



Guidance for Management of Pregnant Women in COVID-19 Pandemic

Pregnant women and their fetuses represent higher-risk populations during infectious disease outbreaks than the general population. Physical and mechanical changes in pregnancy normally increase susceptibility to infections, especially when the cardiorespiratory system is affected, and encourage rapid progression to respiratory failure in gravida. In addition, a pregnancy bias towards the dominance of the T-helper 2 (Th2) system that protects the foetus leaves the mother vulnerable to viral infections, which are more effectively implicated by the Th1 system. These unique challenges mandate an integrated approach for pregnancies affected by SARS-CoV-2.

It is important to be vigilant about the spread of the disease and be able to rapidly adopt implementation of outbreak control and management measures once the virus has arrived in a community. Standard interventions to manage any serious respiratory infection are the foundation of care for any pregnant woman with COVID-19 and should be applied aggressively in a team-based care model.

Principles for Management of Pregnant Women with Confirmed or Suspected Coronavirus Disease 2019 (COVID-19)

- Patients with respiratory symptoms should adhere to respiratory hygiene, cough etiquette, and hand hygiene. Rapid triage of pregnant patients with respiratory symptoms should be ensured. Patients with respiratory symptoms should wear a facemask and wait in a separate, well-ventilated waiting area at least 6 feet from other people.
- Confirmed and suspected cases of COVID-19 should be isolated as soon as possible in an Airborne Infection Isolation Room (AIIR). If an AIIR is not available, they should be transferred to a hospital with an AIIR.
- CDC infection prevention and control procedures for healthcare providers including standard, contact, and airborne precautions should be implemented. Eye protection and properly-fitted N95 respirators should be used. Additional staff training in correct use of personal protective equipment (PPE) including correct donning, doffing and disposal of PPE should be provided.
- Hospital infection personnel should be contacted.
- Relevant specimens for diagnostic SARS-CoV-2 testing should be collected and sent in coordination with local/state health department.
- Access to patient rooms with a confirmed or suspected case for the visitors and healthcare personnel should be limited.

- Pregnancy should be considered a potentially increased risk condition and monitored closely including foetal heart rate and contraction monitoring. Early oxygen therapy should also be considered (target O₂ saturations ≥95% and/or PO₂ ≥70mmHg).
- Early mechanical ventilation with evidence of advancing respiratory failure should also be considered. Non-invasive ventilation techniques may have a small increased risk of aspiration in pregnancy.
- Intravenous fluids should be used conservatively unless cardiovascular instability is present.
- Screening for other viral respiratory infections and bacterial infections (due to risk of coinfections) should be done.
- Empiric antimicrobial therapy (because of risk for superimposed bacterial infections) should be considered.
- Empiric treatment for influenza, pending diagnostic testing should also be considered.
- Corticosteroids should not be used routinely. Use of steroids to promote foetal maturity with anticipated preterm delivery can be considered on individual basis.
- If septic shock is suspected, prompt, targeted management should be instituted.
- Delivery and pregnancy termination decisions should be based on gestational age, maternal condition, foetal stability, and maternal wishes.
- Specialists in obstetrics, maternal-foetal medicine, neonatology, intensive care, anaesthesia, and nursing should be consulted.
- Communication with patients and families regarding diagnosis, clinical status and management wishes should be maintained.

Changes in foetal heart rate pattern may be an early indicator of maternal respiratory deterioration. Based on experience with SARS and MERS, severe respiratory failure might occur in pregnant women; and in the most severe cases, mechanical ventilation might not be sufficient to support adequate oxygenation. If that occurs, limited literature suggests a potential role of extracorporeal membrane oxygenation (ECMO) in pregnancy; but its use should only be considered in centres that have experience with this technique. Whether delivery provides benefit to a critically ill mother is unknown; decisions regarding delivery should be considered based on the gestational age of the foetus and should be made in conjunction with the neonatologist.

Clinical features

Similar to non-pregnant patients, the predominant features of COVID-19 in pregnancy are fever, cough, dyspnoea and lymphopenia

Care of infants born to mothers with COVID-19

- Infant who was diagnosed with COVID-19 suggests the possibility of in utero transmission. It seems reasonable to assume that a newborn, born to a mother with COVID-19 at delivery, could possibly be infected either in utero or perinatally and thus should be placed in isolation to avoid exposure to other newborns.
- There have been no confirmed instances of vertical transmission among the other neonates born to COVID-19 infected mothers reported thus far. This has been supported in turn by evidence demonstrating an absence of viral isolates in the amniotic fluid, cord blood, breast milk and neonatal throat swabs in a subset of many patients.
- Mothers who intend to breastfeed and are well enough to express breast milk should be encouraged to do so.
- Breastfeeding can be instituted after the mother is no longer considered infectious.

Treatment

Symptomatic treatment and pregnancy-specific management of complications such as sepsis and acute respiratory distress syndrome (ARDS) comprise the current standards of care. **Use of drugs in pregnant women needs to be on the basis of solid evidence.** Clinical trials are needed to prove the effectiveness of drugs and the effects of them on the foetus to establish a standardised treatment for pregnant women with COVID-19. As the coronavirus disease 2019 (COVID-19) outbreak continues to spread rapidly, efforts are ongoing in China and around the world to develop effective treatments. Among the drugs being tested for COVID-19 in China is chloroquine, which was reported on Feb 4, 2020, to inhibit severe acute respiratory syndrome coronavirus 2 in vitro. The drug was rapidly pushed to clinical testing as an experimental treatment in China; on Feb 15, 2020, it was included in the sixth version of the COVID-19 treatment guidelines by the National Health Commission of the People's Republic of China. **This guideline established the use of chloroquine nationwide for patients with COVID-19, at a recommended adult dose of 500 mg twice per day for no more than 10 days. The lethal dose of chloroquine in adults is about 5 g.**

In the human body, chloroquine has a large volume of distribution with an elimination half-life of 20–60 days and a tendency to accumulate in metabolically active tissues at higher levels compared with the plasma concentration.

