Lessons Learned so Far from the Pandemic: A Review on Pregnants and Neonates with COVID-19

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ABSTRACT

There are concerns regarding the risk and the course of COVID-19 in pregnancy and in the neonates. In this review, we aimed to present the current understanding of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy and neonatal periods considering diagnosis, treatment, prognosis, and prevention. Few studies on pregnant women with COVID-19 have been conducted between December 2019 and April 2020. The majority of patients applied in the third trimester and presented with fever and cough. Ground-glass opacities and consolidation on computed tomography were reported to be common. COVID-19 was proposed to have a milder course than SARS and the Middle East respiratory syndrome coronavirus in pregnant women. Hydroxychloroquine and antiproteases (lopinavir/ritonavir) were reported to be safe; however, therapeutic efficacy and safety of remdesivir still lack evidence. As ribavirin and favipiravir have teratogenic effects, there are some debates on the use of ribavirin in severe cases. There is still no clear evidence of vertical transmission of SARS-CoV-2 during delivery. Occupational safety issues of pregnant healthcare workers on the frontline should be considered as their risk to develop severe pneumonia is higher because of altered maternal immune response. Knowledge about neonatal outcomes of COVID-19 was based on studies of the last trimester of pregnancy. There is much to be learnt about COVID-19 in pregnant women and in the neonates, especially concerning prognosis- and treatment-related issues.

Keywords: Coronavirus disease 2019, pregnancy, neonate, vertical transmission

Introduction

Coronavirus disease 2019 (COVID-19) is a new respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was reported first in Wuhan, China and promptly spread to other countries across the world. Considering the large and rapidly rising number of cases with COVID-19 and the resultant deaths, the outbreak has become a major health problem in a short period of time [1]. Despite substantial data regarding the high transmission rate of the disease with a broad spectrum of severities, knowledge with respect to two special patient groups, pregnant women and neonates, is still limited.

Previous studies have shown that COVID-19 pneumonia is more prevalent in men, and that fewer cases in children are reported [2, 3]. However, women also experience viral infections severely during pregnancy. Pregnancy itself alters the body's immune system, and immunosuppression makes pregnant women susceptible to infectious diseases [4]. Thus, viral pneumonia, in particular, is one of the important causes of deaths worldwide in pregnancy [5]. Consequently, there are many new questions on how COVID-19 might affect the morbidity and mortality of pregnant women and neonates.

Pregnancy and COVID-19

There have been few studies on pregnancy during COVID-19 pandemic. Between December 8, 2019 and March 20, 2020, 118 pregnant women with 8% having severe disease were reported among COVID-19 cases in Wuhan city in China. The pregnant patients represented 0.24% of all reported patients with COVID-19 [6]. In a study of the Centers for Disease Control and Prevention (CDC) COVID-19 response team, they reported 74,439 cases with COVID-19 between February 12, 2020 and March 28, 2020 in the United States. Among 7,162 patients

with complete information, 143 (2%) were pregnant and four of them admitted to the intensive care unit (ICU) [7]. Previous data on other coronavirus infections suggest that clinical findings during pregnancy can range from no symptoms to severe disease and death [8]. The majority of pregnant patients were found to be in the third trimester. The most common symptoms in pregnant patients with available data were fever and cough. Chest pain, fatigue, dyspnea, sore throat, diarrhea, and headache were less common symptoms [6, 8-10].

Diagnosis of COVID-19 in pregnant women

The laboratory findings in pregnant women with COVID-19 are very similar to other COVID-19 patients. The most common laboratory finding is lymphocytopenia. Less frequently, liver enzyme abnormality has been reported, especially increased alanine aminotransferase or/and aspartate aminotransferase. Elevated C-reactive protein (CRP), procalcitonin, erythrocyte sedimentation rate, and interleukin-6 and D-dimer levels can also be seen [9-12]. In a study, Liu et al. (10) reported that the leukocytosis and elevated neutrophil ratio were more common in pregnants compared with the remaining COVID-19 patients.

Chest X-ray is usually normal and is only useful in severe pneumonia. Computed tomography (CT) scan of chest without contrast should be performed to confirm diagnosis in suspected cases as the risk of radiation exposure to the fetus is very low. The most common CT finding is ground-glass opacity (GGO) with progression to consolidation. The lesions are generally bilateral, peripheral, and predominantly located in the lower lobes [9, 12]. Liu et al. [10] reported that mixed GGO with consolidation and complete consolidation was significantly more frequent in pregnant women compared with the nonpregnant adults. GGO and GGO with reticulation were more frequent in the nonpregnant adults. Pleural effusion is rare in COVID-19 pneumonia. Yang et al. [13] reported that pleural effusion was more common in pregnant women than nonpregnant patients.

