



COVID-19 IN PREGNANCY AND LITERATURE REVIEW

Obstetrics & Gynaecology

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ABSTRACT

COVID-19 pandemic has affected humankind in a major way. Pregnant women are as susceptible to SARS-CoV-2 infection as non-pregnant population. Infections prevention is paramount as pregnancy is associated with increased risk of severe illness, admission to intensive care and mechanical ventilation. Pregnancy poses unique challenges in view of paucity of information regarding safety of drugs used in management of patients with COVID-19 infection. Fortunately SARS-CoV-2 infection during pregnancy does not appear to cause congenital anomalies. Vaccination should not be withheld based on pregnancy and lactation status.

KEYWORDS

SARS-CoV-2, COVID-19, pregnancy, vertical transmission, vaccination

INTRODUCTION:

Corona virus disease (COVID-19) has impacted the world like no other disease before! Many countries were under a lock-down for a period extending from weeks to months during the first wave and lockdown is still being implemented or reinstated in a few countries. This article describes severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) infection and disease and summarized how this disease affects pregnancy outcomes and the effect of pregnancy on the disease manifestations, course and prognosis. Vaccination in pregnancy and lactation has also been discussed.

Virology and Epidemiology:

COVID-19 is caused by SARS-CoV-2. Corona viruses are important animal and human pathogens.¹ SARS-CoV-2 belongs to betacoronavirus family to which severe acute respiratory distress syndrome virus (SARS) and middle east respiratory syndrome (MERS) virus also belong. Structure of receptor-gene binding region of SARS-CoV-2 is very similar to SARS virus and the receptor for cell entry for both the viruses is same, angiotensin-converting enzyme (ACE2).¹

This novel infection was first reported from Wuhan city in Hubei province of China in December 2019. It was declared a pandemic by world health organization (WHO) in February 2020. By 17th of April, 2021, there were about 139,501,934 confirmed cases of COVID-19, including 2,992,193 deaths.² Virus spreads from human to human mainly by respiratory route through droplets i.e., when an infected person coughs or sneezes, droplets containing the virus enter mucosal surface of mouth, nose and eyes. Droplets typically do not traverse beyond 6 feet and hence physical distancing can help prevent transmission. Infection can also spread through fomites i.e., a person touches an infected surface and touch his nose, mouth or eyes.¹ Whether airborne transmission exists i.e., virus staying suspended in air and resulting in transmission is not clear. Heneghan et al suggest that air borne transmission plays a significant role in spreading of SARS-CoV-2.³ There is evidence to suggest transmission from asymptomatic and presymptomatic infected persons.⁴ There is no clarity regarding vertical transmission from mother to baby, transmission intrapartum and through breast feeding.⁵⁻⁷

Nasopharyngeal swabs of few neonates born to mothers with COVID-19 were found to be positive for SARS-CoV-2 RT PCR despite separating the neonate from mother soon after delivery suggesting possibility of vertical transmission but more information is needed in this regard.^{2,7} SARS-CoV-2 has been detected from amniotic fluid, breast milk and vaginal swab samples.⁸ Pregnant women are at same risk of acquiring SARS-CoV-2 infection as that of nonpregnant individuals.

Clinical manifestations:

Many patients may remain asymptomatic or only develop mild illness.⁹⁻¹¹ About 15% of patients develop severe illness requiring admission to a hospital. About 5% of patients may be critically ill requiring admission to an intensive care unit. Mortality ranges from 1 to 3 % depending on risk factors, health care infrastructure etc.¹ Fever, cough, cold, throat pain, myalgia are common symptoms.^{1,9-11} Significant proportion of patients report gastrointestinal symptoms

