

Management of COVID-19 infection in antenatal, laboring, post-partum women and their newborns: a narrative review

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ABSTRACT

COVID-19 outbreak was declared a global pandemic of international concern in March 2020 by the World Health Organization. It has affected millions of people including pregnant women and children across the globe. Severe COVID-19 infection though rare in pregnancy is associated with high chances of maternal and neonatal morbidity and mortalities. The present review briefs the management of mild, severe, and critical COVID-19 infection in antenatal, laboring, and postpartum women and their newborns. Recent literature was searched from various English language peer-reviewed journals from the PubMed database, governmental sites including World Health Organization, centers for disease control and prevention, and the official site of the Royal College of Obstetricians and Gynecologists and American College of Obstetricians and Gynecologists using search terms like COVID-19 infection in pregnant women; Management of COVID-19 infection in pregnancy; breastfeeding and neonatal care in COVID infected mothers, COVID-19 vaccination. Hence, it was observed that appropriate and timely management of COVID-19 infection in pregnancy is essential and can save the lives of both mother and fetus. Furthermore, with the start of vaccination in pregnant and lactating mothers, the chances and severity of disease in both mothers and fetuses can be prevented to a large extent. Prevention from infection, timely management, and vaccination against COVID-19 infection in pregnant and lactating women are the only effective ways of combating this disease.

Keywords: Antenatal care, COVID-19, delivery, newborn, pregnancy.

COVID-19 infection is caused by Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) belonging to the subfamily Coronavirinae, family *Coronaviridae* and order Nidovirales. These enveloped, spherical, or pleomorphic single-stranded RNA containing viruses are known human pathogens.¹ The virus enters the human cell through a multistep process in which it uses its receptor-binding domain located on the spike (S) glycoprotein to identify angiotensin - converting enzyme 2 (ACE2) receptors present on the cells; thereby starting host-cell entry by encouraging viral-host cell membrane fusion by bringing major structural changes in the S protein.²

Search strategy and selection criteria

Recent literature was searched from various English

language peer-reviewed journals from PubMed database, governmental sites including World Health Organization, Centers for disease control and prevention, and the official site of the Royal College of Obstetricians and Gynecologists and American College of Obstetricians and Gynecologists till October 2021 about the antenatal, intranatal and postpartum management of women with COVID-19 infection and care of their newborns using search terms like COVID-19 infection in pregnant women; management of COVID-19 infection in pregnancy; breastfeeding and neonatal care in COVID infected mothers, COVID-19 vaccination.

Transmission

COVID-19 infection is highly contagious. It spreads from

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human to human via droplets or direct contact. It can also spread through indirect routes like when a person with contaminated hands with virus-containing droplets touches the mucous membranes of the mouth, nose, and eyes, leading to infection.³ Recent studies have demonstrated vertical transmission of the virus from mother to fetus, especially in the third trimester.⁴ Hence, with rising cases of COVID-19 infection in antenatal women all over the world and its transmission to the fetus in-utero, intrapartum, or in the early postpartum period is of serious concern.

Symptoms

The incubation period for the COVID-19 infection ranges from 1-14 days⁵ or on average 5.1 days⁶. The symptoms in pregnancy range from mild to severe with the majority of women remaining asymptomatic.⁷ The most common symptoms reported were cough, sore throat, mild fever, headache, and body aches. Less common symptoms include breathing difficulties (dyspnea), myalgia, loss of taste or smell, and gastrointestinal symptoms including nausea, vomiting, and diarrhea. Severe disease though rare in pregnancy, is of major concern, as it is associated with high maternal and neonatal morbidity and mortality.⁸ COVID-19 infection has been classified into four types depending on the severity of the disease as⁹ -

Mild infection: Patients with mild disease have symptoms of upper respiratory tract infection including cough, throat soreness, rhinorrhoea, or anosmia, gastrointestinal symptoms with or without fever or myalgia.

Moderate infection: Patients have mild pneumonia confirmed by chest X-ray, with basal SpO₂ ≥94%, persistent high-grade fever, and do not need vasopressors or ventilatory assistance.

Severe infection: Patients present with features of severe pneumonia, respiratory rate >30/min, breathlessness, chest retraction, SpO₂<94% at room air, need for ventilatory support and or vasopressors, radiological evidence of bilateral infiltrates, hypotension.

Critical infection: The presence of any of these signifies critical disease – acute respiratory distress syndrome (ARDS), sepsis, septic shock, pulmonary embolism, acute coronary syndrome, or ≥1 organ failure.