SARS-CoV-2 RNA is detected by reverse-transcription polymerase chain reaction (RT-PCR). It is considered as the reference standard diagnostic test. Upper respiratory tract (nasopharyngeal and oropharyngeal swabs) specimens are used for RT-PCR. In addition, lower respiratory tract (sputum, endotracheal aspirate, or bronchoalveolar lavage), urine, and stool can be used as specimens. If the first nasopharyngeal test is negative but the suspicion for COVID-19 remains, the test should be repeated. COVID-19 can be excluded if RT-PCRs of swabs are negative twice in a row (sampling interval ≥24 h). Serology should be used as a diagnostic procedure only if RT-PCR is not available [12, 14]. COVID-19 is an atypical disease that is difficult to diagnose at early phases. False-negative tests on initial testing appear to be common. CT has been reported to be superior in early diagnosis compared with RT-PCR [15].

Treatment of pregnant women with COVID-19

Numerous data support that COVID-19 has a better course in pregnant women compared with SARS and Middle East respiratory syndrome coronavirus (MERS-CoV) [16, 17]. In mild or uncomplicated COVID-19 infection, follow up of pregnant women without treatment should be considered primarily. There is no definitive treatment regimen for pregnant women that has been proven useful and safe. Some of the investigational drugs are recommended for treatment. It is important to carefully weigh the benefits of interventions for the mother and fetus with potential risks if necessary.

Chloroquine and hydroxychloroquine have been found effective in SARS-Cov-2 in *in vitro* studies. Although hydroxychloroquine crosses the placenta, there are studies reporting that it can be safely used in pregnant women in all trimesters [18-20]. However, maternal side effects such as QT prolongation and ventricular tachycardia can occur.

Particularly, in China and Turkey, antiprotease drugs, lopinavir/ritonavir (200 mg/50 mg per capsule), are used in the antiviral treatment. It is known to be safe in pregnant women. Oral use is recommended for 10–14 days, two capsules twice a day [14, 21]. It crosses the placenta and may increase the risk for preterm delivery. It is recommended to be taken together with nebulized α-interferon inhalation (5 million IU in 2 mL of sterile water for injection) in China [14]. Remdesivir is a novel nucleotide analog that is known to inhibit SARS-CoV-2 virus *in vitro* [22]. Although there is not enough information about its safety and efficacy, it has been used in pregnant patients with severe COVID-19. Clinical studies searching for alternative treatment solutions are ongoing [12, 14]. Although investigational drugs ribavirin and favipiravir are known as teratogenic, some studies have suggested the use ribavirin in therapy [12, 16, 21].

Lung damage due to COVID-19 increases the risk for secondary bacterial pneumonia. Antibiotics are recommended for those with findings of suspicion of bacterial pneumonia. Intravenous ceftriaxone can be used in pregnant women until specific culture results are evident [11, 12, 14].

The use of steroids is not highly recommended as it has been reported to increase the risk of mortality in influenza and delayed virus clearance in MERS-CoV. Short-term (three to five days) methylprednisolone 1–2 mg/kg is recommended to protect from acute respiratory distress syndrome only in patients with severe pneumonia. The same treatment regimen is recommended for pregnant women with COVID 19 [14, 23, 24]. If preterm labor is expected, antenatal betamethasone is also recommended for promoting fetal lung maturity in pregnant women with suspected or confirmed COVID-19 [25]. Sufficient information about the use of tocilizumab and convalescent plasma in treating pregnant women with COVID-19 is not available.

Both pregnancy and COVID-19 are associated with increased risk for thrombosis [26]. Suspected and confirmed COVID-19 pregnant women should receive prophylactic low-molecular-weight heparin (LMWH) before and after delivery. If the delivery is very close, unfractionated heparin should be preferred instead of LMWH, since it can be readily reversed. It is recommended to continue prophylactic LMWH for at least 10 days after discharge from the hospital in confirmed COVID-19 pregnant women [14, 27].

Support therapies in the service and ICUs are similar in pregnant and nonpregnant patients. It is recommended to regulate the oxygen supplement in pregnant women to ensure that peripheral saturation is ≥95%. In order to maintain oxygen diffusion from the placenta to the fetus, the maternal partial pressure of oxygen in the blood gas should be above 70 mmHg [21, 28].

Pregnancy complications

In some studies, premature rupture of membranes, preterm delivery, and coagulopathy accompanied by liver dysfunction and death of the mother have been reported in pregnant women with COVID-19 [9, 11, 29]. In a review, 39% preterm delivery (<37 weeks) and 96% cesarean delivery were reported in 51 pregnant women [30]. In addition, Elshafeey et al. [31], reported 15% preterm delivery (<37 weeks) and 70% cesarean delivery in 252 pregnant women in a review. Studies have shown that the frequency of spontaneous abortion does not increase [31, 32]. There are studies reporting that pregnancy or delivery does not cause progression in disease symptoms and CT findings [5, 9].

There are no data on the relationship between obstetric diseases, such as preeclampsia, gestational diabetes, and COVID-19. Given the fact that pandemic creates anxiety and stress, pregnant women can experience side effects of anxiety and stress, such as preeclampsia, depression, preterm delivery, increased nausea, and vomiting. In another aspect, pregnant women may request early termination and elective cesarean surgery in order to prevent disease transmission from healthcare settings to themselves or their families during visits [33].

