected COVID-19 mother

A symptomatic mother in the perinatal period with a history of travel to affected countries or affected states/places OR a history of close contact with individuals who travelled to affected countries or affected states/places during the last 14 days prior to symptom onset OR symptomatic antenatal mother when no other etiology explains her clinical presentation OR a health care working antenatal mother who came in contact with a confirmed COVID-19 case in last 14 days prior to the onset of symptoms.

Confirmed COVID-19 mother

Mother with positive reverse transcription-polymerase chain reaction (RT-PCR) for SARS-CoV-2, with or without clinical signs and symptoms.

Suspected COVID-19 neonate

A neonate born to a mother with a history of COVID-19 infection between 2 weeks before, and 4 weeks after birth, OR a newborn directly exposed to individuals infected with COVID-19, including family members, caregivers, visitors, and healthcare professionals (HCPs).

Confirmed COVID-19 neonate

Presence of any one of the following etiological criteria: (a) RT-PCR of respiratory tract or blood specimens positive for SARS-CoV-2 nucleic acid; (b) Virus gene sequencing of the respiratory tract or blood specimens is highly homologous to that of the known SARS-CoV-2 specimens.

Transmission

Epidemiological studies have shown that SARS-CoV-2 is mainly spread via respiratory droplets [9] that are generated when an infected individual coughs, sneezes, or talks. Horizontal transmission of SARS-CoV-2 may occur in the community or in the hospital setting either through aerosols, or fomites, and possibly, feco-orally [4,10-12]. Whether SARS-CoV-2 is vertically transmitted is a question that remains unanswered [13,14], and available evidence is overly controversial. Dong et al. [15] described a term neonate born by caesarean section to a symptomatic COVI-D-19 infected mother in Wuhan. The delivery was conducted in a negative pressure isolation room; the mother wore an N-95 respirator; and never interacted with the neonate. Two hours after birth, the neonate had elevated levels of interleukin (IL)-6, IL-10, and SARS-CoV-2 IgG and IgM antibodies, suggesting a possibility of intrauterine transmission. However, RT-PCR on vaginal fluid and nasopharyngeal swabs of the mother and neonate respectively were found to be negative. In a recent study of 51 neonates, Liu et al. [16] concluded that maternal third-trimester COVID-19 infection does not significantly affect the cellular and humoral immunologic status of the foetus. This was further demonstrated by Alzamora et al. [3] who reported a term neonate with a positive nasopharyngeal swab RT-PCR for SARS-CoV-2 and negative IgM and IgG titres at a postnatal age of 16 hours. A confirmatory RT-PCR at 48 hours was positive for SARS-CoV-2. In this case, the mother received mechanical ventilation due to respiratory insufficiency prior to delivery, the neonate was a preterm born by caesarean section, and strict infection control procedures were adhered to during and after delivery. It is notable that IgM does not cross the placenta. However, false positivity is relatively common, and may not be excluded [17]. As such, it is not surprising that Yan et al. [18], Liu et al [19], and more recently, Salvatore et al. [20] found no evidence of vertical transmission of SARS-CoV-2 infection. In contrast, the study by Zamaniyan et al. [21] of a critically ill 22-year-old mother with confirmed COVID-19 at 32 weeks of gestation highlighted a possibility for intrauterine transmission of SARS-CoV-2. An emergency caesarean section was performed under general anaesthesia and strict infection control procedures. The neonate weighed 2.35 kg; had a normal Apgar score; never had contact with the mother; and was exclusively fed on formula milk. RT-PCR of amniotic fluid was positive for SARS-CoV-2 nucleic acid, whereas the neonate's umbilical cord blood, nasal and throat swabs taken immediately after birth were negative. A repeat RT-PCR performed 24 hours after birth was positive for SARS-CoV-2, as were the two subsequent tests. The lack of sufficient evidence to support the intrauterine transmission potential of SARS-CoV-2 warrants corroboration with further studies using more reliable markers [22]. Notably, current literature has also not established whether viable viruses are shed via human breast milk, and thus, more recent guidelines recommend the continuation of breastfeeding [23,24].