Recognition of the severity of the disease and its time management is key to successful treatment of COVID-19 infected patients especially pregnant women as they may present with sudden deterioration if not managed appropriately.⁹

Management of COVID-19 infection in pregnant women

The management of COVID-19 infection in a pregnant woman depends on the severity of the disease. Figure 1 depicts the severity-wise management of COVID-19 infected antenatal women.

- In mild cases, the woman can isolate herself at home with strict self-monitoring, as most of them do not require hospitalization.¹⁰
- In moderate cases, women should be admitted to the hospital COVID ward for patient care and management.
- In severe and critical cases, women should be admitted to Intensive Care Units (ICU) under the supervision of a multidisciplinary team consisting of a senior obstetrician, pediatrician, neonatologist, pulmonologist, and anesthetist. According to a recent living systematic review, it was found that pregnant women with COVID-19 infection were at a higher risk of admission to the intensive care unit, invasive ventilation, and maternal death.¹⁰

Women with high-risk factors (age ≥35 years, BMI≥25Kg/m², co-morbidities like pre-existing diabetes, chronic hypertension, obstructive pulmonary disease, organ transplant recipient, or on immunosuppressant) should be admitted to the hospital even if they have mild or asymptomatic infections.

Investigations -

Routine investigations including complete blood count

Box 1: Reference values

d-Dimer: 1 st trimester: 167-721 ng/mL
2 nd trimester: 298-1653 ng/mL
3 rd trimester: 483-2256 ng/mL
IL-6: 0-16.4 pg/mL
CRP: Up to 6mg/L
LDH: 200 - 400 IU/L
aPTT: 30-40 seconds
PT: 1 st trimester: 9.7-13.5 seconds
2 nd trimester: 9.5-13.4 seconds
3 rd trimester: 9.6-12.9 seconds

(CBC), blood grouping and Rh factor, viral markers (HIV, VDRL, HBsAg), fasting and postprandial blood sugar levels, and urine microscopic examination should be done in all cases. In addition to this liver function test (alanine transaminase, aspartate aminotransferase, alkaline phosphatase, albumin, and bilirubin) and renal function test should be done. In cases with moderate to severe/critical

disease, d-Dimers, interleukin-6 (IL-6), C-reactive proteins (CRP), lactate dehydrogenase (LDH), coagulation profile (activated partial thromboplastin time, prothrombin time), chest X-ray/computed tomography (with abdominal shield, if needed) and obstetric ultrasound for fetal wellbeing should be done. The reference values for various tests in pregnant women are depicted in box 1.

Management of COVID-19 infection in laboring women

- **Mild/Asymptomatic Cases:** Women with mild or asymptomatic infection should be advised to stay at home in the latent phase of labor and should be advised to visit the hospital for delivery once they enter into established labor.⁸ They should be counseled about the signs and symptoms of active labor (increased frequency intensity and duration of labor pains, presence of show or leaking per vaginum) and warning signs of deterioration of the COVID-19 disease. There is no need for continuous electronic fetal monitoring (CEFM) using cardiotocography (CTG) in such cases and should be considered only when needed as in cases with previous cesarean section, and intrauterine growth restriction.⁸ Furthermore, to date, no evidence suggests that asymptomatic COVID-19 infection results in pathological changes in CEFM.¹¹ A recent study of 224 pregnant women infected with COVID-19 analyzed the correlation of CTG traces with the severity of COVID-19 infection and observed no statistically significant relationship between COVID-19 severity and CTG category. They concluded that though the maternal COVID-19 infection resulted in changes in fetal CTG traces due to maternal hypoxia, inflammatory response, fever, uterine irritability, and placental thrombosis, these changes were not found to be associated with the severity of the disease and adverse neonatal outcomes.¹² Hence, in mild disease, CEFM is not mandatory but may be considered for obstetric causes.
- **Moderate/Severe cases:** These women should labor and deliver in obstetric units. On admission, a thorough assessment of the severity of COVID-19 infection should be done by the senior obstetrician, followed by a detailed examination for confirmation of onset of labor, gestation, pelvis assessment, and fetal status. Continuous electronic fetal monitoring using CTG should be done in all cases for better neonatal outcomes.⁸