Delivery and postpartum care

Timing of delivery, delivery process, and prenatal and postnatal follow-ups for pregnant with suspected or confirmed COVID-19 should be managed by a multidisciplinary team. In severe and critical cases, if the safety of the mother and her baby is at risk, pregnancy can be terminated early, even if the baby is premature. There is no evidence that one mode of delivery is superior to another in terms of risks associated with COVID-19. Therefore, unless the clinical severity and respiratory status of the pregnant require urgent intervention, the mode of delivery should be decided without considering COVID-19. In appropriate patients, vaginal delivery may be considered [14, 27]. No evidence of vertical transmission of COVID-19 from the placenta or during delivery has been demonstrated [34]. COVID-19 tests have resulted negative in babies of COVID-19 mothers who had cesarean or vaginal delivery in different studies. It has been shown that the mode of delivery is not effective in transmission [5, 11, 35]. Liu et al. [5] found that pregnancy and delivery did not exacerbate symptoms and CT findings of COVID-19 pneumonia. Yang et al. [13] also showed that there was no difference before and after delivery in terms of CRP, white blood cell count, neutrophil and lymphocyte count, and proportion in pregnant women with COVID-19.

Before delivery, all pregnant patients should be taken to separate isolated rooms. Contact and air isolation measures should be followed during delivery and antenatal and postpartum periods. Healthcare workers (HCWs) must also wear personal protective equipment (PPE). PPE should always be a priority, even in emergent cesareans or interventions. Relatives of the pregnant should be informed about possible delays of cesarean section because of the period for preparations and to equip healthcare staff with adequate PPE. After delivery, mother and baby should be taken to separate isolated rooms and should be closely monitored. Isolation should be continued at home after discharge [13, 14, 27].

Table 1. Information highlighted in pregnant women with COVID-19

1.	Generally, mild or uncomplicated COVID-19 infection occurs in pregnant women. COVID-19 in pregnant women has a better course than SARS and MERS-CoV.
2.	The leukocytosis and elevated neutrophil ratio were reported more common in pregnant women than nonpregnant patients.
3.	CT has also been reported to be superior in early diagnosis compared with RT-PCR in pregnant or nonpregnant patients. In CT scans, mixed GGO with consolidation and complete consolidation was reported significantly more frequent in pregnant women. The frequency of pleural effusion is also higher than that in nonpregnant patients.
4.	Different antiviral treatments have been used in pregnant women, but there is no definitive treatment regimen with proven efficacy.
5.	If preterm delivery is expected, antenatal betamethasone is recommended for promoting fetal lung maturity.
6.	Owing to the increased thrombotic risk, thromboprophylaxis is strongly recommended before and after delivery.
7.	Delivery has not been shown to cause COVID-19 progression and worsening clinical and laboratory findings.
8.	It was observed that the mode of delivery was not effective in the transmission of COVID-19.
9.	Unless clinical necessity or urgent interventions are required, the mode of delivery should be decided without considering COVID-19.
10.	All isolation and protective measures must be carefully followed to prevent transmission of COVID-19 before, during, and after delivery.
11.	Antepartum and postpartum anxiety and depression risk is high in pregnant women, and they should be followed closely for psychological support.
12.	The top priority is to prevent COVID-19 in healthy pregnant women. Therefore, all necessary protective measures and hygiene rules must be observed.
13.	Pregnant healthcare workers should be employed outside the COVID-19 wards or work from home.

COVID-19: Coronavirus disease 2019; SARS: Severe acute respiratory syndrome coronavirus 2; MERS-CoV: Middle East respiratory syndrome coronavirus; CT: computed tomography; RT-PCR: reverse-transcription polymerase chain reaction; GGO: ground glass opacity

The probability of anxiety and depression increases as mothers' support for their relatives will decrease, and their delivery plans will change owing to the pandemic. Mothers may also be worried about their babies being infected, and postpartum vaccination and follow up may be impaired. If necessary, mothers can be informed about their concerns, and psychological support should be provided by telephone or by other non-face-to-face methods [33].

Prevention of COVID-19 in pregnant women

Although significant process has been achieved in the development of COVID-19 vaccine, an effective vaccine has not been introduced yet. Antenatal care is important. Therefore, regular visits should be done as advised by the obstetrician. Unnecessary traveling, use of public transportation and contact with sick people should be avoided in pregnant women. It is important that they follow personal and social hygiene rules. Pregnant women with symptoms and suspicious history of travel or contact should be quickly isolated in healthcare units and be tested [8, 14, 27].

Pregnant healthcare workers

Pregnancy leads to altered maternal immunity, and pregnant HCWs on the frontline have high risk to develop COVID-19 given the fact that the risk is associated with duration and intensity of exposure as well as immune condition of the host. Therefore, pregnant HCWs should be assigned outside of the COVID-19 wards in order to decrease the risk of transmission. In addition, those with comorbid conditions such as heart disease should be consulted by their obstetricians and considered to work from home [36].