Making the Diagnosis of SARS-CoV-2 in neonates

Clinical characteristics

Neonates born to mothers with confirmed COVID-19 should be tested for SARS-CoV-2, and closely followed up for evaluation of clinical signs and symptoms [20], which may manifest as early as 30 hours after birth [1]. Almost 2% of newborns of women with COVID-19 test positive for the virus within the first 24 to 96 hours of birth [23], the majority being asymptomatic [4]. When symptomatic, they may exhibit a wide-spectrum of predominantly mild non-specific respiratory (cough or difficulty in breathing, nasal congestion, sneezing), neurological (fever), and gastrointestinal (poor oral intake, vomiting, diarrhoea, abdominal distension, gastric haemorrhage) manifestations. Clinical signs may include lethargy, hypotension, tachypnea, apnoea, grunting, tachycardia, and cyanosis, intercostal retractions, temperature instability (fever, normothermia, or hypothermia), feeding intolerance, and mottling of the skin [1,4,8,25,26]. It is known that SARS-CoV-2 attaches to angiotensin converting enzyme-2 (ACE2) receptors to enter cells. Due to the widespread presence of ACE2 receptor on neurons, it is thought that neonates with COVID-19 may develop a pertussis-like respiratory center suppression [6]. Because of the nonspecific clinical presentation of COVID-19 in neonates, it is critical for clinicians to keep in mind the common causes of respiratory distress (Table 1) in this population [27].

Table 1: Common causes of respiratory distress in the newborn

Respiratory	Respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), meconium aspiration syndrome (MAS), neonatal pneumonia, pneumothorax, persistent pulmonary hypertension (PPHN)
Cardiovascular	Congenital heart disease
Neurological	Hypoxic ischemic encephalopathy, intraventricular haemorrhage
Others	Neonatal sepsis, hypoglycaemia, metabolic acidosis

Laboratory evaluation

Confirmatory diagnosis of SARS-CoV-2 infection is accomplished using RT-PCR of a nasopharyngeal or oropharyngeal swab [28]. RT-PCR may be performed on additional samples such as endotracheal aspirate, gastric aspirate, stool, plasma, urine, and saliva [1,5,25,26]. For a neonate whose mother is suspected or confirmed to have COVID-19, the first RT-PCR for SARS-CoV-2 nucleic acid should be done within 24 h of birth, and repeat testing at 48 h of age if the initial test is negative [23,29]. Nonetheless, the optimal

timing of testing after delivery has not yet been determined. Currently, serological tests are not recommended for diagnosis [29].

Diagnosed asymptomatic neonates should have a complete blood count (CBC) and C-reactive protein (CRP) done; whereas symptomatic neonates should also have arterial blood gas analysis, acid-base studies, serum electrolytes, liver and renal function tests, and cardiac biomarkers performed; and other aetiologies of infection systematically excluded. A CBC may reveal non-specific findings such as a normal leukocyte count or leucocytosis, lymphopenia, and mild thrombocytopenia. Elevated levels of CRP (>10mg/L suggests bacterial superinfection), alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, creatine kinase, and lactate dehydrogenase may be observed [8].

Radiological evaluation

Chest X-ray and computerized tomography (CT) may show no abnormalities, or reveal features consistent with pneumonia such as bilateral linear opacities, ground glass opacities, increased lung markings, and consolidation [1,25,26]. In order to minimize radiation exposure, imaging should be performed when clinically necessary. Despite the advantage of reducing the patient's movement across hospital departments, few studies have been published regarding point-of-care lung ultrasound (LUS) in neonates with confirmed COVID-19. Nevertheless, bedside LUS abnormalities such as B-lines and consolidation [30,31] have been described.

