

Review Article

A review of COVID-19: a threat to pregnant women?

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ABSTRACT

The outbreak of Coronavirus disease-2019 (COVID-19) has widely spread worldwide. While, mild symptoms have been observed in a majority but on the other hand, the virus may cause severe pulmonary disease. The major concern has been the pregnant women. In this review, we have tried to cover COVID-19 infections transmission, diagnosis, management, prognosis during pregnancy. The evidence on vertical transmission has been lacking. However, physiological changes during pregnancy, make women more vulnerable to this COVID-19. The problem of anxiety also flares up the disease in pregnancy.

Keywords: Coronavirus-2019, Vertical transmission, Immunosuppression, Hypoxia

INTRODUCTION

Coronaviruses belong to a family of enveloped, single-stranded, positive sense RNA viruses with surrounding spike like projections. Three coronavirus outbreaks have occurred in the world in the last two decades: Severe Acute respiratory syndrome coronavirus (SARS-CoV) in the year 2002, Middle East Respiratory Syndrome (MERS) in the year 2012, and SARS-CoV-2 in 2019.^{1,2} The pattern of high case fatality rate has not been replicated in SARS-CoV-2, as was up to 25% in SARS-CoV and 27% in MERS-CoV.^{3,4}

The route of viral entry is direct via plasma membrane through Transmembrane serine protease 2 (TMPRSS2). Then spike protein of virus undergoes proteolytic cleavage and the viral genome is translocated to produce more genome RNA, messenger RNA, and viral proteins.⁵ Then viral RNA complex and nucleocapsid protein form a helical capsid, which buds between the endoplasmic reticulum and Golgi apparatus. The mature viral particles get packaged in vesicles, transported to the cell membrane, and then get released from the cell.⁵ Perinatal

transmission risk for SARS-CoV2 is low as the virus or viral particles were not found in the products of conception or infants, the transmission of maternal antibodies to fetus has been considered the reason for this.³

WHY A PREGNANT FEMALE IS AT RISK FOR COVID-19?

The physiological changes occurring in innate and adaptive immune function (immune-suppression) and cardiovascular physiology during pregnancy increase the susceptibility to get infected and may cause hypoxic compromise. The estrogen mediated symptoms occurring in late pregnancy such as gestational rhinitis and marked nasal congestion may mask the COVID-19 coryzal symptoms and thus may result in undetected viral shedding and community transmission of the virus. In addition, the physiological dyspnoea occurring in pregnancy, in response to rising metabolism, gestational anemia and rising fetal oxygen demands should be distinguished from pathological breathlessness.⁴ The maternal immune system may adjust during pregnancy as

it provides tolerance to the semi-allogenic fetus but maintains its ability to respond to insults by pathogenic organisms.^{6,7} Data on immune responses to SARS-CoV-2 during pregnancy are lacking but previous pandemics suggest that the risk of acquiring infections and dying are increased during pregnancy in comparison to nonpregnant women.⁸ During the first and third trimester, to promote implantation and labor, pro-inflammatory changes occur in the body, thus women infected during these periods with SARS-CoV 2 infection are at a higher risk for exaggerated response to the virus.⁹ It is now accepted that high levels of pro-inflammatory cytokines could worsen the prognosis.¹⁰ The inflammatory response in COVID-19 as expressed by activation of T helper 1 and 2 immunity, IL-4, and IL-10 release is different from SARS/MERS as expressed by the release of interferon-gamma, interleukin1beta, IL-6, IL-12. Therefore, COVID-19 is a disease of lesser severity in contrast to SARS/MERS.¹¹

In addition, all the components of the Renin angiotensin aldosterone system including ACE2 are raised in normal gestation, which ultimately raises the possibility of greater risk for SARS-CoV2 during pregnancy.¹²

VERTICAL TRANSMISSION?

The possibility of vertical transmission of the infection is conflicting with the available data. As the ACE 2 receptor is expressed widely in the placenta with a similar receptor binding domain structure between SARS-CoV and SARS-CoV-2, which depicts the possibility of vertical transmission of COVID-19.¹³ In recent studies, neonates born to COVID-19 infected mothers were tested positive for SARS-CoV shortly after delivery.^{13,14} However, the vertical transmission has not been confirmed as 46 neonates born to COVID 19 infected mothers have not shown the presence of viral isolates in the amniotic fluid, cord blood, breast milk, and neonatal throat swabs.^{15,16} The risk of vertical transmission has been reported in few case reports, this is due to positive amniotic fluid SARS-CoV-2 PCR test results, however, some patients series have reported the risk of transmission is only mild to negligible.¹⁷⁻¹⁹ Moreover, trans-placental transmission from infected mother to fetus, who underwent caesarean section is not evidenced.^{20,21} No evidence of COVID-19 in vaginal secretion specimen has been evidenced in a case series.²² In a study, conducted in pregnant women in the 3rd trimester, samples of amniotic fluid, cord blood, and throat swab collected from 6 patients (who developed COVID-19 pneumonia in late pregnancy), tested negative for COVID-19 that suggests no evidence of vertical transmission.²³ But whether it spreads via vaginal birth route needs to be found out.²³

