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Updates on the Management of Sar-Cov-2 Infection in Pregnancy and Postpartum

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Abstract

Coronavirus disease (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2. The disease sparked a global health crisis that claimed more than 6 million lives worldwide. Pregnant women are particularly susceptible to the disease due to altered hemodynamic, respiratory and immunological responses. The aim of this chapter is to provide a holistic insight into the management of COVID-19 in pregnancy and postpartum from the perspective of India and the world.

Keywords: SARS-CoV-2; Coronavirus; Immunological Responses; Hemodynamic Respiratory; Postpartum; Pregnancy; Glycoproteins; Envelope Proteins; Severe Acute Respiratory Distress Syndrome; Epidemiology; Sexual Transmission

Abbreviations: SARS: Severe Acute Respiratory Distress Syndrome; ACE2: Angiotensin-Converting Enzyme 2; qRT-PCR: Quantitative Reverse Transcriptase Polymerase Chain Reaction; IL6: Interleukin-6; JAK: Janus kinase Inhibitors; SMFM: Society of Maternal Fetal Medicine; EMCO: Extracorporeal Membrane Oxygenation; WHO: World Health Organisation; ACOG: American College of Obstetricians and Gynaecologists; RCOG: Royal College of Obstetricians and Gynaecologists.

Introduction

SARS-CoV-2 is a beta coronavirus with a core and an envelope containing spike glycoproteins, envelope proteins and membrane proteins. It contains a positive strand of RNA as genetic material. The virus belongs to the same subgenus as the severe acute respiratory distress syndrome (SARS) virus. Infection with SARS-CoV-2 leads to COVID-19.

Epidemiology

Source of infection – Bats are the primary source of infection. The role of the intermediate host in the transmission of the coronavirus is unknown.

Route of Transmission

- The main mode of transmission is inhalation or direct contact of the infected respiratory droplets with mucous membranes at a close range (within six feet or two meters of face to face for fifteen minutes).
- Transmission though fomites (touching of mouth, eye, or nose after touching contaminated surfaces).
- Aerosol transmission (at a contact distance of more than two meters), especially in closed, poorly ventilated

environments.

- Transmission through feco-oral route
- Sexual transmission is not known for coronavirus

The host is most contagious just before the onset of symptoms and during the first five days, when the concentration of the virus in the respiratory tract is highest.

Pathogenesis

The virus target cells bearing angiotensin-converting enzyme 2 (ACE2) receptors are located primarily in the upper respiratory tract and oropharynx and, to a lesser extent, in the conjunctiva and gastrointestinal tract. The spike protein on the coronavirus envelope binds to the above target receptors and to the host's trans membrane serine protease 2. This promotes membrane fusion, releasing the viral genome into the host's cytoplasm, where the virus replicates its genome and synthesizes viral proteins. This is followed by virus assembly, maturation and release. In mild illness, the host immune response (particularly the T cell response) can effectively clear the infection. However, an increased and overwhelming immune response leads to organ damage, severe morbidity and death.

Clinical Features

The incubation period of 5 to 6 days is followed by a symptomatic illness featured by cough, fever, mayalgia, headache, dysopnea, sore throat, diarrhoea, nausea/ vomiting, anosmia, ageusia, rhinorrhoea, chills/rigors, fatigue, confusion, and chest pain.

Risk Factors for Severe Disease Include

- Type 1 or type 2 diabetes
- Chronic kidney, heart diseases (acquired or congenital), liver, or lung disease
- Patients on renal replacement therapy
- Confection with HIV
- Obesity (body mass index of 25 kg/m^2 or more)
- Hemoglobinopathies (sickle cell anaemia, thalassemia)
- Pregnancy or a history of recent pregnancy
- Immunocompromised patients or patients on immunosuppressive therapy
- Organ transplant recipients
- History of venous thromboembolism

Diagnosis

- Viral RNA in respiratory swabs can be detected by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) for approximately 17 days (up to 83 days maximum) after the infection. They are not a reliable measure of infectiousness.

Viral Culture: Upper respiratory tract viral load peaks in the first week after symptoms appear. After that it gradually decreases. Therefore, culture is rarely positive after 9 days of symptom onset. However, prolonged viral shedding via respiratory droplets may be observed in immunocompromised patients.

