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Pregnancy and COVID-19

Sushruti Kaushal and Harpreet Kaur

Abstract

Pregnancy is a physiological state that alters the body's response to infections. COVID-19 has been found to cause severe disease in pregnancy with morbidity and mortality that is higher than in non-pregnant adults. There is risk of transmission of SARS-CoV2 infection to fetus during ante-natal period, intra-partum and post-delivery from an infected mother. It is necessary to provide an un-interrupted ante-natal care and delivery services to pregnant women during the pandemic. Tele-consultation is important modality to reduce the physical exposure of pregnant women to the hospital environment and should be utilised. Screening, isolation, testing and treatment for SARS-CoV2 infection in pregnant women should follow the local guidelines and remain essentially the same as in non-pregnant adults. Admission, if required, should be in a facility that can provide obstetric maternal and fetal monitoring in addition to care for COVID-19 illness. Use of nitrous oxide and inhalational oxygen for fetal indication should be avoided during labor. Second stage of labor is considered an aerosol generating procedure and should be managed with adequate precautions. Mode of delivery should be as per obstetric indications. Regional anaesthesia should be preferred during caesarean. COVID-19 is not a contra-indication to breast feeding. For antenatal women, COVID-19 vaccination can be considered after shared decision making.

Keywords: Pregnancy, COVID-19, vaccine, labor, delivery

1. Introduction

Pregnancy is a physiological state that alters the body's immune system and response to viral infections. Pregnant women have been found to have higher risk of complications during the previous corona virus outbreaks, namely Severe Acute Respiratory Syndrome (SARS) in 2002–2004 and Middle East Respiratory Syndrome (MERS) in 2012. The risk of maternal morbidity and mortality was high with these infections. With Covid-19, though initially there were different opinions but currently there is sufficient evidence to suggest that pregnant women are at increased risk for complications of COVID19. Additionally, there is evidence to support risk of transmission of infection to fetus intra- or postpartum and concerns about obstetrical outcome.

2. Physiological changes in pregnancy and SARS-CoV2 infection

Pregnancy induces changes in all organ systems of body, notable one being a state of altered immunity and body's response to various infections. This results in increased severity of illnesses during pregnancy as evidenced in previous respiratory disease outbreaks.

Changes in pregnancy that alter the response to illness are:

2.1 Immune system

- a. Shift in population of CD4+ T Cells population towards Th2 phenotype promoting humoral immunity in place of cellular immunity [1].
- b. Decrease in the population of natural killer cells, possibly altering viral clearance [2].
- c. Phagocytic dendritic cells are decreased and so, interferon response to viruses is altered [3]
- d. Hormonal changes in the form of increased progesterone, oestrogen and androgens alter the body's immune system because of immunomodulatory properties [4]. Whether these hormones predispose to severe disease or have protective effect is yet to be known.

2.2 Respiratory system

- a. Elevation of diaphragm due to gravid uterus leading to reduction in lung volume and total lung capacity.
- b. Increase in tidal volume (30–40%)
- c. Decrease in functional residual capacity, residual volume and end expiratory volumes
- d. Decreased clearance of secretions

These changes make pregnant women more susceptible to severe disease [5].

2.3 Coagulation pathway

Pregnancy is a hypercoagulable state with:

- a. increase in thrombin and other coagulation factors
- b. increased fibrinolytic factors such as plasmin

Covid 19 is associated with high rate of thromboembolic complications which is compounded by changes of pregnancy.

2.4 Vascular system

Pregnancy increases maternal blood volume, heart rate and cardiac output while systemic resistance decreases. There is an increase in intravascular inflammation [6]. These vascular changes have the potential to impact endothelial function which is a major factor in development of Acute Respiratory Distress Syndrome (ARDS) with Covid19.

Preeclampsia is an important complication of pregnancy associated with endothelial cell dysfunction and higher rates of preeclampsia have been noted in pregnancies complicated with Covid19 [7].

3. Physiology of placenta and placental transmission of COVID-19

Placenta acts as a barrier for transmission of pathogens by various mechanisms. Placental decidua contains large number of NK cells, macrophages and T cells. Decidual macrophages perform antimicrobial functions while CD8+ T cells protect the fetus from viral infections [8]. Additional protection is provided by syncytiotrophoblast and cytotrophoblast mediated by toll-like receptors. Placenta also has antimicrobial peptides which prevent fetal transmission of various pathogens [9].