Highlights of COVID-19 infection in pregnant women are summarized in Table 1.

Intrauterine transmission of COVID-19

COVID-19 infection may have a risk of vertical transmission, like previously seen in SARS, because of the widely expression of angiotensin converting enzyme-2 receptor in the placenta. This possibility can be explained with the similar receptor-binding domain structures shared by SARS-CoV-1 and SARS-CoV-2. Consequently, the risk of vertical transmission for COVID-19 might be as low as that was reported for SARS-CoV-1 infection [37].

Recently, higher risk of preterm birth within pregnant women was reported from China. There was one case of intrauterine fetal death and one case of neonatal death with respiratory distress and disseminated intravascular coagulation (DIC). In contrast, the samples for COVID-19 virus of the baby born from an infected mother were negative [5, 11, 12, 35, 37]. Most recently, two neonates from COVID-19 infected mothers had positive results for SARS-CoV-2 following delivery. One of these

cases has been confirmed at 17 days after birth, and this baby had a close contact history with two other confirmed cases (her mother and caregiver); the other case has been confirmed at 36 h after birth, and the possibility of close contact history could not be excluded. There are few reports demonstrating the absence of viral isolates in the amniotic fluid, cord blood, breast milk, and neonatal throat swabs in a subset of patients born from infected mothers [38-42]. However, three neonates demonstrated elevated SARS-CoV-2 immunoglobulin M (Ig M) antibodies increasing the concern of vertical transmission, although repeated nasopharyngeal samples from the infants were negative [9, 14, 43].

Despite these concerns, there is still no evidence of vertical transmission of SARS-CoV-2 during delivery. Larger data are needed to exclude transplacental vertical transmission of COVID-19.

Intrauterine complications

No information is available either about the effect of COVID-19 on fetal malformations, fetal growth abnormalities, and organ maturation and or about the transmission of infection across the placenta in the first and second trimesters of pregnancy.

Previous studies have demonstrated that SARS-CoV-1 infection during perinatal period is associated with high prevalence of maternal and neonatal effects, including DIC, abortion, preterm birth, intrauterine growth retardation, and neonatal intensive care unit (NICU) admission [44-46]. However, a recent review of the literature showed that pregnant women infected with COVID-19 and their neonates had less problems compared with SARS-CoV-1 infection. Fetal complications of COVID-19 have been reported as preterm birth (39–47%), intrauterine growth restriction (10%), and abortion (2%) according to recent literature. Respiratory insufficiency in pregnant women increases the risk of fetal growth restriction owing to maternal hypoxia, placental hypoperfusion, and reduced oxygen delivery to the fetus [46]. Zhu et al. [35] also reported that perinatal COVID-19 infection may have adverse effects on neonates, causing problems such as fetal distress and premature birth.

In a retrospective study, Zhang et al. [47] have compared the effect of COVID-19 on pregnancy outcomes and neonatal prognosis between 16 women infected with COVID-19 and 45 women without COVID-19. There were no significant differences in fetal distress, meconium-stained amniotic fluid, preterm birth, and neonatal asphyxia between the two groups.

The World Health Organization (WHO) does not recommend the routine use of systemic corticosteroids because of delaying viral clearance, although they do not cross the placenta. However, in terms of preterm delivery, the decision of using corticosteroids to induce fetal maturity and to minimize peripartum complications should be individualized. Recent studies have defined remdesivir and chloroquine as strong candidate drugs for the treatment of COVID-19 that are safe in pregnant women. Although chloroquine crosses the placenta, it may be safely used in all trimesters of pregnancy with no increased risk of adverse perinatal outcomes. Viral protease inhibitors such as lopinavir and ritonavir are also safe in the management of COVID-19, and they have no risk of fetal anomalies, preterm birth, or low birth weight in infants reported up to date [42].

Ribavirin, an antiviral guanosine analog commonly used in coronavirus treatment, is teratogenic and induces miscarriage, craniofacial, and limb defects in the embryos of pregnant mice. It should be avoided in early pregnancy [42]. Another drug, alpha interferon in early pregnancy, has the risk of fetal growth restriction and developmental delay [48].

The treatment response of mother's clinical condition will improve the fetal status. As long as the pregnant women have good response to the treatment, pregnancies should be allowed to continue to term. However, if a pregnant woman is critically ill, her clinical deterioration may lead to intrauterine fetal death or loss of both mother and the infant. In these conditions, early delivery may be warranted. The indications for early delivery depend on the mother's clinical status, gestational age, and fetal well-being condition [48].

Neonatal management after delivery

Available data are insufficient about the optimal mode of delivery for infected mothers, considering both maternal morbidity and infection risk to neonate. The mode of delivery should be decided based on obstetric factors and clinical emergency. Although recent data do not establish a risk of vertical transmission, early cord clamping and avoiding skin-to-skin contact following delivery are still suggested. Samples, including vaginal secretions, umbilical cord blood, amniotic fluid, placenta, and neonatal throat swab, should be collected during delivery to determine the potential intrauterine vertical transmission of COVID-19. However, infection may develop in neonates via close contact [48-51]. Because there is the close contact between mother and child, the mother should wear a face mask to reduce the risk of droplet transmission [51].