Mode of delivery

Time and mode of delivery should be decided based on maternal status, co-morbidities, gestational age, and patient preferences. COVID-19 status of antenatal women does not alter the mode of delivery.^{8,13} This is supported by a recent cohort study conducted in SARS-CoV-2 infected pregnant women giving birth in Spain to establish any association between mode of delivery (vaginal vs cesarean delivery) and maternal and neonatal birth outcomes. The study observed that none of the patients with vaginal delivery developed severe adverse outcomes, whereas 13.5% of women delivered by cesarean section required intensive care unit admission. Furthermore, only 19.5% of neonates delivered vaginally required NICU admission as compared to 29.7% delivered by cesarean section. Hence, concluded that women with vaginal birth had better outcomes.¹⁴ Other studies have also reported that the COVID-19 status of pregnant women is not the deciding factor for the mode of delivery, instead, the mode of delivery should be individualized and based on obstetric indications and maternal-fetal condition.^{15,16} Hence, the mode of delivery should be discussed in detail with the woman and her family. Unless indicated all women should be allowed to go into spontaneous labor. For obstetric indications labor can be induced using various pharmacological or non-pharmacological methods like misoprostol, cerviprime gel, foley's catheter, etc. or a planned cesarean section can be done.

Elective or planned cesarean sections should be done at the end of the posted operating list, whereas emergency cesarean sections of positive women should be done in a separate operation theater taking all universal precautions and wearing PPE by the health professionals and staff.⁸

Time of delivery

- **Mild/ Moderate Cases:** The timing of delivery should be decided by the obstetric indications and not by the maternal COVID-19 infection status and the delivery can be safely conducted at ≥ 39 weeks, in absence of any medical/obstetric indications for prompt delivery.¹³
- **Severe/Critical Cases:** Delivery should be conducted between $>32-34$ weeks of gestation to prevent further worsening of the pulmonary situation and maternal hypoxemia leading to fetal compromise.^{17,18} Steroids for fetal lung maturity and magnesium sulfate as fetal neuroprotective agents should be considered in these cases.⁸ Furthermore, due to lack of evidence, it was concluded by an expert consensus panel that the route and timing of delivery should be individualized based

on obstetrical indications, maternal-fetal status, and gestational age at the time of delivery.¹⁶

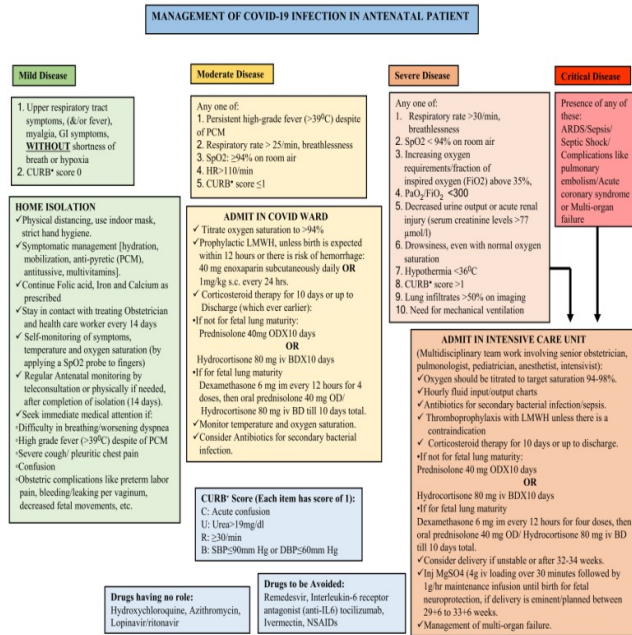


Figure 1: Management of COVID-19 infection in the antenatal patient

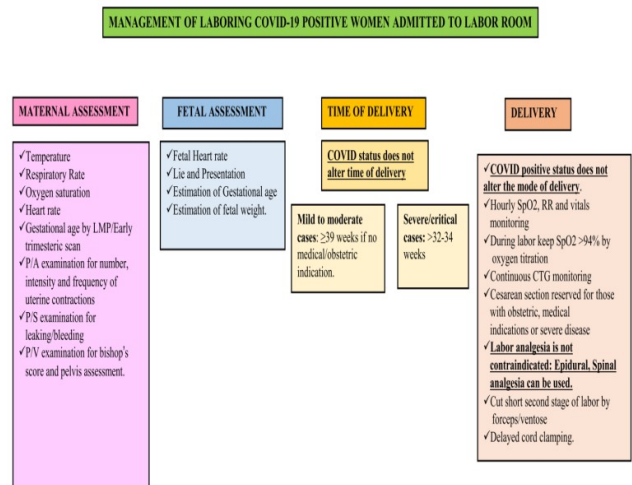


Figure 2: Depicts labor management in women with COVID-19 infection.

