

Vertical Transmission of Coronavirus Disease 19 (COVID-19) from Infected Pregnant Mothers to Neonates: A Review

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Abstract- The Coronavirus Disease 19 (COVID-19) infection has been prevalent in China and eventually spread to other countries. There are a few published cases of COVID-19 occurring during pregnancy and due the possibility of mother-fetal vertical transmission, there is a concern that the fetuses may be at risk of congenital COVID-19. **Methods:** We reviewed the risk of vertical transmission of COVID-19 to the fetus of infected mothers by using data of published articles or official websites up to March 4, 2020. A total of 31 infected pregnant mothers with COVID-19 were reported. No COVID-19 infection was detected in their neonates or placentas. Two mothers died from COVID-19-related respiratory complications after delivery. Currently, based on limited data, there is no evidence for intrauterine transmission of COVID-19 from infected pregnant women to their fetuses. Mothers may be at increased risk for more severe respiratory complications.

Index terms- Corona Virus, COVID-19, vertical transmission, placenta, pregnant mothers, neonate

INTRODUCTION

Pregnancy is a state of partial immune suppression which makes pregnant women more vulnerable to viral infections, and the morbidity is higher even with seasonal influenza. Therefore, the COVID-19 epidemic may have serious consequences for pregnant women. Although the vast majority of cases of COVID-19 are currently in China, the risk of outward transmission appears to be significantly raising global concern. Human to human transmission of the virus is proven to occur,^{1, 2} perhaps even from asymptomatic patients,^{3, 4} and the

mortality is substantial, especially among frail, elderly patients with comorbidities.⁵ Although there have been some criticisms surrounding suppression of early warnings, and slow initial response followed by heavy-handed quarantine measures, as well as concerns expressed about the capacity to cope with the large number of patients, and shortage of protective equipment and in-hospital infections leading to deaths among a substantial number of healthcare professionals,^{6, 7} China's effort to contain the disease and slow down its spread in China and world-wide has been commendable. A large number of cases requiring hospitalization and intensive care is a serious burden even for affluent countries with well-developed healthcare systems. However, the Chinese government, its health professionals, and the public, have set a new standard for handling the epidemic, and they have certainly contributed to reducing the potential risk of outbreak in neighboring countries with weaker healthcare systems. Furthermore, Chinese researchers and health professionals have generously shared their data, knowledge, experience and expertise that has helped to develop diagnostic tools, clinical management algorithms, set up clinical trials, and accelerate vaccine development. Clinical course and outcome of a substantial number of COVID-19 patients have been reported, and recommendations regarding the care of such patients have been issued by several national health authorities across the world. However, the practices seem to vary considerably.

COVID-19

As COVID-19 virus is still spreading, more infections in pregnant women are likely to be seen. Whether COVID-19 increases the risk of miscarriage, stillbirth, preterm delivery, fetal tachycardia and fetal distress is unknown. According to the official website of Ministry of Health and Medical Education (MOHME) in Mazandaran and Zanjan provinces, Iran, three infants were born from infected pregnant mothers. Among these three cases of COVID-19 infection there were two mothers who developed acute respiratory distress syndrome (ARDS) after delivery and died. According to the websites, their neonates were negative when tested for COVID-19 [11]. It seems that COVID-19 infection in pregnant patients may increase the risk of maternal mortality. Chen et al., reported the clinical characteristics and placental pathology from three women with confirmed COVID-19 infection. No COVID-19 nucleic acid was detected in the placentas or neonatal throat swabs by RT-PCR. Moreover, they found that the clinical characteristics of infected pregnant women in late pregnancy were similar to those of non-pregnant patients, and no severe adverse pregnancy outcome was found in the three cases [12]. In other study, Chen et al., evaluated clinical records, laboratory results, and chest computed tomography (CT) scans among nine pregnant women with laboratory-confirmed COVID-19 who were referred to Zhongnan Hospital of Wuhan University, Wuhan, China, between January 20 and January 31, 2020. Their results revealed that the clinical characteristics of COVID-19 in pregnant women were similar to infected non-pregnant women. They reported nine live births and none of the patients developed severe COVID-19 or died, and all samples tested negative for the virus in neonates. Their findings supported that there is currently no evidence for vertical transmission in infected mothers in late pregnancy [13]. In a retrospective study, Zhang et al., evaluated the effect of COVID-19 on pregnancy outcomes and neonatal prognosis between 16 infected women with COVID-19 and 45 women without COVID-19 women undergoing cesarean section (CS) in Hubei Province. There were no significant differences in fetal distress, meconium-stained amniotic fluid, preterm delivery, and neonatal asphyxia between the two groups. They did not find 2019-nCoV infection in neonates delivered from pregnant mothers with COVID-19. In the treatment of uterine contraction

fatigue, carbetocin or carboprost tromethamine was used more in CS for infected pregnant mothers compared to healthy mothers. They observed that timely termination of pregnancy after 32–34 weeks of pregnancy by CS was not associated with an increased risk of maternal complications in pregnant women with indications for obstetric surgery or critical illness of COVID-19, but it was beneficial for the treatment and rehabilitation of maternal pneumonia