like diarrhoea. Anosmia is an early symptom in a few patients. Anosmia has been projected as an important indicator of COVID-19. Patients with severe infection may present with shortness of breath, altered sensorium etc. Severe infection can result in respiratory failure, acute respiratory distress syndrome (ARDS), shock, renal failure, liver involvement, central nervous system involvement, disseminated intravascular coagulation (DIC) and multi organ dysfunction.¹ Patients with moderate to severe Covid-19 are increased risk of thromboembolic events. Risk factors for severe infection include diabetes mellitus, hypertension, obesity, cardiac disease, chronic kidney disease, moderate to severe asthma, smoking, obesity, active cancer, HIV and patients on immunosuppressive agents.¹ Disease severity can be classified as mild, moderate and severe.¹ Patients with mild disease may manifest with fever, cough, myalgia etc but have no respiratory distress, oxygen saturation (spo₂)>93% and normal radiological imaging of chest. Presence of radiological abnormality in lungs with no breathing difficulty and spo₂>93% is classified as moderate disease. Patient with spo₂<93%, respiratory rate>30/min, P/F ratio<300 or lung infiltrates>50% is considered to have severe disease. Critical illness is characterized by respiratory failure, septic shock and/or multi organ dysfunction.

Pregnant women present with similar symptoms but more women may complain of shortness of breath, especially in third trimester due to expanding uterus and some amount of pre-existing respiratory compromise due to physiological changes of pregnancy. Pregnant women are at risk of developing severe illness with Influenza infection (both seasonal and H1N1) but it is not certain if pregnant women are at increased risk of severe illness with SARS-CoV-2 infection. Initially a few published small case series of pregnant women with COVID-19 did not suggest pregnancy as a risk factor for severe illness.¹¹⁻¹⁴ Recent analysis by centre for disease control (CDC) revealed increased risk of severe illness among pregnant women. Pregnant women are at increased risk of ICU admission due to COVID-19 and at increased risk of mechanical ventilation but there was no increase in mortality noted.¹⁵ More research is needed regarding effect of SARS-CoV-2 infection in antenatal period on foetus.^{16,17} In a few women affected with COVID-19 during pregnancy, foetal growth restriction was noted.¹

Diagnosis:

Main stay of diagnosis is by detection of SARS-CoV-2 RNA by nucleic acid amplification tests (NAAT), common method being used is reverse transcriptase polymerase chain reaction (RT-PCR) from nasopharyngeal specimens.¹ Positive test usually confirms the diagnosis, negative test can be a false negative test at times as sensitivity of RT PCR test from nasopharyngeal swab is about 65%. Newer assays have improved sensitivity. Accuracy of antibody tests is variable and data on antigen test utility is limited.¹

Other laboratory findings include leukopenia (leukocyte count is normal in majority), lymphopenia, elevated liver enzymes etc. Elevated C reactive protein (CRP), D-dimer, LDH, ferritin, troponin may indicate poor prognosis or risk of severe illness. However, leukopenia may be masked in pregnancy as normal pregnant women often have leucocytosis. D-dimer is elevated in normal pregnancy as well.

Prevention of infection:

Pregnant women need to follow the same infection prevention measures as nonpregnant persons i.e., maintaining physical distance of six feet from others, wearing masks outdoors and frequent hand washing especially after touching potentially infective surfaces.¹ Women are encouraged to obtain antenatal care via teleconsultations when feasible. However, antenatal care should not be compromised fearing risk of infection.

Management:

Management is mainly symptomatic and supportive treatment. Management includes symptomatic and supportive treatment (oxygen support etc), antiviral therapy, prophylactic anticoagulation and anti-inflammatory therapies. Asymptomatic mothers do not need any specific treatment.¹ Mild symptomatic patients need only symptomatic treatment and can be managed at home. Mild symptomatic patients with comorbidities or women with moderate to severe illness need hospitalisation. Antiviral agents like Remdesivir which is indicated in patients with severe illness has been used in pregnant women with COVID-19 on compassionate basis.¹ Usage of Remdesivir in a few pregnant women with Ebola was not associated with any foetal toxicity.^{1,18} Hydroxychloroquine and lopinavir-ritonavir are safe in pregnant women but efficacy of these drugs in COVID-19 is questionable.^{1,19,20} Dexamethasone has been found to be useful in severely ill patients. Since dexamethasone crosses placenta, prednisolone 40 mg orally or hydrocortisone 80 mg twice daily (intravenously) for 10 days or till recovery may be used instead of dexamethasone.^{1,19,20} However, if patients needs steroids for foetal lung maturity, dexamethasone can be used initially and later converted to oral prednisolone. Interleukin-6 (IL-6) inhibitors like tocilizumab has been used in COVID-19 patients outside pregnancy in selected patients who are very ill with high level of IL-6. In a retrospective study of 61 patients who received tocilizumab around conception, there was no foetal harm noted but safety of tocilizumab usage during pregnancy is not known.^{21,22} Baricitinib in addition to Remdesivir has been shown to improve outcomes, however there is very limited experience with this drug in pregnancy. Costanzo et al published a case report of a pregnant woman with rheumatoid arthritis on Baricitinib during early pregnancy till 17 weeks of gestational age with normal born baby.²³ COVID-19 is associated with increased thromboembolic events (though data is limited). Prophylactic anticoagulation should be considered in pregnant women with COVID-19 who are hospitalised and in postpartum period. Unfractionated heparin is preferred in women who may need delivery soon otherwise enoxaparin 40 mg once a day can be given.