The first prerequisite for transmission of any virus through placenta is viremia, which, in case of SARS-CoV2, may be present for a relatively short duration. Although earlier studies documented viremia in only 1–15% of patients infected with SARS-CoV2 virus, recent study using WHO RT-qPCR protocol demonstrated viremia in up to 80% patients, although mostly with low levels of viral load [10].

The second element necessary for fetal transmission is placental tropism or the ability of the virus to infect placental cells. In lungs, SARS-CoV2 uses ACE-2 receptor to enter cells and a serine protease named TMPRSS2 to cleave the spike glycoprotein, facilitating fusion. Although ACE-2 and TMPRSS2 have not been shown to be co-expressed in placental cells, they have been demonstrated in trophoblast, blastocyst and hypoblast. It has been suggested that SARS-CoV2 could enter placenta using other proteases like DPP4, CD147 or trypsin [11].

Another route for this virus to enter the placenta could be through infected blood cells like lymphocytes and macrophages but this has not been proven yet for SARS-CoV2. Transcytosis of free virus particles can infect the fetus, as in case of HIV but this method is thought to be less important with maternal SARS-CoV2 infections because of low viremia.

Infection may also cross over to fetus through cervico-vaginal secretions which would raise concerns for the mode of delivery of the fetus. The evidence we have till now does not favour this mode of transmission as one study on ten infected women did not find viral RNA in vaginal secretions in any patient [12].

There is convincing evidence that placental transmission of the virus causing COVID-19 is possible, though rarely. Presence of SARS-CoV2 viral RNA in placenta and SARS-CoV2 virions in syncytiotrophoblast has been reported in multiple cases. IgM antibodies directed against SARS-CoV2 virus have been documented in neonates born to mothers with SARS-CoV2 infection, making a strong case for in-utero transmission of this virus [13].

Placental histology in parturient women who contracted SARS-CoV2 infection during the ante-natal period shows vascular malperfusion, chronic villitis, placental infarcts and fibrin deposition [14].

It has been estimated that maternal to fetal transmission occurs in 3.2% of pregnant women infected with SARS-CoV2 virus. Viral positivity rate for placental and cord samples and fetal serology fall in the same range, supporting the transmission rate of 3.2% [13].

4. Effects of SARS-CoV 2 infection on pregnant women

Pregnancy is an immuno-deficient state and high morbidity has been reported during previous corona virus outbreaks, both MERS and SARS. Earlier studies done in China showed key outcomes in pregnant women infected with SARS-CoV2 virus to be similar to those in non-pregnant adults [15, 16]. These studies were limited by small sample sizes and a retrospective design. A national analysis of all Covid related ICU admissions in Sweden was one of the first studies to report increased morbidity

during pregnancy [17]. Studies later done in France and the USA supported these findings. The largest study addressing this topic was the review of all laboratory confirmed cases of Covid19 from January to June 2020 in the USA. They found increased risk of hospitalisation, ICU admission and mechanical ventilation but not mortality [18]. This data was recently updated through October 2020 to report increased risk of hospitalisation, ICU admission, mechanical ventilation, extracorporeal membranous oxygenation (ECMO) and death [19]. Though risk appears to be increased when compared with non-pregnant adults, absolute risk remains low.

Clinical course of COVID-19 is believed to be mild in majority (86%) of pregnant females, severe in 9% and critical in 5% [20]. This is similar to incidences reported in non-pregnant Covid19 patients.

In data reported from the UK, most women with more severe illness were in third trimester of pregnancy or postpartum [21]. Risk factors associated with hospital admission in pregnant women include Black, Asian or minority ethnicity, pre-existing co-morbidity (e.g. diabetes, hypertension, asthma), obesity/overweight and maternal age more than 35 years. It has been postulated that this risk is due to genetic differences, socio-economic disparity or difference in response to infection. Vitamin D deficiency has been associated with respiratory infections and ARDS, a common complication of Covid19. South Asian population has been documented to be deficient in Vitamin D and this could be a factor in increased morbidity in this population [21].

COVID-19 increases the risk of thromboembolic complications and pregnancy is itself associated with increased risk of thrombo-embolism. Royal College of Obstetricians and Gynaecologists (RCOG) has emphasised the risk of thromboembolism in COVID-19 with pregnancy and recommends appropriate use of thromboprophylaxis.