Management

Neonates with COVID-19 should be managed by a multi-disciplinary team comprising of obstetricians, neonatologists, intensive care specialists, radiologists, specialists in infection prevention and control (IPC), and specialist nurses, who must be oriented in SARS-CoV-2 management and IPC strategies. Both clinicians and families should routinely receive psychological support by social workers and psychologists [6,8]. At this point, it is important to understand that as the pandemic is evolving, scientific evidence is changing rapidly. As such, clinicians need to be updated with current protocols [6].

Of note, no randomized controlled trial has been published on neonates with COVID-19, and thus, no single antiviral agent has been approved for use in infected neonates. Principally, treatment is supportive [1,8], involving hemodynamic stabilization, fluid and electrolyte management, respiratory support, parenteral or enteral nutrition, close monitoring of vitals, and other daily care [32]. Several recommended therapies, including respiratory management are not evidence-based; being derived from expert consensus and extrapolation of results from studies in adults [33,34].

Antibiotic therapy is reserved for patients with probable or confirmed bacterial infection; and should not be prescribed for empirical use. Preliminary Chinese expert consensus guidelines proposed that high-dose pulmonary surfactant, inhaled nitric oxide, and high-frequency oscillatory ventilation may be effective for neonates with acute respiratory distress syndrome manifested by complete opacification of lungs [8]. Interestingly, the majority of neonates do not require invasive ventilation [1,25]. Intravenous glucocorticoids or immunoglobulin may be tried in some difficult cases. In addition, continuous renal replacement and extracorporeal membrane oxygenation may be required in critically ill neonates [8]. However, the efficacy of these treatment modalities has not yet been evaluated.

Neonates who have no fever for at least 72 hours; improved respiratory symptoms; resolution of previously abnormal chest radiographic findings; and two SARS-CoV-2 negative nasopharyngeal and nasal swabs taken at least 24 hours apart may be discharged [23,35]. Follow up can be done using phone calls, telemedicine, home or out-patient clinic visits.

Outcomes

Based on current evidence, the clinical course and prognosis of neonates with COVID-19 is good. Compared to adults, neonates are less likely to develop severe complications [1,4,25]. The duration of hospitalization ranges from 6 to 25 days [1,5]. The reason for these favourable outcomes is unclear. Previous studies have also not investigated the long-term effects of COVID-19 in neonates, which warrants close monitoring.

Infection prevention and control

In as much as the global number of confirmed newborns with COVID-19 is still small, their vulnerability to this infection has not changed. The crucial role of IPC mechanisms cannot be over-rated [20,36], although these measures may be augmented by effective vaccines in the future [37]. Therefore, to safeguard the mother-newborn dyad, their families, and HCPs from SARS-CoV-2, health facilities should develop, and/or adopt a strict multifaceted IPC policy and suit the realities in their setting [6,20,23,24,36,38-43]. That said, marked variability has been observed among countries regarding COVID-19 prevention guidelines [33]. Because recommendations are rapidly changing, HCPs need to be regularly updated regarding COVID-19 IPC measures. This can be accomplished by means of a pre-defined electronic or physical space where the latest information is presented [6]. Clinicians must remember to engage parents at all levels of decision making; and the hospital IPC team should be notified of all suspected or confirmed pregnant women with COVID-19 [38]. The following IPC strategies are based on previous articles.

Prenatal strategies

Given that HCPs lie at the epicentre of the COVID-19 pandemic, health facilities should conduct simulation training on management of mothers with suspected or confirmed COVID-19 and their newborns, intended to identify gaps and consolidate learning opportunities. In the same regard, HCPs should be trained on the correct use (sequence of donning and doffing) and disposal of personal protective equipment (PPE); and safety monitors to detect and immediately rectify any PPE breaches.