Optimal management in the delivery room is important for further follow up of these neonates. Delivery should be performed in a negative pressure room whenever possible. Obstetricians and pediatricians should be in closed cooperation, and the neonatologist should be informed at least 30 min before any planned delivery. Clinicians should use airborne, droplet, and contact precautions because of increased maternal virus aerosol transmission and should be prepared for possible intubation, airway suction, and positive pressure ventilation interventions. Regarding neonatal management of suspected, probable, and confirmed cases of maternal COVID-19 infection, the umbilical cord should be clamped promptly, and the neonate should be transferred to the resuscitation room [50, 51].

Routine neonatal care and the initial steps of neonatal resuscitation, including drying, tactile stimulation, assessment of heart rate, placement of pulse oximetry, and electrocardiograph leads, are unlikely to be aerosol-generating. Suction of the airway after delivery should not be performed routinely for clear or meconium-stained amniotic fluid. Suctioning is an aerosol-generating procedure and is not indicated for uncomplicated deliveries. Endotracheal instillation of medications, such as surfactant or epinephrine, includes aerosol-generating procedures. Intravenous delivery of epinephrine by umbilical venous catheter is the preferred route of administration during neonatal resuscitation. The neonate should be placed in an incubator instead of radiant warmer during the postnatal care [50].

Neonates of the suspected COVID-19-infected mother should be transferred to the neonatal isolation room immediately if they are in good general condition. Mother and neonate should be separated to minimize the risk of postnatal infant infection from maternal respiratory secretions. Neonates should be bathed as soon as possible after birth to remove virus potentially present on the skin surfaces. If the maternal nucleic acid test is negative for two consecutive tests, the neonate may be transferred out of the isolation room. The contact precautions and use of PPE should be provided during the postpartum period, until the mother tests are negative for COVID-19 [48-50]. First molecular assay testing should be done at 24 h of age, and repeat testing should be done at 48 h of age.

If the maternal nucleic acid test is positive or if a maternal infection is confirmed, neonates should be isolated for at least 14 days. The neonate and the mother with confirmed COVID-19 should be isolated in different rooms, and they should be screened very carefully. The neonate should be closely monitored for clinical manifestations of infection.

The frequency of NICU admission was also low according to recent reports. However, the neonates requiring NICU should be admitted to a single negative pressure patient room (or other air filtration systems). Airborne, droplet, and contact precautions should be taken for the care of neonates requiring continious positive airway pressure (CPAP) or any form of mechanical ventilation [49-51].

COVID-19 in neonates

"Life is a flame that is always burning itself out, but it catches fire again every time a child is born." — George Bernard Shaw

Knowledge about neonatal outcomes of COVID-19 is very limited and based on studies that are observed in the last trimester of pregnancy. Both SARS-CoV and MERS-CoV have been found to cause severe complications in pregnant women and neonates; however, SARS-CoV-2 seems to cause milder complications [52-58]. Immaturity of innate and adaptive immune system makes the neonates highly vulnerable to infections [59]. Dysregulation of factors, such as cytokines and complement cascade, and also some treatments given to mothers or neonates, such as high dose corticosteroids, can have detrimental consequences on brain development and function [44, 57, 58]. Fortunately, majority of neonates born to mother with COVID-19 did not become infected and had very few symptoms at birth, and to date, very few neonates have been reported that have affected by COVID-19.

In a systematic review of 18 studies (between December 8, 2019 and April 1, 2020) examining 108 pregnancies, neonatal data were obtained from 86 deliveries, and 22 women were still pregnant at study time. Of these, one intrauterine fetal death and one neonatal death were reported. Despite eight neonates had symptoms and clinical findings, such as fever, thrombocytopenia, vomiting, and pneumonia, they recovered in a short time and were discharged from hospital [44]. In a case control study where 16 COVID-19 confirmed pregnant women and 18 COVID-19 suspected pregnant women were included, maternal and neonatal complications were compared with 242 pregnant women without COVID-19 who delivered in 2019 and 2020. COVID-19 was not detected in neonates, and no severe neonatal complications were observed [45].

COVID-19 continues to spread worldwide. Since the information is limited only to the last period of pregnancy, it should be emphasized how to approach the neonates. Owing to the potential risk of infection, neonates born from an infected mother should be evaluated in this respect.

COVID-19 diagnosis in neonates

Baby born to mother with suspected or confirmed COVID-19 should be assessed clinically, and tests should be performed for identifying SARS-CoV-2. Neonates with COVID-19 may be asymptomatic or may have respiratory and gastrointestinal symptoms. Fever, tachycardia, vomiting, lymphocytopenia, thrombocytopenia, abnormal liver function, neonatal pneumonia, multiple organ failure, and DIC were reported in very few neonates till now [44, 45].