Delivery issues:

Pregnant women with mild to moderate COVID-19 illness and in labour do not need alteration of mode of delivery.²⁴⁻²⁶ Mode of delivery needs to be decided as per obstetric indications. Critically ill mothers or mothers on ventilatory support may benefit with delivery as offloading pressure on the chest due to gravid uterus, delivery decision in such patients needs to be individualised. Scheduled induction of labour and caesarean section need not be postponed in asymptomatic patients. In mild symptomatic patients, it's better to avoid postponing scheduled delivery for medical indications as illness may worsen during second week.¹ Neuraxial anaesthesia is preferred for analgesic and anaesthetic purpose as general anaesthesia is considered an aerosol generating procedure hence appropriate personal protective equipment needs to be used.²⁴⁻²⁶ In critically ill women with COVID-19 and preeclampsia, magnesium sulphate should be used with caution as it can cause respiratory depression.¹

Postpartum and breast feeding concerns:

Thromboprophylaxis with low molecular weight heparin needs to be considered in postpartum period in women with COVID-19.^{1,27} In patients with postpartum haemorrhage, some authors suggest avoiding tranexamic acid as it may increase risk of thrombosis in women with COVID-19. There is no evidence to suggest transmission of infection through breast milk. Most breast milk specimens from infected mothers tested negative for SARS-CoV-2 RNA. Expressed breast milk feeding is preferred but if mother chooses to breast feed directly, she should use a mask, gown, follow hand hygiene and minimise duration of contact with the neonate.²⁸ Post discharge, mother should adhere to isolation protocol for the duration as per local guidelines which is seventeen days from symptom onset or test date (in asymptomatic patients) in India.

Vaccination during pregnancy and lactation:

Pregnant women have been excluded from all COVID-19 vaccine trials so far. Phase 2/3 trial in pregnant women is now underway for mRNA vaccine by Pfizer and BioNtech. Most scientific bodies do not advise withholding vaccines based on pregnancy and lactation alone.²⁹ However, COVID-19 vaccines may be recommended for deserving pregnant and lactating women on individual basis after discussing paucity of safety and efficacy pregnancy and lactating mothers.²⁹⁻³⁵ Information from animal studies, small cohort studies with pregnant women have supports safety of COVID-19 vaccines in pregnancy. A small cohort study with mRNA vaccine including 84 pregnant women and 31 lactating women revealed equivalent antibody titres compared to non-pregnant women and antibodies were demonstrated in umbilical cord blood and breast milk inferring passive protection to neonates and infants of vaccinated pregnant and lactating mothers.³⁰

CONCLUSION:

Pregnancy poses additional challenges in management of COVID-19. Pregnancy was not considered a risk factor for severe illness initially but evidence is emerging to associate pregnancy with risk of severe illness though pregnant women are not at increased risk of mortality due to COVID-19. There is paucity of data on safety of various drugs used in management of COVID-19 in pregnancy. Infection prevention practices and management is similar to that of nonpregnant patients. Emphasis should be given to thromboprophylaxis especially in postpartum period. Vaccination should not be denied to pregnant and lactating women and decision to vaccinate should be individualised.

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