Mothers with suspected or confirmed COVID-19 should be managed in an airborne infection isolation room until delivery. Dedicate a delivery room and operating theatre; preferably with negative pressure. Keep these rooms free from unnecessary materials which may occur as fomites. A clear method of communication between teams in and outside the delivery room should be established. Similarly, set up a multidisciplinary team with well-defined responsibilities, comprising of midwives, obstetricians, anesthesiologists, and neonatologists, with a minimum number of health

caregivers (at least 2) for neonatal resuscitation; and have back-up personnel available for emergencies and other responsibilities. Prepare separate packages with PPE, including caps, N-95 masks or higher-level respirator, goggles or face shield, disposable long sleeve water-proof gowns, and gloves for each team member in the delivery room. Check for the availability and functionality of resuscitation equipment and medicines based on the National Resuscitation Program (NRP), and European Resuscitation Council (ERC) guidelines. Designate a room equipped with an infant radiant warmer next to the delivery room. If not available, put a neonatal resuscitation bed >2 metres (6 feet) from the mother's bed. Health facilities with less infrastructure and logistics which may not be designated for care of these patients should design appropriate referral pathways.

Perinatal strategies

Delivery should be conducted in a designated hospital, where an area should be dedicated for screening procedures. If not possible, organize a separate path for suspected or diagnosed COVID-19 cases. HCPs should wear PPE before contact with a laboring mother, who should wear a surgical mask. Deliver in an airborne isolation room or designated operating theatre. The mode of delivery depends on the progression of labor and routine obstetric indications. If the mother is in incipient respiratory insufficiency, general anesthesia for Cesarean section should be considered. Unless contraindicated, delay cord clamping below the introitus or abdominal incision. Converse to previous recommendations, current guidelines recommend skin-to-skin contact as soon as possible after birth, provided that recommended IPC measures are implemented [43]. Follow neonatal resuscitation and essential newborn care steps as usually indicated in the NRP or ERC guidelines. If available, use a self-inflating bag and mask (avoid T piece resuscitation) with an attached viral filter, disposable Ambu-bag and laryngoscope blade.