There are different recommendations for testing time and methods for COVID-19 in neonates with several limitations. Diagnosis of fetal/neonatal infections are based on the detection of the organism in culture or nucleic acid amplification tests or body fluid samples that identify the presence of the RNA or DNA of the pathogen in amniotic fluid before birth or in appropriately collected fetal/neonatal tissues, or histopathologically showing the organism in fetal/neonatal tissues. In addition, serology is used for certain congenital infections such as toxoplasmosis, cytomegalovirus, and herpes simplex virus. Antigen detection and rapid molecular diagnostic tests are also available, but they have several limitations and may have suboptimal sensitivity in ruling out disease [60]. RT-PCR-based assays performed in a laboratory on respiratory specimens are the reference standards for COVID-19 diagnosis having 71% sensitivity [60, 61]. To date, since maternal infections were observed in the late phase of pregnancy, there may not have been sufficient time for the generation of antibodies. Thus, the use of serology in the diagnosis of neonate is still controversial. Three neonates with elevated SARS-CoV-2 IgM despite negative molecular testing have been reported [62, 63]. Following these articles, tendency of IgM assays to false negative and positive results along with cross reactivity and testing challenges were pointed out in an editorial [64].

Currently, RT-PCR is noted as the gold standard test for diagnosis of SARS-CoV-2 [65]. A classification system based on sample site, method, and timing was suggested for neonatal SARS-CoV-2 infections such as congenital infection in live born room neonate, neonatal-infection-acquired intrapartum, and neonatal-infection-acquired postpartum [66]. Congenital infection in live born neonate could be defined in neonate and mother with SARS-Cov-2 infection with/without clinical features of infection and confirmed by detection of the virus by RT-PCR in umbilical cord blood or neonatal blood collected within first 12 h of birth or amniotic fluid collected prior to rupture of membrane. Neonatal-infection-acquired intrapartum could be defined in neonate and mother with SARS-Cov-2 infection with/without clinical features of infection and confirmed by detection of the virus by RT-PCR in nasopharyngeal swab at birth (collected after cleaning the baby) and at 24–48 h of age, and other explanations should be excluded in symptomatic babies. Neonatal-infection-acquired postpartum could be defined in neonate at older than 48 h of age with clinical features of infection, and parent or caregiver may or may not have SARS-CoV-2 infection or were not tested. The diagnosis could be confirmed by detection of the virus by RT-PCR in nasopharyngeal/rectal swab in at least 48 h after the birth and when respiratory sample tested negative by PCR at birth [66].

Usually, neonatal testing is recommended in the first 12–24 h after birth, while earlier test is likely to reflect maternal infection. In addition, a second test is recommended 24 h after the first test to confirm result. Subsequent testing is recommended if baby becomes unwell, after maternal test negative result or as recommended by infectious disease team [67]. Single swab that samples first oropharynx and then nasopharynx should be used for collecting. Rectal swab testing may be considered if available in centers, especially for sick infants requiring prolonged hospital care [68]. Two consecutive negative tests 24 h apart are considered as clearance. Swab is preferably obtained in a negative pressure room or in isolation with adequate PPE, which should include fit-tested mask/powered air-purifying respirator (PAPR) or goggles with an N95 mask plus gown and gloves. After obtaining the sample, PPE should be discarded, and the room should be cleaned [65].

Symptomatic neonates should be evaluated in terms of symptoms and examination findings. Complete blood count, liver, and renal function tests, if needed coagulation parameters, and other tests considered according to the neonates' findings could be performed. If a neonate with COVID-19 exhibits respiratory symptoms,

chest X-ray is performed; however, radiological features of COVID-19 in neonates have not been well characterized [69].

Although most of the studies did not find any evidence for intrauterine transmission, radiological findings, lymphocytopenia and thrombocytopenia, have been repeatedly reported in healthy seen babies born to SARS-CoV-2-infected women. Therefore, clinicians should closely monitor the neonates born from mothers with COVID-19 infection.

Treatment, discharge, and follow up of neonates with COVID-19

Currently, there is no definitive treatment for COVID-19 in neonates. Treatment options are based on adult studies that have contradictory results. Treatment options such as hydroxychloroquine/chloroquine, azithromycin, lopinavir/ritonavir, remdesivir, corticosteroids, and tocilizumab were recommended in adult patients according to patients' condition [70]. Unfortunately, there is no randomized controlled trial for neonates and children. Most of the neonates and children do not need treatment, and treatment decision is based on the clinical status of children. Symptomatic and supportive care can be given in children with upper respiratory tract infection, pharyngitis, and acute gastroenteritis. Supplementation of oxygen, maintenance of water–electrolyte, and acid–base balance are the mainstay of therapy for patients with COVID-19. If severe acute respiratory distress syndrome is present in neonate, high-dose pulmonary surfactant, inhaled nitric oxide, high-frequency oscillatory ventilation, and extracorporeal membrane oxygenation may be useful [39]. There is no evidence supporting that administration of immunoglobulins, antivirals, and steroids improves outcomes of neonates with severe COVID-19. Ivermectin, plasma infusion, and dornase alpha are other candidates that may be proposed for treatment; however, there is no evidence for use in children especially in neonates [71, 72].