CLINICAL FEATURES

The virus spreads via inhalation of respiratory droplets either by coughing or sneezing of an infected individual, but also through direct contact of contaminated

surfaces.^{20,21} SARS-CoV 2 is also found live in the stool of COVID-19 patients, thus it carries survival capacity in faeces and due to this, the fecal-oral route of transmission has been hypothesized.²⁰ Moreover, contaminated droplets could also infect the human conjunctival epithelium, and thus the transmission via ocular surfaces should be taken into consideration.²⁴ Coronaviruses are known to cause infection in respiratory, gastrointestinal, hepatic, and neurologic systems with a broad range of clinical presentation varying from asymptomatic to severe disease occurrence.^{25,26}

The most common complaints as fever, cough, fatigue, headache, sore throat, myalgia, hemoptysis, dyspnoea, diarrhea have been reported.^{10,20} The median time between the onset of symptoms and dyspnoea is 5 days, for hospitalization is 7 days and for ARDS is 8 days. The period from being symptomatic to a death varies from 6 and 41 days with an average of 14 days.²⁷

DIAGNOSIS

A well-structured classification and case definition has been provided by Shah et al.²⁸ (Table 1).

Table 1: Categorisation of COVID-19 infection during pregnancy.

Maternal infection during pregnancy	Category	Case definition
Symptomatic	Confirmed	Detection of the virus by PCR in a respiratory sample
	Possible	No testing done
	Unlikely	No detection of the virus by PCR in a respiratory sample and no cause identified
	Not infected	No detection of the virus by PCR in a respiratory sample and other cause identified
Asymptomatic with positive contact history	Confirmed	Detection of the virus by PCR in a respiratory sample
	Unlikely	No detection of the virus by PCR in a single respiratory sample
	Not infected	No detection of the virus in two respiratory samples taken at different time points

The laboratory findings between pregnant and other COVID-19 patients are very similar, lymphocytopenia being the most common finding. The levels of CRP,

Procalcitonin, ESR, IL-6, and D-dimer are also raised in COVID-19.^{4,24,29} In comparison to other COVID-19 patients, leukocytosis and elevated neutrophil ratio are more common in pregnant females.²⁹

Ground glass opacity with progression to consolidation and complete consolidation on CT scans are more frequent in pregnant women. In contrast to non pregnant patients, pleural effusion is more common in pregnant. [30] In the early diagnosis of COVID-19, compared with RT-PCR, CT scan has been reported to be superior in early diagnosis of COVID-19.³¹ In particular, the early detection and assessment of disease severity, the high resolution CT scan of the chest is considered to be necessary.³² The diagnostic tests which are invasive such as Chorionic villous sampling, amniocentesis, and cordocentesis are associated with a theoretical risk of vertical transmission of the infection and may directly correlate with the risk of feto-maternal hemorrhage.²⁰

COMPLICATIONS IN PREGNANCY

The vast majority of pregnant women with SARS-CoV-2 infection have remained asymptomatic for respiratory symptoms.³³ However, respiratory compromise and hypoxia may potentiate vasoconstrictors (endothelin-1 and hypoxia-inducible factor) release, which ultimately potentiates placental hypoperfusion, thus increasing fetal growth retardation. Host inflammatory response to infection may lead to the release of prostaglandins and thus pregnant women with pneumonia may more likely deliver before 34 weeks of gestational age.^{34,35}

In pregnant women with COVID-19 infection, premature rupture of membranes, preterm delivery, and coagulopathy (might have deleterious effects in pregnancy) accompanied by liver dysfunction and even death have been reported in certain studies.^{6,8,21} However, studies have reported no increase in the frequency of spontaneous abortions.²⁴ The risk of increased evidence of pre-eclampsia, a disease associated with poor placental perfusion and altered vascular function, has been related to placental malperfusion and thrombosis.³⁶

The disease has been linked to preterm premature rupture of membranes and preterm labor have been suggested as the underlying mechanisms.³⁷ Maternal vascular malperfusion which is further linked to oligohydramnios, fetal growth restriction, preterm birth, and stillbirth.³⁸

TREATMENT

The guidelines are being developed by the professional perinatal societies such as by the Society for maternal-fetal Medicine (SMFM), the American College of Obstetricians and Gynecologists (ACOG) from the United States, the Royal College of Obstetricians and Gynaecologists (RCOG) from the United Kingdom, the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG), the Centres for Disease Control

and Prevention (CDC) and the World Health Organization (WHO).^{39,40}

To ensure the best pregnancy outcomes, antenatal care is a must. Suspected, probable as well as confirmed cases of COVID-19 infection should be managed initially by designated tertiary hospitals equipped with effective isolation facilities and protection kits. Suspected or probable cases should be treated in isolation whereas confirmed cases should be managed in a negative-pressure isolation room. A designated tertiary hospital is mandatory for managing suspected, probable, or confirmed cases of COVID-19.³⁹

