

Novel corona virus disease (COVID-19) in pregnancy: What clinical recommendations to follow?

Huan Liang¹ | Ganesh Acharya^{2,3} 

¹Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China

²Division of Obstetrics and Gynecology, Department of Clinical Science, Intervention and Technology, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden

³Women's Health and Perinatology Research Group, UiT-The Arctic University of Norway and University Hospital of North Norway, Tromsø, Norway

Correspondence: Ganesh Acharya
Email: ganesh.acharya@ki.se

1 | 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.

Interim guidance has been issued by the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) on managing COVID-19, which include some recommendations specific to pregnant women, mostly drawn on experience from previous coronavirus outbreaks.^{8,9} Chinese expert recommendations for the care of pregnant women with suspected and confirmed COVID-9 were developed and disseminated in China quite early following the outbreak in Wuhan.¹⁰ These recommendations have been dynamic, evolving as more knowledge about epidemiology, pathogenesis, disease progression and clinical course among infected pregnant patients has been gathered. Limited clinical experience in managing pregnant women with COVID-19 and their neonates has been reported from China recently based on a case series of nine pregnancies with confirmed COVID-19 treated in Zhongnan Hospital of Wuhan University and 10 neonates (nine pregnancies) delivered at five different hospitals,^{11,12} although many more cases (>100) of suspected or confirmed COVID-19 have been treated and delivered in several hospitals in China according to the news releases and media reports. So far, no maternal deaths have been reported.

There appears to be some risk of premature rupture of membranes, preterm delivery, fetal tachycardia and fetal distress when the infection occurs in the third trimester of pregnancy. However,

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there is no evidence suggesting transplacental transmission based on very limited data, as the analysis of amniotic fluid, cord blood, neonatal throat swab, and breast milk samples available from six of the nine patients were found to be negative for SARS-CoV-2. Whether virus shedding occurs vaginally is also not known.

Whether COVID-19 increases the risk of miscarriage and stillbirth is unknown. Concerns have been expressed by experts in the media about women undergoing termination of pregnancy for fear of congenital infection and teratogenicity. However, information on the effect of COVID-19 on the course and outcome of pregnancy in the first and second trimesters is not available yet.

As COVID-19 still appears to be spreading, more infections in pregnant women are likely to be encountered in different regions, countries, and continents. Therefore, it is important that pregnant women and their families, as well as the general public and health-care providers, receive as accurate information as possible. Here is our attempt to summarize some important practical clinical aspects of managing COVID-19 in pregnancy:

2 | 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.

3 | 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.

4 | MANAGEMENT

Pregnant women suspected of COVID-19 should be isolated and investigated. Those diagnosed with infection should be promptly admitted to a negative pressure isolation ward, preferably in a designated hospital with adequate facilities and multi-disciplinary expertise to manage critically ill obstetric patients. They should be triaged and stratified into mild (symptomatic patient with stable vital signs), severe (respiration rate $\geq 30/\text{min}$, resting $\text{SaO}_2 \leq 93\%$, arterial blood oxygen partial pressure (PaO_2)/ oxygen concentration (FiO_2) ≤ 300 mmHg) or critical (shock with organ failure, respiratory failure requiring mechanical ventilation or refractory hypoxemia requiring extra-corporal membrane oxygenation) categories based on clinical evaluation, and managed by a multidisciplinary team of midwife, obstetrician, specialist in intensive care medicine, microbiologist, anesthesiologist and neonatologist. All medical staff caring for COVID-19 patients should use personal protective equipment including gown, N95 masks, goggles, and gloves. Special consideration should be given to physiological adaptations in pregnancy when treating pregnant women with COVID-19 infection.

4.1 | Supportive therapy

Adequate rest, hydration, nutritional support, and water and electrolyte balance should be ensured. It is essential to monitor vital signs and oxygen saturation closely. Depending on the severity of the

disease, supplemental oxygen inhalation (60%-100% concentration at a rate of 40 L/min) should be given via high-flow nasal cannula depending on the severity of hypoxemia. Intubation and mechanical ventilation or even extra-corporal membrane oxygenation (ECMO) may be required to maintain oxygenation. Other complications may include septic shock, acute kidney injury, and virus-induced cardiac injury. Therefore, it is important to check arterial blood gases, lactate, renal function, liver function and cardiac enzymes as indicated by the clinical situation.

4.2 | 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.

4.3 | 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.

4.4 | 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.

5 | 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 evidence for vaginal shedding of virus and vertical transmission is lacking, vaginal delivery may be considered in stable patients.

6 | 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.¹⁵

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 an 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.⁹

7 | 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, clinical course and response to treatment may differ. Guidelines will evolve as more data become available and experience is gathered. Therefore, complete data on all pregnancies affected by COVID-19 should be collected and made publicly available. Sharing data, knowledge and expertise, and helping countries with poor resources and weaker healthcare systems are important in this respect.

ORCID

Ganesh Acharya  <https://orcid.org/0000-0002-1997-3107>

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