Serology: It takes up to 2 weeks for antibodies to the virus spike protein and the nucleocapsid to appear in the serum.

Other Laboratory Parameters: The following laboratory markers are deranged in a SARS-CoV-2 infection

- Hemogram – Neutrophilia, lymphopenia (absolute lymphocyte counts below 800/microlitre in severe disease).
- Increased levels of serum lactate, lactate dehydrogenase (more than 245 U/L in severe disease), C-reactive protein (≥ 75 mg/L in severe disease), ferritin (more than 500 mcg/L in severe disease), interleukin-6 (IL6), ACE-2, D-dimer (more than 1 microgram/mL indicates severe disease) and troponin (twice the upper limit of normal).
- Others- Procalcitonin, liver and kidney function tests.

Lung Imaging: Chest X-ray and Chest CT scans- linear and fluffy opacities.

Treatment-General Principles of Management

- The approach to treating of COVID-19 depends on the severity of the disease and the need for supplemental oxygen therapy and ventilatory support.
- Drugs primarily used in the treatment of COVID-19 include:
- Dexamethasone
- Remdesivir - A nucleotide analogue that inhibits RNA-dependent RNA polymerase.
- Immunomodulators – Tocilizumab (a recombinant humanized IgG1monoclonal antibody against interleukin 6 (IL6), and baricitinib (Janus kinase/JAK inhibitor with immunomodulatory and antiviral properties).
- Others
- Ivermectin – An anthelminthic used for the prevention of strongyloidiasis
- Vitamin D, in the presence of vitamin D deficiency
- Convalescent plasma
- Infliximab (TNF inhibitor), abatacept (a selective T-cell stimulatory blocker), anakinra (interleukin-1 inhibitor), viloblimab (monoclonal antibody against complement C5a).

Depending on the Severity, COVID-19 can be Broadly Categorized into the Following Categories:

Mild Disease: It is characterized by fever, malaise, cough, and upper respiratory tract symptoms without dysopnea.
Moderate Disease: Features of mild disease with dyspnoea with or without pulmonary infiltrates on chest X-ray that do not fall into the severe illness category.

Severe Disease: It is characterized by hypoxemia, i.e, oxygen saturation (SpO_2) of 94% or less on room air with or without the need for oxygen or ventilatory support.

The Society of Maternal Fetal Medicine (SMFM) has also laid down a classification system and standard of care for the management of COVID-19 in pregnancy [1]. (see the section on COVID-19 and pregnancy) (Table 1).

Category of Illness	Asymptomatic Infection	Mild Disease	Moderate Disease	Severe Disease	Critical Disease	Refractory Hypoxemia
Signs and symptoms	No symptoms	Flu-like symptoms (fever, cough, myalgias, and anosmia without dyspnoea)	• Lower respiratory tract disease	• RR >30 bpm	• Multi-organ failure	Persistent inadequate oxygenation and/or ventilation (PaO_2 <70 mm Hg or a PF ratio <150 mm Hg) despite substantial and appropriate measures
			• Pneumonia on chest imaging	• SpO_2 <94%	• Shock	
			• Temperature ≥102.2°F not relieved by acetaminophen	• Imaging shows >50% lung involvement	• Respiratory failure requiring mechanical ventilation or high flow oxygen therapy	
			• SpO_2 ≥ 94% on room air	• PF ratio of <300 mmHg		
Management	If no comorbidities/ obstetric complications/ high risk factors for severe disease: Home isolation		Inpatient management in ward	In patient management in ICU		
	If any present: In patient management in ward					

Table 1: The SMFM classification of COVID-19 in pregnancy [1].
PF ratio, PaO_2/FiO_2; SpO_2, oxygen saturation; RR, respiratory rate; bpm, breaths per minute

Further Management of COVID-19 depends on the need for Supplemental Oxygen and Ventilation:

I. Those who are not eligible for supplemental oxygen therapy:

- Remdesivir should be initiated in the presence of risk factors for severe illness.
- In an absence of risk factors for severe illness, remdesivir is not indicated and supportive therapy is the main stay.