5. Risks to the fetus

Many studies have shown increased chances of preterm delivery in SARS-CoV2 infected women. Most of these preterm births have been seen to be iatrogenic. Most of the preterm babies have been delivered by caesarean section due to intrauterine foetal distress. Symptomatic women have been found to have increased risk of preterm delivery compared to asymptomatic SARS-CoV2 infected women. Some studies have shown a decrease in mean gestational age at the time of delivery in women who were diagnosed with COVID-19 within 14 days before delivery. One study also reported increased chances of stillbirth in foetuses born to SARS-CoV2 positive mothers [22].

Till date no association has been found with first trimester losses or teratogenicity and COVID-19 infection is not an indication for medical termination of pregnancy. Though this is ever changing situation and we may get more information in future as the evidence is pooled in. Amniocentesis to diagnose fetal infection is also not recommended at present [23].

6. Diagnostic testing for SARS-CoV2 infection in pregnancy

The criteria for testing pregnant women for SARS-CoV 2 infection remain the same as for general population. Local testing guidelines as per the local, state and regional governments should be followed. Basically, it includes testing symptomatic women, contacts of SARS-CoV2 positive people and those with history of travel.

Nasopharyngeal swab is the recommended sample for testing, oropharyngeal swab is also acceptable. Lower respiratory samples are recommended in intubated patients and in those with severe illness and negative nasopharyngeal swabs.

RT-PCR is the most commonly used test in pregnancy. Nucleic Acid Amplification Tests (NAAT) can be used as per availability and regional guidelines.

Rapid antigen tests and serological tests can all be used in pregnancy as per regional protocols and there are no specific considerations for diagnostic testing in pregnancy [24].

7. Ante-natal care during COVID-19 pandemic

Providing adequate antenatal care during the COVID-19 pandemic is a priority and a minimum number of antenatal visits should be ensured. Federation International of Gynaecology and Obstetrics (FIGO) suggests a minimum of six in-person antenatal visits i.e. at 12 weeks, 20 weeks, 28 weeks, 32 weeks, 36 weeks and at 37–41 weeks. Telemedicine can be used for any additional advice and facilities should be made available for tele-consultation.

Appointments should be taken before consultation and screening for any symptoms for COVID-19 should either be done telephonically or before entering the antenatal area [25]. Screening should include symptoms suggestive of COVID-19 illness, any history of recent travel, history of exposure to infected person and any history of immune-suppression [25].

FIGO recommends that any pregnant women testing positive on screening should have a minimum waiting period, should be tested for severity of symptoms, and evaluated as per local guidelines [25]. Screen-positive women should be isolated and not allowed near other pregnant women.

Screen-positive woman who contacts telephonically should be advised to defer the visit for 14 days unless there is an urgent need.

During antenatal visits, pregnant woman should be counselled about the general measures to prevent spread of infection like social distancing, use of face masks and respiratory hygiene. They should be educated about the symptoms of SARS-CoV2 infection and that even if they become infected, they are likely to have mild disease in most cases. They should be told that if they develop severe symptoms or recovery is delayed, they should seek care [25].

Pregnant women should be allowed only one accompanying person and he/she should also be screened at entrance to hospital.

They should also be counselled about the possible modifications in her antenatal plan in view of the ongoing pandemic. She should be told about dedicated COVID facilities in her neighbourhood and facilities where SARS-Cov2 positive women can deliver.

She should be advised to keep taking her routine health supplements e.g. folic acid during pregnancy.

There should a mechanism in place to track antenatal women who miss scheduled visits and they should be contacted telephonically.

Clinicians should be aware of the increased risk of psychological problems and domestic abuse during the pandemic and appropriate steps should be taken to address these issues including looking for signs, counselling and referral if needed. Particular concern has been raised about the increased need of psychological counselling and support services to the antenatal women during this time of pandemic when face to face consultation is not possible [25].

8. Antenatal care for women with suspected/confirmed covid-19

Care of symptomatic pregnant women suffering from Covid-19 should be a multidisciplinary team approach.