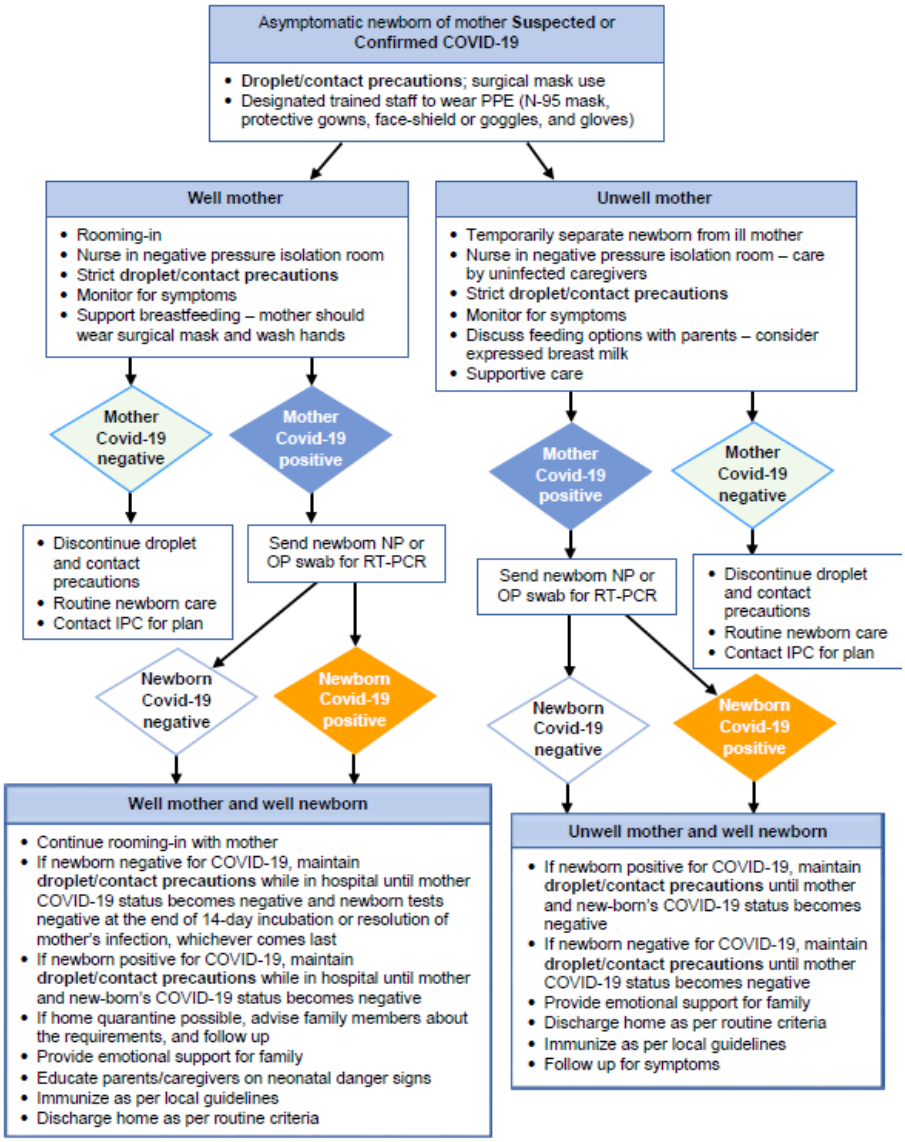

Figure 1: Flow chart for postnatal management of asymptomatic newborns of suspected or confirmed mother with COVID-19

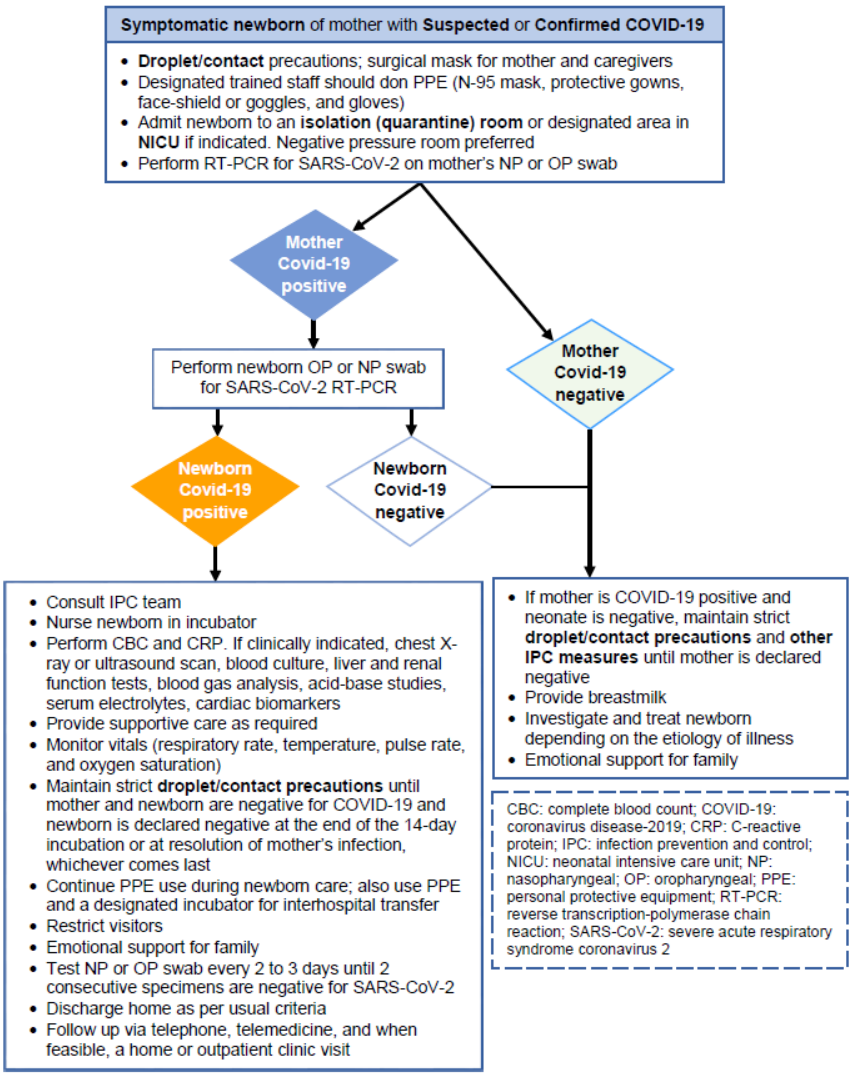

Figure 2: Flow chart for postnatal management of symptomatic newborns of mothers with suspected or confirmed COVID-19