II. Those who are eligible for supplemental oxygen therapy or ventilatory support.

a. Low Flow Oxygen

- Remdesivir should be initiated when oxygen requirement is very low i.e., 1-2 L/min
- For low flow oxygen requirement greater than 1-2 L/ min.
- Treatment with low dose dexamethasone and remdesivir is initiated.
- Baricitinib or tocilizumab should be administered on a case-by-case basis, if the need for oxygen supplementation increases or the levels of inflammatory mediators rise within 96 hours of admission.

b. High-Flow Oxygen or Non-Invasive Ventilation

- Dexamethasone is started in low doses.
- Treatment with baricitinib or toculizumab is initiated within 24 to 48 hours of ICU admission and within 96 hours of hospitalisation.
- Remdesivir can be started in immunocompromised patients.

c. Mechanical Ventilation or Extracorporeal Membrane Oxygenation (EMCO)

- Dexamethasone is initiated in low doses

- Baricitinib or toculizumab should be added within 24 hours of ICU admission and 96 hours of hospital admission.
- Remdesivir is not required, unless the duration of endotracheal intubation is short. However, clinical evidence to support this practise is lacking.

If dexamethasone is not available, hydrocortisone, methylprednisolone or prednisone can always be used.

SARS-CoV-2 Infection during Pregnancy and Postpartum

Effect of Pregnancy on the Course of COVID-19

- Pregnancy is one of the risk factors for severe COVID-19 illness. However, pregnancy per se does not increase the risk of SARS-CoV-2 infection, and most (>90%) of the pregnant women infected with the virus develop mild or asymptomatic COVID-19 illness and recover without hospitalisation.
- Severe COVID-19 illness is more common during pregnancy if the woman has symptoms, is older than 35 years of age or has one or more of the risk factors (see section on risk factors for severe illness).

Effect of COVID-19 on Pregnancy

COVID-19 is also associated with the risk of preterm birth and neonatal mortality. However, there is no increase in stillbirth rates compared to the general population.
Most COVID-19 positive new-borns remain healthy.

- Vertical transmission of COVID-19 during pregnancy has been reported in 0.3% of cases.
- The diagnostic criteria for congenital COVID infection (intrauterine transmission) were developed by Shah PS, et al. [2]. It requires a positive SARS-CoV-2 PCR test in one or more of the following samples:
  - Umbilical cord blood at the time of birth. It indicates a confirmed infection
  - Neonatal blood collected within the first 12 hours after birth. This indicates a probable infection
  - Amniotic fluid collected before membrane rupture. This indicates a possible infection [2].

Additional criteria for diagnosing intrauterine transmission of COVID-19 are based on the positive RT-PCR nasopharyngeal swab tests in the first 24 hours of life which persists even upon retesting. There are in addition theoretical concerns about hyperthermia related neural tube defect and spontaneous abortion if the infection was acquired during the organogenesis period. Recent evidence also suggests an increased risk of preeclampsia, stillbirth, and psychiatric disorders in these women, as well as long term neurocognitive abnormalities in their offspring's. Furthermore, there is an increased risk of adverse fetal outcomes if the infection occurs in the second half of pregnancy.

Management of COVID-19 during Pregnancy-General Considerations

- The number and duration of each hospital visit may be shortened depending on the risk assessment.
- No additional testing is recommended for asymptomatic or mildly symptomatic women.
- Routine prenatal examinations should be postponed until the end of the isolation period.
- Invasive fetal testing does not increase the risk of intrauterine transmission of the virus.

Home Isolation in Asymptomatic or Mildly Symptomatic Cases [3]

- The woman should stay in a well-ventilated room with cross ventilation.
- Sharing personal items is not recommended
- Surfaces should be cleaned with 1% hypochlorite solution.
- Women should wear a triple layer mask, which should be discarded every 8 hours or sooner.
- Hand hygiene (frequent washing of hand with soap and water for at least 40 seconds/ cleaning of hand with an alcohol-based sanitizer) and respiratory etiquettes should be followed.
- The woman should remain rested (prone or lateral position), drink enough fluids and eat a balanced diet.
- Symptomatic treatment of fever, running nose and cough is recommended [3].