Infants under investigation and symptomatic neonates should be cared for in an isolated room if a negative pressure room is not available. Contact and droplet precautions should continue if infant is undergoing aerosol-generating procedures, such as intubation/extubation, CPAP, and deep suctioning, in which case airborne precautions (PAPR or N95 mask plus goggles, gown, and gloves) are indicated [69]. If baby is stable and does not need NICU care, there are some opinions about contact with mother and separation. The decision should be made on a case-by-case basis using shared decision-making between the mother and the clinical team. Clinical condition and SARS-CoV-2 testing results of mother and baby, desire of mother to feed at the breast, facility capacity to accommodate separation or colocation, and the ability to maintain separation upon discharge and other risks and benefits of temporary separation of a mother with known or suspected COVID-19 and her infant should be considered [73]. If separation is not undertaken, other measures to reduce the risk of transmission from mother to infant should be considered, such as using physical barriers such as curtains between the mother and neonate and keeping the baby at least 2 m away from the mother. If mother is breastfeeding or not breastfeeding, but there is no other healthy person present in the room, she must use face mask and practice hand hygiene before each feeding and other close contact with her neonate [73]. If temporary separation is undertaken, infants with suspected COVID-19 should be isolated from other healthy infants. If another healthy family or staff member is present to provide care such as diapering, bathing, and feeding for the neonate, they should use PPE. For healthy family members, appropriate PPE includes gown, gloves, face mask, and eye protection [73].

Well neonates or neonates completed the treatment should be discharged from the birth hospital based on the center's normal criteria. Infected infants confirmed with molecular tests (or whose condition cannot be determined because of lack of testing), but without symptoms of COVID-19, can be discharged on a case-by-case basis with appropriate measures and frequent outpatient follow-up contacts (telephone, telemedicine, or in-office) within 14 days after delivery. All caregivers should use PPE, and uninfected individuals above 60 years of age and individuals with comorbid conditions should not care these neonates [68]. Infants with a negative SARS-CoV-2 molecular test should be best discharged to the care of a designated healthy (noninfected) caregiver. If the mother is in the same house, she should maintain a distance of at least 2 m for as long as possible, and when she is close to the neonate, she should use a mask and hand hygiene for neonate care up to mother without fever for 72 h without using antipyretic, improvements of symptoms, and has negative results from a molecular assay for detecting SARS-CoV-2 from at least two consecutive nasopharyngeal swab samples collected at 24-h intervals, or another family member may care the baby in this time period [66, 68]. Other caregivers in the home who are under observation for the development of COVID-19 should use standard procedure masks and hand hygiene and should be 2 m away from the neonate until their condition is resolved [68]. After discharge of baby from hospital, a check-up and pharyngeal swab for SARS-CoV-2 should be received at the 14th day, and neonatal COVID-19 follow up could be stopped on the 28th day after discharge if the baby is well and SARS-Cov-2 found to be negative in the swab test [74]. Table 2 summarizes the suggested management for neonates who were born from COVID-19 infected mothers.

Breastfeeding

Breastfeeding has several lifelong benefits. Breastfeeding shapes the developing neonatal gut microbiota at an early age, both through exposure of the neonate directly to breast milk microbiota and, indirectly, through breast milk factors and bioactive substances that affect bacterial growth and metabolism [75]. Multiple studies have shown that breastfeeding not only reduces the risk of death and illness in early life, but also has permanent health benefits throughout adult life. Moreover, long-term and exclusive breastfeeding has been associated with improved cognitive development in infants [76]. To date, there has been no evidence showing viral transmission to neonates via human milk could not be proven; however, contagion by droplets and by contact with the respiratory secretions of infected people should not be ignored [11, 74, 77]. The CDC recommends to mothers to decide with other family members and healthcare providers how to start and continue breastfeeding. If the mother is sick and chooses to direct breastfeed, they recommend wearing a face mask and washing hands before each feeding. In addition, if the mother is sick and chooses to express breast milk, they recommend expressing breast milk to establish and maintain milk supply, providing a dedicated breast pump, washing hands before touching any pump or bottle parts and before expressing breast milk, after each use, cleaning all parts that come into contact with breast milk, and, if possible, considering having someone who is well feed the expressed breast milk to the infant are recommended [78].