After delivery of a mother with suspected or confirmed COVID-19, remove all PPE; place in plastic bags; and have them disposed. Promptly clean and disinfect the delivery room/operating theatre and equipment. To remove virus that may potentially be present on skin surface, bathe and dry the neonate as soon as possible after birth. Adopt standard precautionary measures for aerosol-generating procedures such as endotracheal intubation, bronchoscopy, and non-invasive ventilation. Collect and send the mother's specimens for SARS-CoV-2 testing (placenta, amniotic fluid), and test the baby for SARS-CoV-2 (nasal and oropharyngeal swabs) 24 h after delivery.

Considering the well-established benefits of breastmilk, current guidelines encourage breastfeeding unless another contraindication is present, although mothers should adhere to contact and droplet precautions such as breast cleansing, meticulous hand hygiene, and use of a tripple-layered surgical or cloth face mask. As evidenced in a cohort study of 120 newborns of mothers with COVID-19 in New York [20], none was infected at 24 h of life. Repeat RT-PCR of 79 neonates was negative for SARS-CoV-2 on day 5-7, and yet, all mothers were allowed to breastfeed. Furthermore, if the mother is sick and chooses to express breast milk, encourage her to use a dedicated manual or electric breast pump; and to wash hands and equipment before and after each feed. The neonate can be fed on fresh expressed breast milk, without the need for pasteurisation. The mother/caregivers should wash hands before and after changing diapers. If possible, use gloves to dispose stool off in an appropriate place.

When inter-hospital transfer of a neonate is indicated, a designated incubator should be used, and PPE (for HCP, driver), disinfectant solution, and hand sanitiser should be made available. In the absence of a transport incubator, an open care system with a cling wrap cover can be utilized. The ambulance spaces must be strictly closed and isolated. As such, the car and cab should be isolated. Disinfect the ambulance and transport incubator before and after

neonatal transfer.

Designate a minimum number of HCP attending to a mother and baby with suspected or confirmed COVID-19. They should consistently wear PPE and be tested for SARS-CoV-2 (nasal and oropharyngeal swabs) every 2–3 weeks. The selected HCPs should not work in the regular neonatal intensive care unit (NICU) or special care baby unit (SCBU). In addition, diagnostic and treatment equipment for suspected or confirmed newborns with COVID-19, such as a stethoscope and thermometer must be for individual use only.

Manage a mother with suspected or confirmed COVID-19 in an isolated room with clear signage outside the room indicating infection precautions needed before entering the room. Provide care for the baby in an incubator, possibly >2 m (6 feet) from the mother or in a different room, although priority should be given to rooming-in, especially if the mother is asymptomatic or paucisymptomatic. If intensive care is indicated, nurse the infant in an incubator, instead of a radiant warmer, in an isolated room ('quarantine zone') next to the NICU. The quarantine room should be a negative pressure room, equipped with an air cycle system that is discrete from the rest of the facility. Incase an infant incubator is used, it is important that the mother, caregivers, and HCPs are educated on its proper use, including latching of doors, in order to prevent the newborn falling out.

Restrict visits to the patient's parents or legal guardians; as long as they are not suspected or confirmed for COVID-19 or have home contact with a person with the disease. Furthermore, educate mothers and their families regarding the importance of rigorous hand hygiene (following WHO five moments of hand hygiene), appropriate use of a face mask, covering the mouth when coughing or sneezing, and social distancing while caring for newborns.