Fever

- Acetaminophen is the preferred antipyretic and analgesic, including in the first trimester. Doses up to 2 g of acetaminophen may be administered unless severe hepatic impairment is present.
- NSAIDs may be added if fever is not controlled with the maximum dose of acetaminophen. NSAIDs should be administered at the lowest effective dose and only when indicated and preferably for less than 48 hours due to the risk of oligohydramnios and premature ductus closure.
- Aspirin therapy is not indicated to improve COVID-19 related outcomes; however it may be used for obstetric indications, such as prevention of preeclampsia.

If cough or fever persists for more than 5 days, inhalational budesonide (DPI/MDI) with spacer can be administered at a dosage of 800 mcg twice daily for 5 to 7 days. Ivermectin and doxycycline should not be administered during pregnancy.

Self-Monitoring and Recording of Temperature, Heart Rate and SpO_2 should be done four times daily, and the Woman should Contact a Doctor Immediately if she Experiences any of the Following Danger Signs/Symptoms.

- Worsening of dyspnoea or presence of tachypnoea
- Unable to tolerate oral fluids or medications
- Persistent pleuritic chest pain
- New onset lethargy or confusion
- Obstetrical conditions such as preterm labour, vaginal bleeding, reduced fetal movement
- Incessant fever above 30 °C despite antipyretics
- SpO_2 <95% at rest or during exertion
- Cyanosis (peripheral or central)

Timing of Obstetric Ultrasound

If the infection was acquired during, First Trimester: An obstetric ultrasound should be advised between 18 and 22 weeks after recovery.
Later Trimesters: Ultrasound obstetrics, if indicated, can be performed after 2 weeks of infection.

Inpatient Management of Covid-19 Positive Patients

- Testing for COVID-19 – The Government of India recommends that no delivery procedure should be withheld or the patient denied treatment due to the unavailability of testing procedures [3].

- **Investigations:**

➢ CRP and D-dimer levels are usually elevated during pregnancy and therefore should not be used to assess disease severity.

➢ Chest x-rays in pregnant women involve very low levels of radiation exposure (0.01 milligray). CT chest examination should not be withheld when indicated because exposure is low (0.01–0.66 milligray) and is not associated with congenital fetal anomalies or fetal loss. Lung ultrasound can be a useful aid in pregnant women when radiation exposure is a concern.

Prone Position

- For pregnant women at 24 weeks of gestation, padding should be applied at top and bottom positions to relieve aortocaval compression in the prone position. If the woman cannot achieve such a position, a left-lateral position is acceptable.

Drug Therapy for COVID-19 during Pregnancy

- **RNA Polymerase Inhibitor– Remdesivir**

➢ It is also used to treat Ebola and Marburg virus infections in pregnancy.

➢ It is not known whether it can cross the placenta, however, no major fetal adverse effects on fetus have been reported from its use.

➢ **Dose:** Intravenous 200 mg of the drug is administered on the first day, then 100 mg for a total of 5 to 10 days; it should preferably be started within 10 days of the onset of illness.

- **Immunomodulators IL-6 Inhibitor – Tocilizumab and Baricitinib**

➢ **Dose:** Tocilizumab – Intravenous 8 mg/Kg of the drug is given as a single dose; Baricitinib – Oral 4 mg is given once a day for 14 days or less.

➢ There are very few data on the use of other cytokine inhibitors in pregnancy like such as Sarilumab (anti-IL-6 inhibitor), Siltuximab (direct IL-6 inhibitor), and Anakinra (IL-1 inhibitor).

➢ To date, tocilizumab has not been associated with major fetal toxicity.

- **Janus kinase (JAK) Inhibitors**

➢ It is not known for certain whether baricitinib can cross the placenta. Studies in animal models have shown the risk of fetal skeletal anomalies and reduced fertility with JAK inhibitors. The patient should be informed about the risks and benefits before starting therapy.

➢ Tofacitinib can also be used. To date, no drug related fetal toxicity has been reported with this drug.