MERS-CoV or SARS-CoV

Studies have not yet reported ongoing transmission of MERS-CoV or SARS-CoV within communities outside of health care settings. In 2004, Lam et al., in a case-control study including 10 pregnant mothers infected by SARS-CoV and 40 non-pregnant women with SARS evaluated the clinical course and outcomes of pregnancy in women with severe acute respiratory syndrome. Their results revealed that pregnancy appeared to have no effect on clinical symptoms or time to presentation after symptom onset. However, complications and adverse outcomes including longer hospital stay, renal failure, sepsis, and disseminated intravascular coagulopathy (DIC) in pregnant women were statistically significantly increased. They reported the need for mechanical ventilation and rate of mortality among them were more frequent than non-pregnant women [15]. Other studies in the USA, Canada and Hong Kong reported that these pregnant women required mechanical ventilation, hemodialysis due to acute renal failure, developed seizures and positive cerebrospinal fluid for SARS-CoV more frequently [16,17]. Those studies did not report any stillbirths among the infected mothers. According to those studies all mothers recovered and their neonate's tests for SARS-CoV RNA were negative. In another study, Maxwell et al., reported that of seven pregnant mothers infected with SARS-CoV at a designated SARS unit, two mothers died and four mothers required intensive care unit (ICU) hospitalization and mechanical ventilation. Two infected mothers recovered and maintained their pregnancy but had infants with intrauterine growth restriction (IUGR). Among the live newborn infants, none had clinical or laboratory evidence for SARS-CoV infection [18]. Ng et al., in a study evaluated the placental pathology in seven pregnant women infected with SARS-CoV.

In two women who were convalescing from SARS-CoV infection during the 1st trimester of pregnancy, the placentas were normal. In three mothers, the placentas demonstrated increased subchorionic and intervillous fibrin, which could be associated with abnormal maternal blood flow to the placenta.

PREVENTION

Incubation period of COVID-19 is about 2-14 days, but infected persons can transmit the virus via close contact and respiratory droplets perhaps even before they become symptomatic. Physiological changes in the immune and respiratory system may make pregnant women more susceptible to COVID-19 infection during the epidemic. No effective vaccine is available at present. Therefore, it is advisable that pregnant women refrain from unnecessary travel, avoid crowds, public transport, contact with sick people, and more importantly, practice and maintain good personal and social hygiene. Pregnant women with symptoms of fever, cough, fatigue, myalgia, sore throat or shortness of breath should seek timely medical consultation and help. Women with a travel history to endemic areas and those with a clinical suspicion of infection should be isolated and investigated. Some pregnant women may develop severe anxiety and depression requiring professional psychological support to prevent adverse outcomes.

DIAGNOSIS

The main clinical manifestations are fever, fatigue, myalgia, dry cough, and shortness of breath. Few patients may present with nasal congestion, runny nose, sore throat, hemoptysis, or diarrhea. Peripheral white blood cells count is normal or decreased in early stages, and the lymphocyte count may be reduced. C-reactive protein may be increased. Some patients may have mild thrombocytopenia, elevated levels of liver enzymes and creatine phosphokinase.

A computed tomography (CT) scan of the chest without contrast is the most useful investigation to confirm or rule out viral pneumonia, and should be performed in suspected cases as the risk of radiation exposure to the fetus is very small. In a recent report, sensitivity of chest CT in diagnosing COVID-19 was shown to be greater than that of RT-PCR (98% vs 71%).¹³ Radiological signs of viral pneumonia were

present in an overwhelming majority of reported pregnancies with COVID-19 infection.

SARS-COV-2 is the etiologic agent of COVID-19, and its viral nucleic acid detection using real-time polymerase chain reaction (RT-PCR) is considered the reference standard for the diagnosis. Specimens should be obtained from saliva, upper respiratory tract (nasopharyngeal and oropharyngeal swabs), lower respiratory tract (sputum, endotracheal aspirate, or bronchoalveolar lavage), urine and stool if possible. Repeated testing may be required to confirm the diagnosis. If the SARS-COV-2 nucleic acid is not detected in respiratory tract samples taken on two consecutive occasions at least 24 hours apart, COVID-19 can be ruled out. Serology as a diagnostic procedure should be used only if RT-PCR is not available.

To screen for other respiratory infections, samples should also be tested for other viruses (such as influenza virus A and B, adenovirus, respiratory syncytial virus, rhinovirus, human metapneumovirus, SARS-CoV), bacterial pneumonia, chlamydia and mycoplasma pneumoniae.

It is important to take blood cultures for bacteria that cause pneumonia and sepsis ideally before initiating antimicrobial therapy.

Antiviral treatment

Antiviral treatment has been routinely used to treat COVID-19 infection in China, and is also recommended for pregnant patients. Combination therapy with antiproteases Lopinavir/Ritonavir has been the preferred drug regimen as it is known to be relatively safe in pregnancy. The recommended dose is two capsules of Lopinavir/Ritonavir (200 mg/50 mg per capsule) orally together with nebulized α -interferon inhalation (5 million IU in 2 mL of sterile water for injection) twice a day.