When dealing with a newborn with suspected COVID-19 infection, carryout investigations based on exposure to infected persons and clinical history, regardless of their symptoms. Closely monitor the neonate born to a COVID-19 infected mother for clinical and laboratory manifestations of the disease. Those found to be SARS-CoV-2 positive should be isolated and clinically monitored for 14 days. However, admission of these neonates to the NICU is not necessarily required. When a newborn is admitted, mothers with COVID-19 should not visit the NICU until they are afebrile without the use of antipyretics for at least 72 h, with improvement of respiratory symptoms, and two negative RT-PCR tests for SARS-CoV-2.

Maintain a minimum distance of one meter between incubators and cribs, and suspend discussions at the patient's bedside. Adopt a strict disinfection protocol in settings (such as incubators, cots, infusion pumps, weighing scales, monitors, phototherapy units, ventilators, shelves, tables, seats, and door handles) with newborns suspected or confirmed to have COVID-19; preferably using hydrogen peroxide atomization (dilute 100 ml of H2O2 10% v/v solution with 900 ml of distilled water) or a preparation spray containing chlorine. Use a double-layer infectious waste bag to collect hospital waste generated during the care of newborns with suspected or confirmed COVID-19; treat it with a chlorine-containing preparation for at least 10 minutes; and then disposed in the same way as infectious medical waste.

Well neonates should be discharged based on routine hospital guidelines, including the ability to feed well and maintain adequate hydration, ability to maintain normothermia, and normal physical examination. Neonates treated for COVID-19 should be discharged after at least two consecutive SARS-CoV-2 nucleic acid results performed ≥24 hour apart are negative [1,23]. Pre-discharge, mothers and close family members should be educated about neonatal danger signs and advised to return to the health facility if the neonate develops any of these signs. They should also be advised to continue face mask use and hand hygiene whilst directly caring for the newborn, until all the following criteria are met;

a. Mother is afebrile for ≥24 h without using antipyretics;
b. ≥10 days since onset of symptoms (if mother was asymptomatic, consider ≥10 days since positive RT-PCR);
c. Symptoms have improved.

At discharge, an information brochure also containing contact numbers for the health facility should be provided. In addition, well neonates should be immunized as per country-specific guidelines. While at home, the mother, baby, and family members should be strictly followed-up using telephone calls and/or telemedicine, to assess for signs of infection, review home isolation precautions, and discuss routine concerns such as feeding and jaundice. When possible, using video conferencing, neonates should be weighed on a digital home scale, providing opportunity for the pediatrician to visualize the neonate's tone, color, and respiratory status. Depending on the human resource capacity and setting, a home visit by a designated HCP may be considered, and a pharyngeal swab for SARS-CoV-2 performed 14 days after discharge.

Conclusions

The COVID-19 pandemic has become the most prodigious public health challenge of the twenty-first century. In the context of limited data on SARS-CoV-2, coupled with ongoing research, our understanding of COVID-19 in neonates is rapidly evolving. There is limited evidence regarding the intrauterine transmission potential of SARS-CoV-2. In the meantime, HCPs should have a high level of vigilance when evaluating neonates exposed to adults with suspected or confirmed COVID-19 infection. HCPs should also keep track on new developments regarding COVID-19 in this high-risk group, because recommendations are continually being modified as more scientific evidence is generated.

Abbreviations

CBC: Complete Blood Count; COVID-19: Coronavirus Infectious Disease-2019; CRP: C-Reactive Protein HCP: Health Care Professional; IPC: Infection Prevention and Control; NICU: Neonatal Intensive Care Unit; PPE: Personal Protective Equipment; RT-PCR: Reverse Transcription-Polymerase Chain Reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.

Authors' contributions

WIE conducted the literature search, drafted the first and subsequent versions of the manuscript, and all authors substantially contributed to manuscript writing and editing. All authors read and

approved the final manuscript.

Competing interests

The authors have no conflict of interest to declare.

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