Supplemental Oxygen Therapy and Ventilation

- In pregnant patients, an oxygen saturation of 95% or more and no less than 92% is desirable.
- A maternal PaO_2 of >70 mmHg the desired PaO2 and PCO2 with is required for adequate placental perfusion.
- Patients who cannot maintain oxygenation should receive other methods of ventilation (non-invasive or invasive ventilation). Important points to consider in this regard are:

➢ $PaCO_2$ should be aimed at the range of 30-32 mmHg as respiratory alkalosis reduces uterine blood flow.

➢ During ventilation with high positive end-expiratory pressure (PPEP) >10 mmHg, close maternal and fetal monitoring should be performed due to the risk of excessive decreases in cardiac preload and afterload.

➢ In cases of refractory respiratory failure, extracorporeal membrane oxygenation is indicated during pregnancy.

- **Invasive Ventilation is Indicated if, an Oxygen Saturation (SpO_2) of 95% is maintained with the Following:**
  - Oxygen therapy at a rate of 15 L/minute through a mask or nasal cannula.
  - Oxygen therapy at a rate greater than 40-50 L/minute through a High Flow Nasal Cannula.
  - Oxygen therapy with a venturi mask at a FiO_2 of more than 60% [3].
  - Airway protection is required due to an altered mental status.

Venous Thromboembolism Prophylaxis

- The risk of venous thromboembolism appears to increase in pregnant women with SARS-CoV-2 infection, particularly in those with severe disease.
- Women should walk and drink enough fluids. Heparin is recommended for the prevention of venous thromboembolism in all, but not in asymptomatic patients unless indicated for other reasons [4].
- Low molecular weight heparin is recommended in prophylactic doses for mild disease and in therapeutic doses for moderate to severe disease. Treatment should be continued for 10 days after hospital discharge or longer if morbidity persists. Heparin may be discontinued in post-caesarean section patients if discharge and home isolation are planned

Steroid Therapy

- Pregnant women with COVID-19 who are receiving supplemental oxygen therapy or mechanical ventilation should receive dexamethasone 6 mg orally or intravenously once daily for 10 days or until discharge, whichever is less.
- If steroid therapy is also indicated for fetal lung maturity, the SMFM recommends administration of the standard fetal lung maturity dose (intravenous dexamethasone 6 mg, every 12 hours for 4 doses) followed by oral/intravenous dexamethasone 6 mg once daily for 10 days or until discharge, whichever is earlier. However, WHO and the Government of India recommend switching from dexamethasone to hydrocortisone or methylprednisolone (0.5–1 mg/kg in two divided doses for 5 to 10 days) after the standard fetal lung maturity dose is completed to reduce fetal steroid exposure.
- Pregnant women with gestational or pregestational diabetes should have their blood sugar monitored regularly and the target blood glucose level should never exceed 180 mg/dL.
- Inhaled steroid therapy with budesonide can be administered with or without pneumonia or when proinflammatory markers are significantly raised.

Antibiotics

- The Indian government recommends antibiotics to treat bacterial pneumonia or fever that lasts five or more days.

Mode and Timing of Delivery – The Government of India Recommends

- Performing a cesarean section only for obstetric indications. Caesarean section does not play a role in preventing COVID-19 infection in newborns. However, it may be required in severe or critical illness with refractory hypoxemia. The timing of delivery should be individualized based on the gestational age, the severity of the disease, and the presence of obstetric comorbidities.
- Termination of pregnancy should be planned,
  - No earlier than 37 to 38 $^{+6/7}$ weeks in women with asymptomatic or mild illness.
  - By ≥ 39 weeks in the presence of moderate illness.
  - After stabilisation in cases of severe disease.
- Care should be taken to discontinue low molecular heparin for at least 24 hours and unfractionated heparin for at least 6 hours before planning induction of labour.

Pain Management in Labour

- Epidural analgesia and pudendal blocks can be given

Post-Partum Care

- General recommendations for personal protective practices, hydration and nutrition should be followed.
- The baby's face and mouth should not be covered with a mask.
- Women should be screened and counselled for mental health problems.
- Breastfeeding, kangaroo mother care and rooming in are considered compatible as long as 10 days have elapsed after a positive RTPCR test in clinically asymptomatic women or after the onset of the first symptoms (an interval of 20 days is recommended for women with severe or critical illness or for women who are severely immunocompromised) and at least 3 days of defervescence without antipyretic. However, the following points should be emphasized:
  - Mother wears a mask all the time
  - Hand hygiene is maintained at all times
  - The nipples are cleaned with a soft damp cloth before each feeding.
  - Respiratory etiquette is adhered to
  - Expressed breast milk can be given when the mother is unable to feed the baby.