WHO advises caution and careful risk-benefit analysis before using investigational therapeutic agents in pregnant women outside clinical trials. Remdesivir, a nucleotide analog, and chloroquine, an antimalarial drug, are promising drugs against COVID-19 as they are known to inhibit SARS-COV-2 virus in vitro.¹⁴ Clinical trials have already started in China and are planned elsewhere.

Antibacterial treatment

The extensive lung damage by the virus substantially increases the risk of secondary bacterial pneumonia. Antibiotics are indicated only if there is evidence of secondary bacterial infection. However, antibiotics should be administered without delay if bacterial sepsis is suspected. Intravenous Ceftriaxone can be administered initially while awaiting culture and sensitivity results.

Corticosteroid therapy

In general, use of corticosteroids in the treatment of COVID-19 pneumonia is not recommended as it may delay the virus clearance from the body. However, short-term (3-5 days) administration of methylprednisolone (1-2 mg/Kg bodyweight per day) has been used frequently in China, especially when dyspnea and hypoxemia are severe, in an attempt to ameliorate lung inflammation and prevent acute respiratory distress syndrome. This regimen is also recommended for pregnant women with COVID-19, although data on its effectiveness and safety need further evaluation. Administration of Betamethasone 12mg intramuscularly followed by another dose 24 hours later should be considered to promote fetal lung maturity when preterm delivery is anticipated.

TIMING AND MODE OF DELIVERY

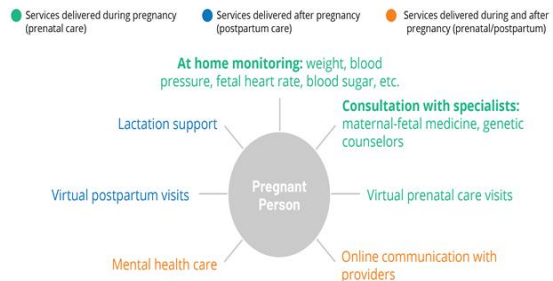
Timing of delivery should be individualized based on disease severity, existing comorbidities such as preeclampsia, diabetes, cardiac disease etc, obstetric history, and gestational age and fetal condition. In mild and stable cases responding to treatment and in the absence of fetal compromise, pregnancy may be continued to term under close surveillance. Regular monitoring of maternal vital signs (temperature, heart rate, blood pressure, respiration rate and oxygen saturation by pulse-oximetry). Dynamic assessment of electrolytes and fluid balance, arterial blood gases, and acid-base status is required. Ultrasound examination of the fetus and fetal heart rate monitoring are recommended to assess fetal wellbeing.

In critical cases, continuing pregnancy may endanger the safety of the mother and her fetus. In such situations, delivery may be indicated even if the baby is premature, and termination of pregnancy should be considered as an option before fetal viability is reached in order to save the pregnant woman's life

after careful consultation with the patient, her family and an ethical board.

Mode of delivery is mainly determined by obstetric indications. Careful consideration should be given in regards to choice of anesthesia when a delivery by cesarean section is required. In two published reports from China involving a total of 18 pregnant women with COVID-19, all but two were delivered by cesarean section, and none of the neonates were infected by SARS-COV-2. As the of evidence for vaginal shedding of virus and vertical transmission is lacking, vaginal delivery may be considered in stable patients.

During The COVID-19 Pandemic, Many Pregnancy-Related Services Could Be Delivered Via Telemedicine



CARE OF THE NEWBORN

Limited data obtained from cases of pregnant women with COVID-19 suggest that the transplacental transmission is unlikely in late pregnancy close to term, as the virus was not identified in the amniotic fluid, placenta, breast milk of these mothers or in the nasal secretions of their neonates. However, infection can occur in neonates via close contact. Two such cases of neonatal COVID-19 infection have been confirmed so far at 36 hours and 17 days after birth, and both appear to have been infected postnatally.

Therefore, early cord clamping and temporary separation of the newborn for at least 2 weeks is recommended to minimize the risk of viral transmission by avoiding longer, close contact with the infected mother. The neonate should be cared for in isolation ward and carefully monitored for any signs of infection. During this period, direct breast feeding is not recommended. A possible option is for the mother to pump her breast milk, which can be fed to the baby by a healthy caregiver.

CONCLUSIONS

As the COVID-19 epidemic continues to spread around the world, we need to plan and prepare ourselves proactively. Providing appropriate clinical management and support to patients while adequately protecting healthcare professionals should be our goal. A multi-disciplinary team approach should be adopted in managing these patients as it allows to effectively share the expertise as well as responsibility, and treat our patients with dignity and compassion. However, there are many challenges to overcome, such as shortage of protective equipment, depleting supply of medicines and blood products (reduced blood donations), infected pregnant women showing up directly to delivery rooms in advanced labor, psychological pressure and panic, just to mention a few. In hospitals, the transmission of the virus and deaths among healthcare professionals are serious concerns. Improving healthcare governance, as well as supporting, educating and training healthcare personnel in infection control and self-protection need to be prioritized. Clinical recommendations for managing COVID-19 infection in pregnancy should be based on data from the current epidemic rather than drawing on limited experience from previous outbreaks of different types of corona viruses, as their epidemiology, clinica

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