Assessments such as monitoring Blood pressure should be done at home.⁴¹ Nonurgent routine appointments such as growth scans, antenatal or secondary care appointments should be delayed in symptomatic till after the period of recommendation of self-isolation.⁴¹ In cases of septic shock, acute organ failure, and fetal distress, an emergency caesarean section should be considered.⁴² At delivery, preventive measures as nasopharyngeal suction before first birth and cleansing infant soon after birth should be considered to reduce viral load.³

There is no proven, safe, and effective treatment for COVID 19 in pregnant women. CQ and HCQ have been effective in *in vitro* studies. However HCQ crosses the placenta, but some studies report its safety in pregnancy.^{43,44} Doxycycline an ionophore has been shown to inhibit viral replication *in vitro* by increasing intracellular zinc concentrations.⁴⁵ The drug is known to inhibit metalloproteinase MMP-9, and IL-6 (both are key regulators of cytokine storm).⁴⁶ Even at a low dose, doxycycline is found to inhibit CD147/EMMPRIN expression *in vivo*, which might be necessary for SARS-CoV-2 entry into T-lymphocytes.⁴⁷ In addition, the drug carries the potential to inhibit papain-like proteinases and 3C-like main protease (essential for replication of virus).⁴⁸

An antiviral agent Remdesivir that inhibits viral RNA-dependent RNA polymerase and results in premature termination is safe in pregnancy.⁴⁹ Viral protease inhibitors such as lopinavir/ritonavir have also been beneficial in the COVID-19 adjunctive management.⁵⁰ These agents have not been studied in pregnant women but are known to be safe in population based surveillance in HIV-positive pregnancies.⁵¹ The efficacy has been established in *in vitro* studies against SARS-CoV2.⁵²

The use of LMWH prophylactically (Enoxaparin 40 mg/24hrs if maternal weight is <80 kilograms and if >80 kilograms then 60 mg/24hrs) in the postpartum period is indicated as the COVID-19 is associated with the risk of DVT and pulmonary embolism.⁵³ A JANUS-KINASE inhibitor, Baricitinib, being used as a potential agent for COVID-19 treatment, has demonstrated embryotoxicity in animal studies.⁵⁴

Interferon-alpha being an antiviral drug was effective in SARS-CoV-1 and MERS-CoV, acts by activating antiviral protein genes and also by modulating immune cell function.⁵⁵ In a systemic review by Brojeni et al its safe use in pregnant women has been suggested.⁵⁶ Arbidol, a broad-spectrum antiviral drug that acts by inhibiting enveloped virus membrane fusion has shown effectiveness against SARS-CoV-2, in vitro.³³

Corticosteroids, reduce the progression to respiratory failure and death, however, the drug is advised to be used at the right dose, in the right patient, when the patient requires respiratory support.⁵⁷ This is so because high dose or early administration of the drug may suppress the immune system and thus may help in virus proliferation instead of reducing inflammation.

As there is no evidence of vertical transmission from the placenta or during delivery, thus inappropriate pregnant, vaginal delivery can be considered.⁵⁸ However, it has been shown that the disease transmission is not affected by the mode of delivery.²⁴

The important point to consider is that in many trials (pharmacologic and nonpharmacological interventions), pregnant women have not been mentioned either in inclusion or exclusion criteria.⁵⁹ However, the drugs under experiment are being used in pregnant women.⁶⁰

In a systemic review conducted by Elshafeey et al has included 33 studies, concluded mild (95.6%), severe (3.6%), critical (0.8%) symptoms in pregnant women, with the need for ICU admission in (4.4%), mechanical ventilation in (1.6%) women. The percentage of maternal deaths was 0.3% in this review.⁶¹ The data regarding vertical transmission was extracted as samples from cord blood and amniotic fluid tested negative in those four neonates who had positive RT-PCR, thus the mode of transmission was uncertain.⁶¹

A review by Yang et al, where 18 studies were included, has concluded 91% underwent caesarian delivery, 5.3% had a severe or critical illness, and 0.9% needing ECMO.⁶²

PROGNOSIS

The risk of adverse outcomes including spontaneous abortion, preterm birth, and intrauterine growth retardation have been associated with previous infections as in middle east respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS).⁶³ This pattern of severity as was in SARS and MERS has not been seen in COVID-19 infection in pregnancy.⁴ Unfortunately, a potentially high risk of respiratory decompensation and hypoxaemic respiratory failure in symptomatic pregnant women may contribute to the emerging risk of critical care admission. The risk of fetal growth restriction increases due to maternal hypoxia, which results in placental hypoperfusion and reduced oxygen delivery to

the placenta as a result of the release of potent vasoconstrictors. The vulnerable group in any infectious disease outbreak is pregnant women, due to physiological changes. Special precautions are mandatory to safeguard the fetus and also to decrease the risk of cross-infection of health care workers.

Conclusion: Pregnant women become more vulnerable to suffer from infections. But data on the use of drugs during pregnancy is lacking, thus preventive measures should be given priority. The use of PPE kits should be preferred. Moreover, management of pregnant women should be undertaken by a multidisciplinary team. The process of delivery (timing as well as mode) should be individualized. The importance of social isolation should be emphasized as advised by health authorities to prevent further spread. The most important is the psychological well-being of pregnant should be given equal importance.

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