Labor analgesia/anesthesia -

Epidural analgesia in early labor in women with symptomatic COVID-19 infection is safe and beneficial as it obviates the need for general anesthesia in cases where

urgent intervention is needed for the fetal outcome. Both epidural and spinal analgesia or anesthesia are not contraindicated in laboring women with COVID-19 infection,⁸ instead, neuraxial anesthesia is the preferred technique for operative deliveries in pregnant women with COVID-19 infection.^{19,20}

Care during the intrapartum period⁸ -

- Women should wear a mask throughout their delivery.
- Titrate oxygen flow to maintain saturations between 94-98%.
- The second stage of labor can be cut short using forceps or ventose to avoid maternal exhaustion or distress.

Delayed fetal umbilical cord clamping: A recent randomized controlled study of immediate versus delayed umbilical cord clamping in infants delivered by cesarean section reported that infants with delayed cord clamping had greater hematocrit and bilirubin values at 72 hours as compared to infants with immediate cord clamping.²¹

Drugs/Medications for pregnant women with severe COVID-19 infection

- Steroids: Corticosteroids modify the inflammatory response resulting in a state of immunosuppression by reducing the concentration of circulating proinflammatory mediators like tumor necrosis factor-alpha, interleukin-1, and interleukin-6, and hence, prevent the development of ARDS, a major cause of death in patients with severe COVID-19 infection.²² Oral prednisolone or intravenous hydrocortisone is recommended in pregnant women with moderate-to-severe COVID-19 infection.^{23,24}
- Low molecular weight heparin: Coronavirus induces inflammatory response and activates thrombin as evidenced by the rise in D-dimer concentrations (>1 µg/mL) which is considered an indirect marker of increased thrombin generation and is associated with increased risk of mortalities. Anticoagulant treatment with low-molecular-weight heparin should be considered in pregnant women with severe COVID-19 infection.²⁵⁻²⁷
- Remdesivir: Remdesivir (GS-5734), acts as an inhibitor of the viral RNA-dependent RNA polymerase and prevents in vitro viral replication.²⁸ As human data for the use of this drug in pregnant women with COVID-19 is very scarce.²⁹ Hence, its use in pregnant women is not recommended, unless and until the physicians

believe that its benefits outweigh the risk associated with its use.

- Anti-SARS-CoV-2 monoclonal antibodies: The anti-SARS-CoV-2 monoclonal antibodies can be recommended in pregnant people with COVID-19, who are at risk for severe disease due to the presence of additional risk factors.³⁰

Oxygen therapy in pregnant women with COVID-19 infection: when, how, and how long?

Oxygen therapy is the initial treatment for pregnant women with features of hypoxemia. It is recommended to start oxygen therapy in pregnant patients when SpO₂ values drop below 94% as compared to <92% in nonpregnant cases. This is due to physiological changes associated with pregnancy including increased oxygen demand and partial pressure of oxygen. Therapy should be titrated in such a way as to avoid SpO₂ levels above 96%.^{31,32} Oxygen therapy can be given by using the following ways: Conventional nasal cannula with an oxygen flow of 1-6L/min (provides oxygen concentration between 24%-40%); Conventional face mask with an oxygen flow rate of 5-10L/min (provides oxygen concentration of 40%); Venturi mask, similar to conventional face mask but provides a more controlled FiO₂ (oxygen concentration 24-50%); Partial rebreather mask with an oxygen flow of minimum 10L (provides oxygen concentration of 60-70%) and Nonrebreather mask with an oxygen flow rate of minimum 10L (provides oxygen concentration of 80%).³² In pregnant women who fail to improve with conventional oxygen therapy and have no indication for immediate intubation, can be put on a high-flow nasal cannula. These nasal cannulas allow oxygen flow as high as 60 L/min, and FiO₂ can be titrated more accurately as compared to conventional nasal cannulas. It is used with an initial flow of 50-60 L/min with a FiO₂ of 1.0 (100% oxygen) and once the FiO₂ is maintained at 0.4 - 0.5, the flow can be decreased gradually by 5 - 10 L/min every 4-6 hours till the SpO₂ levels of more than 94% are maintained by the patient. Another major advantage of the high-flow nasal cannula is that it does not increase the risk of transmission of respiratory viruses including coronavirus.³² In pregnant women with cardiogenic pulmonary edema or chronic obstructive pulmonary disease, noninvasive positive pressure ventilation is ideal, but unlike high-flow nasal cannula, noninvasive positive pressure ventilation is associated with an increased risk of disease transmission to health care professionals due to its aerosol-generating properties.^{32,33}