The safety of breastfeeding when mother is on a COVID-19 treatment with diverse drugs should be evaluated. However, there are no data regarding the use of some of the medications. One of the drugs used in treatment is remdesivir. There are ongoing studies about this issue, and nothing is known about the use of remdesivir in pregnancy and passage into the breastmilk [69, 79]. Hydroxychloroquine is a potential treatment option in COVID-19, and it is reported as acceptable during breastfeeding

Table 2. Suggested management for neonates who were born from COVID-19 infected mothers

1.	Delivery should be performed in a negative pressure room whenever possible, and mother should wear a face mask to reduce the risk of droplet transmission during delivery.
2.	Recent data do not prove the risk of vertical transmission; however, early cord clamping is suggested, and skin-to-skin contact should be avoided following delivery.
3.	Neonate should be transferred to the resuscitation room and neonatal care, and the initial steps of neonatal resuscitation, including drying, tactile stimulation, assessment of heart rate, placement of pulse oximetry, and electrocardiograph leads, should be routinely performed.
4.	Suction of the airway after delivery should not be performed routinely for clear or meconium-stained amniotic fluid.
5.	Endotracheal instillation of medications includes aerosol-generating procedures and should be performed carefully.
6.	The neonate should be placed in an incubator instead of radiant warmer during the postnatal care.
7.	Mother and neonate should be separated to minimize the risk of postnatal infant infection.
8.	Neonate should be bathed as soon as possible after birth to remove virus potentially present on skin surfaces.
9.	If the maternal nucleic acid test is positive or if a maternal infection is confirmed, neonates should be isolated for at least 14 days. The neonate and the mother with confirmed COVID-19 should be isolated in different rooms.
10.	The neonate should be closely monitored for clinical manifestations of infection during isolation.
11.	If the maternal nucleic acid test is negative for two consecutive tests, the neonate may be transferred out of the isolation room.
12.	For neonates, first molecular assay testing (RT-PCR) should be done at 24 h of age, and repeat testing should be done at 48 h of age.
13.	The contact precautions and use of personal protection equipment should be provided during the postpartum period, until the mother tests are negative for COVID-19.
14.	Neonates requiring NICU should be admitted to a single negative pressure patient room (or other air filtration systems).
15.	Airborne, droplet, and contact precautions should be taken for the care of neonates requiring CPAP or any form of mechanical ventilation.
16.	Symptomatic neonates should be evaluated according to symptoms and examination findings. Chest X-ray, complete blood count, liver, and renal function tests, if needed coagulation parameters, and other tests should be considered.
17.	Most of the neonates and children do not need treatment, and treatment decision is based on the clinical status of children.
18.	If separation of mother and neonate is not undertaken, measures to reduce the risk of transmission from mother to infant should be considered, such as using physical barriers such as curtains between the mother and neonate and keeping the baby at least 2 m away from the mother.
19.	There is no evidence showing viral transmission to neonates via human milk. If the mother sick and chooses to direct breastfeed, mother should wear a face mask and wash hands before each feeding.
20.	If the mother is sick and chooses to express breast milk, it may be provided by a dedicated breast pump.
21.	Wash hands before touching any pump or bottle parts and before expressing breast milk, and after each use, clean all parts that come into contact with breast milk. In addition, if possible, consider having someone who is well feed the expressed breast milk to the infant.
22.	Well neonates or neonates completed the treatment should be discharged from the birth hospital based on the center's normal criteria.
23.	Infants who are found to be infected with molecular tests (or whose condition cannot be determined because of lack of testing), but without symptoms of COVID-19, can be discharged on a case-by-case basis with appropriate measures and frequent outpatient follow-up contacts (telephone, telemedicine, or in-office) within 14 days after delivery. All caregivers should use PPE and uninfected individuals above 60 years of age, and individuals with comorbid conditions should not care these neonates.

COVID-19: Coronavirus disease 2019; RT-PCR: reverse-transcription polymerase chain reaction; NICU: neonatal intensive care unit; CPAP: continious positive airway pressure; PPE: personal protective equipment

[80]. Ritonavir/lopinavir is an antiviral treatment used in HIV infection, and experience with ritonavir/lopinavir during breastfeeding is limited and mostly for HIV infection. In the United States, avoiding breastfeeding is recommended; however, in countries in which no acceptable, feasible, sustainable, and safe replacement feeding is available, WHO guidelines recommend that all women with an HIV infection who are pregnant or breastfeeding should be maintained on antiretroviral therapy for at least the duration of risk for mother-to-child transmission [81-84]. No recommendation is available for COVID-19 now. For azithromycin, lower levels in breast milk, and higher doses used in infants, it is not expected to cause adverse effects in breastfed infants [85]. Manufacturers suggest that the decision to breastfeed during azithromycin therapy should be considered according to the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother [86]. Corticosteroids are generally considered acceptable when used in normal doses in lactating women; however, it is recommended to monitor the nursing baby [87]. Little information is present about tocilizumab, and it is recommended to be used with caution during breastfeeding. The risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother should be considered [88, 89]. It should be kept in mind that there are no data available about the effect of all these treatments on breastfeeding in COVID-19, and care should be taken in these terms.

In conclusion, although COVID-19 in pregnants and neonates has not been associated with severe disease or worse clinical outcomes so far, the availability of limited data on this topic should be emphasized. Thus, it is possible that all approaches can be changed and renewed. Updated information in diagnosis and new treatment approaches for these vulnerable groups of patients should be considered. As Voltaire has stated: "It is said that the present is pregnant with the future."

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