Discharge from Hospital

- **When to Discharge?**

➢ Mild disease/asymptomatic illness: Discharge can be planned after 24-48 hours of vaginal delivery and 48-72 hours of caesarean delivery.

➢ Moderate to severe disease: Plan for discharge when symptoms subside and 10 to 20 days (severe disease/ critical disease/ immunocompromised status) after the onset of symptoms and with at least 72 hours of defervescence without antipyretic use.

What should be Counselled to the Patient at the Time of Discharge from Hospital?

➢ Danger signs should be duly explained

➢ The woman should be asked to follow COVID precautions at home

➢ Details of teleconsultation services, if available, should be provided to the woman

➢ Routine post-partum care advise should be given including advise on contraception

Prevention of COVID-19 during Pregnancy and Postpartum Period

Personal Protective Measures

Frequent hand washing, maintaining physical distance, avoiding crowded areas, and wearing a double layered mask.

Vaccination

International Stands on Vaccination

- The WHO, ACOG, and RCOG support the vaccination of pregnant women against COVID-19 [5-7].
- The WHO and ACOG do not recommend pregnancy testing prior to vaccination in women of childbearing potential, nor do they recommend delaying or terminating a pregnancy due to vaccination.
- Furthermore, the ACOG recommends vaccination of all pregnant women under 50 years of age despite theoretical concerns about the rare risk of thrombosis with thrombocytopenia syndrome with mRNA-based vaccines.

India's Stand on COVID-19 Vaccination in Pregnancy
Who to Vaccinate?

➢ All pregnant women at high risk of exposure (health care or a front-line workers, community with a high or increasing rate of COVID-19 infection, frequent contact with people outside the household, crowded household where social distancing is not possible)

➢ Women having one or more risk factors for severe COVID-19 disease.

When to Vaccinate?

➢ The vaccination can be started at any time during pregnancy.

➢ Women who have an active COVID-19 infection in the current pregnancy should be vaccinated after-delivery.

What are the Side Effects of Vaccination?

➢ The adverse effects of the vaccine are mild and are unrelated to health of the mother or the fetus. However, long term effects of the vaccine on the mother and child are unknown.

➢ In 1 in 100,000-500,000 cases, the patient may experience dyspnoea, chest pain, limb pain/swelling, petechial haemorrhages/bruising, persistent abdominal pain or headache with/without vomiting, seizures, weakness/paralysis, persistent vomiting, or blurred vision/eye pain within the first 20 days after vaccination, which may require treatment.

What are the Contraindications to Vaccination?

➢ Absolute contraindication – History of hypersensitivity/ anaphylactic reaction to the vaccine or any of its components.

➢ Relative contraindications – 12 weeks after COVID-19 infection or 4-8 weeks after recovery, active COVID-19 infection, treatment of COVID-19 with monoclonal antibodies or convalescent plasma.

Types of Vaccine

- **MRNA Vaccine**

➢ Moderna – Three doses of 0.5 mL (containing 50 mcg) vaccine at 0, 4 and 8 weeks.

➢ BioNTech vaccine from Pfizer – Three doses of 0.3 mL (containing 3mcg) vaccine at 0, 3, and 7 weeks.

Recombinant Protein (Adjuvanted Protein)

➢ Novavax – Two doses of 0.5 mL (containing 5 mcg spiked protein per 50 mcg adjuvant doses) vaccine, 3 to 8 weeks apart.

Conclusion

Infection with SARS-CoV-2 leads to COVID-19. The severity of the illness and the requirement for oxygen therapy and ventilatory support determine how COVID-19 is managed. A small percentage of women may develop serious illness that necessitates close observation, but the majority will only show mild signs of illness and recover without any sequelae. Successful pregnancy outcomes require adherence to protocols for limiting and treating the infection.

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