Need for intubation in a pregnant woman with COVID-19 infection

According to a recent study around 5-10% of pregnant women with COVID-19 require intubation and mechanical ventilation.³⁴ Severe COVID-19 infection in pregnant women is associated with high maternal mortality. Hence, intubation and mechanical ventilation are recommended in pregnant women with severe disease,³⁵ and the two main indications for intubation in pregnant women include ARDS and respiratory failure.^{36,37} A recent cohort study on 64 hospitalized pregnant women with COVID-19 infection with 44 having severe disease, and 20 critical COVID-19 diseases observed that intubation was performed on day nine of disease in most of the cases with severe disease. Prone positioning was tried in 20% of women with the critical disease and the rate of ARDS was 70%, with the requirement of reintubation in 20% of cases.³⁵ Hence, intubation and mechanical ventilation should be considered in women with severe/critical diseases.

Management of COVID-19 infection in postpartum women and their newborns^{8,13}

- “Rooming-in” of mother and newborn should be allowed if both are in stable condition.
- For preterm or low birth weight baby kangaroo care by the mother is not contraindicated.
- Breastfeeding should be recommended to all women.
- Wash hands before touching the baby or breast pumps.
- Wear a face mask while feeding the baby.
- Avoid coughing and sneezing while feeding.
- Wash hands before and after touching the baby.
- The baby should not wear a mask.
- Avoid visitors.
- Contraception advises.
- Prophylactic anticoagulation in women with severe/critical disease.

Newborn care^{8,13}

- Test for SARS-CoV-2 RNA by Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) at 24 hours of age, if negative repeat at 48 hours of age.
- Take either a single swab of the nasopharynx or a single swab of the throat followed by the nasopharynx, or two separate swabs from the nasopharynx and throat.
- Neonatal rooming-in with mother and start breastfeeding as early as possible.
- Consider routine Immunization of baby.

Vaccination of pregnant and lactating women against COVID-19 infection

Recent guidelines have recommended vaccination of all women including pregnant, breastfeeding, trying to get pregnant, or who might become pregnant in the future against COVID-19. Vaccine against COVID-19 is found to be safe in pregnant and lactating women.³⁸ A study reported that COVID-19 vaccines generate strong humoral immunity in pregnant and lactating women and result in immune transfer to the neonates through placental and breast milk as the SARS-CoV-2 specific antibodies were found in breast milk and umbilical cord blood of these mothers.³⁹ Both the American College of Obstetricians and Gynecologists and RCOG recommends that all pregnant women and lactating mothers should receive the vaccine against COVID-19, as vaccination is the only way to protect pregnant women and their newborns from the risks of COVID-19.^{40,41} Furthermore, COVID-19 vaccines can be safely administered within 14 days of receipt of another vaccine, including influenza and Tdap vaccine which are routinely given to pregnant women.⁴¹ A recent study from 366 human milk samples taken from 26 lactating women reported the presence of SARS-CoV-2 specific antibodies in human milk after vaccination with mRNA-based COVID vaccine. They also concluded that these SARS-CoV-2 specific IgA antibodies in breast milk can be transferred to newborns thereby playing a crucial role in the passive transmission of protection to infants against COVID-19.⁴² Another study in 122 pregnant women vaccinated against COVID-19 during pregnancy reported that all women and their fetal umbilical cord blood samples after delivery (except for one), had detectable IgG antibodies by 4 weeks after the first dose of vaccine. They observed that the levels of maternal IgG increased over time and the increasing levels of placental IgG transfer ratio with time might help in deciding the timing between vaccination of pregnant women and birth so that there is a maximum transfer of antibodies to the baby.⁴³ Hence, it has been recommended to vaccinate pregnant and lactating mothers against COVID-19 and these vaccines are not found to be associated with any adverse outcomes in mothers and neonates.⁴⁴

Conclusion

Management of COVID-19 infection in pregnant women is in itself a major topic as it involves two lives. With the rising number of cases amongst antenatal women and increasing evidence that it is associated with adverse maternal and neonatal outcomes, its management becomes

very crucial. Limited data is available on the impact of COVID-19 infection on pregnancy and its management to date and many new guidelines are emerging as we are getting a better understanding of the virus and its complications.

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