American College of Obstetricians & Gynaecologists (ACOG) has developed an algorithm for management of outpatient pregnant women with suspected or confirmed COVID-19. If a woman has no symptoms to suggest infection with SARS-CoV2, she should receive routine prenatal care. If she has symptoms, severity of symptoms should be assessed. Assessment of severity of illness should include any shortness of breath, coughing up blood, dizziness, chest pain, not being able to keep down fluids and any history of confusion. If any of these are present, pregnant woman is at elevated risk and should be asked to seek care in an emergency department in a centre that has facilities for antenatal and obstetric care. If the woman has symptoms but those are not severe, she should be screened for any co-morbidities and any obstetric complications. If any co-morbidities or obstetric complications are present, she is categorised as having moderate risk and should be evaluated in ambulatory setting as soon as possible and should be investigated for severity of illness. CT Scan with abdominal shielding should be done if clinically indicated. If the woman does not have any high risk factors, she should be sent for symptomatic care at home, including hydration and rest and evaluated repeatedly for development of any of the above symptoms [26].

Indian Council of Medical Research (ICMR) recommends that symptomatic women with fever $>38^{\circ}\text{C}$ and respiratory symptoms should be hospitalised in a tertiary care centre with facilities for maternal and fetal monitoring. Seriousness of maternal situation is assessed by quick SOFA score, parameters of severity being systolic blood pressure < 100 mmHg, respiratory rate > 22 , and Glasgow consciousness scale < 15 . Any pregnant woman with more than one of these factors should be admitted in Intensive Care Unit (ICU) [27].

FIGO recommends anomaly scan at 18–23 weeks in women with confirmed SARS-CoV2 infection and monthly scan after that for fetal growth. ICMR (Indian Council for Medical Research) recommends a growth scan 14 days after recovery from acute illness [25].

9. Management during labor

9.1 Preparation before admission

Admission for labor and delivery represents a unique scenario in that admission, though planned, cannot be delayed. The basic principles remain the same as those for outpatient visits, i.e., to avoid unnecessary hospital visits, maintain social distancing and other measures to prevent spread of SARS-CoV2. Women should be advised to quarantine themselves or work from home at least 14 days before planned admission for delivery or caesarean. This should start in most women by 37 weeks of gestation. Woman and her birthing partner should be screened for symptoms of COVID-19 telephonically one day before admission [28].

9.2 Screening on arrival

All women arriving for admission for delivery should be screened verbally for fever, cough and respiratory symptoms. Birthing partner should be similarly screened. Those testing positive should be sent for testing and care by Obstetric care

provider. Some women would already be diagnosed with SARS-CoV2 infection and they should directly be delegated to area dedicated for infected patients.

Case can be made for testing all women at the time of admission to labor and delivery unit because of high number of asymptomatic infections [20]. Local guidelines could also mandate testing at the time of admission.

After screening at the time of admission, women will be categorised into one of the three categories: infected, suspect and non-infected. Under ideal circumstances, all health care facilities caring for pregnant women should have well demarcated zones with separate passageways for all of these categories. These zones should include separate wards, intensive care areas and operation theatres. If not possible, all care should be taken to avoid infected and non-infected people coming in proximity of each other.

9.3 General precautions during admission

All women and their birthing partners should wear triple layer surgical masks throughout admission. All healthcare providers should wear triple layer surgical mask for each patient contact. Hands should be sanitised with alcohol based hand-rub after every patient contact. Droplet precautions should be used when caring for women with respiratory symptoms. This requires the use of gloves, gown, surgical mask and face shield. Gown, gloves, face shield and N95 mask should be used for any woman with suspected COVID and during any aerosol generating procedure including second stage of labour [28]. Disinfection of rooms should be done between patients.

Women should be allowed to have one birthing partner who should stay throughout admission. Other support persons should be given option to provide support through video. Visitors should not be allowed in person, although visitation may be considered in end of life situations.

Shifting of woman from one area to other should be avoided and all efforts should be made to provide services at women's bedside.

All preoperative investigations needed for caesarean should also be done on the day of admission to decrease the number of pre-admission hospital visits.

9.4 Intrapartum care

Management of first stage of labour remains essentially the same as in a woman not infected with Covid-19. Women with mild disease require management of fluid-electrolyte balance during labor, in addition to symptomatic management and close monitoring of maternal well-being. Woman should be encouraged to take oral fluids to maintain hydration. Intravenous fluids should be used with caution because of association of Covid-19 with Acute Respiratory Distress Syndrome (ARDS) [25]. Early use of oxytocin for slow and dysfunctional labour is recommended to avoid the stress and complications of a prolonged labor. Use of Nitrous Oxide during labour should be avoided because of insufficient data about cleaning, filtering and potential aerosolization of nitrous oxide systems [28].