In view of these properties, the recommended dose of 500 mg twice per day can quickly approach danger thresholds with sustained use. At the maximum course of 10 days, this regimen is substantially more aggressive than recommended regimens for the use of chloroquine as an antimalarial. The effects of chloroquine poisoning are well documented and include retinopathy and immunosuppression, with contraindications in several conditions including pregnancy.

On Feb 26, 2020, the treatment guidelines were revised, shortening the maximum course to 7 days while recommending a lower dose for patients weighing less than 50 kg and highlighting contraindications including pregnancy.⁵

It is encouraging that an appropriate adjustment with improved consideration for the toxicological properties of the drug was made so quickly given the urgency of the situation. However, we advise continued caution in bringing new treatments to clinical use in such a rapid manner. Recommended doses should be established with close reference to pharmacological profiles and side-effects must be closely monitored. The less toxic hydroxychloroquine should also be considered as an alternative. Finally, the potential toxicities of experimental treatments should be meticulously reported in peer-reviewed publications to avoid potentially misleading accounts and the risk of dangerous self-medication by the public. The rapid identification and development of such novel treatments is encouraging and will be instrumental in the battle against COVID-19, as long as prudence and rigour continue to be practised in both implementation and reporting.

- Remdesivir and Chloroquine are strong candidate drugs for the treatment of COVID-19 but in case of pregnant women this medicine needs to be used only under expert medical supervision.
- Remdesivir is a novel, broad-acting antiviral nucleotide prodrug which effectively inhibits replication of SARS-CoV-2 in-vitro and that of related coronaviruses including MERS-CoV in non-human primates. **It was originally tested in Ebola patients, has emerged as one of the top near-term hopes for COVID-19 patients.** In addition to carrying out its own clinical trials, Gilead has made the drug available to studies run by other sponsors, as well as to more than 1,700 people on a compassionate use basis. Last week, The New England Journal of Medicine published data from 53 patients with severe disease, but that data set also lacked a control group.
- Chloroquine phosphate is a ubiquitous antimalarial quinolone compound with broad-spectrum antiviral and immunomodulating activity. It has been shown to block coronavirus infection by increasing the endosomal pH required for cell fusion and by interrupting the glycosylation of cellular receptors of SARS-CoV in cell culture. Although chloroquine and its metabolites cross the placenta.

Note:

In USA, the FDA's chief scientist Denise Hinton said: “Based on the totality of scientific evidence available to [the] FDA, it is reasonable to believe that chloroquine phosphate and hydroxychloroquine sulfate may be effective in treating COVID-19”, she wrote, without providing references to studies supporting that conclusion. Although the efficacy of the drugs as a COVID-19 treatment might be uncertain, their side-effects are not.

“What I know for sure as a cardiologist is that these powerful medications have important side-effects including rarely sudden cardiac death”, said Michael Ackerman, a genetic cardiologist and director of Mayo Clinic's Windland Smith Rice Genetic Heart Rhythm Clinic. He said that at least 1% of patients will be at increased risk for a hydroxychloroquine or chloroquine QT reaction capable of triggering drug-induced sudden cardiac death (especially if used in combination with azithromycin). Although such reactions are rare, if millions of people receive the drugs, thousands of lives could be at risk from medications that were supposed to help them to recover from the virus, he said. Ackerman believes such dire consequences can be avoided easily if physicians carefully evaluate vulnerable patients.

WHO guidance and some clinical evidence do not recommend the use of corticosteroids for COVID-19.

Infection control measures and diagnostic testing

All patients, including pregnant women, should be evaluated for fever and signs and symptoms of a respiratory infection. Ideally, screening procedures begin before arrival on a labour and delivery unit or prenatal care clinic.

When scheduling appointments,

- Patients should be instructed what to do if they have respiratory symptoms on the day of their appointment or if a patient calls triage prior to presentation.
- Respiratory signs and symptoms should be assessed over the telephone.
- Those patients with respiratory symptoms should be separated from other waiting patients and a facemask should be placed on them.
- Patients who meet criteria for a Person Under Investigation should be immediately placed in an Airborne Infection Isolation Rooms (single-patient rooms at negative pressure).
- Once in isolation, the patient's facemask may be removed.
- Healthcare personnel should adhere to standard, contact and airborne precautions.
- Infection control personnel and local/state health departments should be notified immediately; local/state health departments can help to arrange testing of relevant specimens (upper and lower respiratory specimens and serum are currently recommended; other specimens [stool and urine] may also be sent).

Conclusion

Pregnant women are likely to cause any contagious disease outbreaks due to their altered physiology, susceptibility to infection, and compromised mechanical and immunological functions.

The need to protect the foetus adds to the challenge of managing the health of the mother. Special precautions are required to reduce cross-infection of healthcare providers, while performing procedures that require clinical contact and promote droplet proliferation, such as vaginal delivery.

The majority of the obstetric management is based on consensus and best practice recommendations as to clinical efficacy data regarding anti-viral medical and corticosteroid use is evolving. This narrative represents an integrated framework to provide appropriate levels of care for these patients and hospital staff during the COVID-epidemic.

Md. Mohammad Faiyaz Anwar
Project Scientist, Vigyan Prasar