Oxygen is used intrapartum for fetal benefit, to increase fetal oxygenation. A recent meta-analysis has shown that it does not provide fetal benefit and may even be harmful [29, 30]. ACOG recommends against the use of oxygen therapy for fetal resuscitation during labour [28].

Second stage of labour is considered an aerosol generating procedure and should be managed with appropriate precautions. Obstetric management remains the same as before the pandemic.

Blood resources have become scarce during the pandemic because of inability to conduct donation drives. Maintaining pre-delivery haemoglobin is the most efficient way to decrease the use of blood during labour and delivery admissions. Utmost importance should be given to aggressively treat anaemia detected during pregnancy. Blood transfusion should only be used when absolutely necessary and in minimum quantity.

Misoprostol and tranexamic acid should be used prophylactically in third stage of labor to decrease blood loss after delivery.

10. Management of pregnant woman with COVID-19

A pregnant woman with SARS-CoV2 infection should be counselled about the risk of serious infection and the methods to protect family members from infection. Next step is to assess systemic status of woman for severity of infection and need of hospitalisation.

Management of infection should be same as management of non-pregnant patients with COVID-19. If the patient needs hospitalisation, she should be admitted in a facility where maternal as well as fetal monitoring can be done [31]. The facility should be able to provide fetal and uterine contraction monitoring, individualised delivery planning and team based approach including obstetrician, paediatrician, anaesthetist and respiratory medicine specialist. The basic principles and medications remain the same as in non-pregnant patients. Potentially effective treatment for COVID-19 should not be withheld from pregnant women due to theoretical concerns regarding safety. Decisions regarding treatment options should be made keeping in mind safety of the medication, the severity of maternal disease and in shared decision-making with the patient [31].

A very important limitation is exclusion of pregnant women from most clinical trials involving new treatment modalities and the safety data remains scarce.

In most cases, timing of delivery should not be altered by maternal COVID-19 infection [32]. Patients who get infected in early pregnancy and subsequently recover do not require any change in the timing of delivery. For patients who contract SARS-CoV2 infection in the third trimester of pregnancy, attempt should be made to postpone delivery till negative SARS-CoV2 report or lifting of quarantine status to decrease the risk of perinatal transmission. Maternal COVID-19 infection is not an indication for caesarean section, which should be done for obstetric indication or on maternal request [32]. Because the risk of transmission from umbilical cord blood is low, delayed cord clamping should be continued as pre-pandemic. Similarly, umbilical cord blood banking can be done if the parents desire.

11. Lactation and COVID-19

Several studies have detected SARS-CoV2 nucleic acid in breast milk. However, infectious virus particles have not been detected in breast milk [33]. Also, antibodies specific to SARS-CoV2 have also been detected in breast milk, which could potentially protect the neonate. Therefore, it is recommended to continue breast-feeding in mothers with SARS-CoV2 infection, with precautions. These precautions include hand hygiene before breast feeding and wearing a face mask. Breast milk may be expressed after hand-hygiene and fed to infant by uninfected care-provider after disinfection (pasteurisation) [33].

12. Pregnancy and COVID-19 vaccines

Clinical trials to determine safety and efficacy of SARS-CoV2 vaccines have excluded pregnant women and so data on safety of vaccines in pregnancy is sparse. However, the vaccines that are not live attenuated are generally considered safe in pregnancy. Also, the animal studies done for safety and efficacy of the current vaccines for SARS-CoV2 have not shown any evidence of teratogenicity. RCOG recommends that SARS-CoV2 vaccine should be offered to pregnant women at the same time as general population [34]. ACOG recommends that mRNA vaccines for SARS-CoV2 should not be withheld from pregnant women and should be offered to lactating women [35]. It would be prudent to make the decision regarding use of SARS-CoV2 vaccines in pregnancy keeping in mind the activity of virus in community, risks and potential severity of illness in woman, efficacy of vaccine and risks to mother and fetus due to vaccination [35].

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Author details

Sushruti Kaushal and Harpreet Kaur*
Obstetrics and Gynecology, All India Institute of Medical Sciences (AIIMS),
Bilaspur, Himachal Pradesh, India

*Address all correspondence to: drharpreetsidhu7@gmail.com

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