

## Clinical Care of Pregnancy with Covid-19

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### Introduction

COVID-19, or novel corona virus disease made its debut in December 2019. Whilst its origins are a matter of speculation and debate, the problems it can cause are not. The coronavirus outbreak was declared as a public health emergency of international concern by the World Health Organisation (WHO) on 30<sup>th</sup> January, 2020 and as a “pandemic” on 11<sup>th</sup> March, 2020 [1]. Emerging data over the past year and half has shown some unique problems when Covid-19 infection occurs in pregnancy [2]. To add to this mix, have been the ever changing treatment protocols for Covid-19 that are being trialled and implemented and sometimes discarded after initial recommendation. Pregnant women represent a subset where experimental treatments are not tried straightaway, and data on what is safe in pregnancy is gradually evolving. This article will attempt to look at Covid-19 infection with respect to its impact on pregnancy and delivery and briefly touch upon vaccination during pregnancy and lactation, based on the evidence available to date.

One needs to be aware of the basic virology of Covid-19 virus. The incubation period is 5 - 10 days. Early antibody response is IgM which peaks within 7 days of infection and continues in the active phase (generally 2 weeks). Specific IgG and IgA antibodies develop several days after IgM and remain for several weeks. Exposure to SARS-CoV-2 may result in asymptomatic or symptomatic infection, the latter being categorised into mild, moderate and severe based on clinical and laboratory parameters [3]. In the early phase of infection viremia, occurs with constitutional symptoms of fever, dry cough, headache, diarrhoea and tiredness. The pulmonary phase starts with shortness of breath. Depending on host inflammatory response, it culminates in recovery or a hyperimmune response with cytokine storm and ARDS.

### Risk of infection during pregnancy

During pregnancy women experience physiological and immunological changes and a higher risk has been observed with SARS and MERS infections [2]. However, Pregnant women do not appear more likely to contract Covid -19 infection than the general population [4]. Pregnancy may worsen the clinical course of COVID-19 compared with non pregnant individuals of the same sex and age. Nearly 75 - 85% women admitted in labour may be asymptomatic from large UK and US databases (PRIORITY (Pregnancy CoRonavirus Outcomes RegIS-Try) study) [5]. Most symptomatic women experience only mild or moderate cold/flu-like symptoms - mostly cough and fever.

Though pregnancy does not increase susceptibility to SARS COV-2 infection, it worsens the clinical course of disease. Compared to non-pregnant women with COVID-19, pregnant women have higher rates of ICU admission and compared to pregnant women without COVID, the outcomes are slightly worse, with an increased risk of death. Severe illness appears to be more common in later pregnancy [6].

### Prenatal care

The American College of Obstetricians and Gynecologists (ACOG) [7] and the Society for Maternal-Fetal Medicine (SMFM) [8] recommend modifying traditional protocols of antenatal visits [7,8]. Fewer visits and more tele consultations help reduce the risk to health care providers. Protocol is tailored as per each woman's risk category. Aim is to reduce the total visits to only essential ones and routine ultrasonography can be delayed by 1 - 2 weeks easily. Unless it's an emergency, routine interventions and testing can wait till the woman becomes negative on RT-PCR for Covid.

### Complications during pregnancy

Global maternal and fetal outcomes have worsened during the COVID-19 pandemic, with an increase in maternal deaths, stillbirth, ruptured ectopic pregnancies and maternal depression. There is considerable disparity between high-resource and low-resource settings [9]. The adverse effects are both due to disease as well as delay in seeking care, due to lockdown and disruption of transport and healthcare facilities [10]. A systematic review and meta-analysis of studies on the effects of the pandemic on maternal, fetal and neonatal outcomes has been conducted recently evaluating 40 studies from different parts of world [11].

### Maternal effects

Pregnant women with symptomatic COVID-19 have a higher risk of intensive care unit admissions, mechanical ventilation and death compared to non-pregnant reproductive age women [12]. Increases in preterm birth and still birth have also been observed in pregnancies complicated by the viral infection though it varies a lot from place to place [13-16]. Maternal COVID-19 is also associated with an increased rate of caesarean birth - 49% caesarean birth rate, mostly for maternal or fetal compromise, but also for obstetric reasons (e.g. slow progress in labour, previous caesarean birth) or maternal request. Of the women having a caesarean birth, 20% required general anaesthesia, due to maternal respiratory compromise or to facilitate urgent delivery. Risk of exposure is higher for front-line workers with use of general anaesthesia [17,18]. There is also increase in mental health problems including anxiety and depression during pregnancy and post partum period [19-21].

### Fetal effects

In initial studies vertical transmission was not considered. Currently few studies have reported cases with probable vertical transmission [22,23]. The extent of vertical transmission (in utero, intrapartum, early postnatal period) remains unclear. Covid-19 Maternal infection within 14 days of delivery has led to congenital infection in approximately 2% of neonates [24].

There is no increase in congenital anomalies. The incidence of fetal growth restriction is also at the background rate, possibly because the condition is one of acute compromise, not chronic hypoxia. Pregnant women with asymptomatic COVID-19 were not, however, at increased risk of preterm birth. Symptomatic maternal COVID-19 is associated with a two to three times greater risk of preterm birth, principally from iatrogenic preterm birth to improve maternal oxygenation. The systematic review [11] identified significant increases in stillbirth rate (pooled OR 1.28 [95% CI 1.07 - 1.54]; higher preterm births in poor countries and lower than normal in high income countries. Overtime a decrease in preterm births is being reported [25,26]. Lockdown resulted in higher stillbirth and lower preterm birth rate [27].

### Management during pregnancy

There is no specific treatment for Covid -19 infection. Management is highly individualized depending on severity of symptoms.

**Home care vs in-patient care**

As stated earlier majority are with mild disease. At all stages of pregnancy, women with mild disease should self-isolate, wear a triple layer mask and be in a well ventilated room with cross ventilation. Mask should be discarded and replaced with a new one after 8 hours of use or if becomes wet. Hands should be washed with soap and water for at least 40 seconds each time, alternatively hand sanitizer is used periodically. Household items should not be shared with other family members, and common surfaces should be disinfected with 1% hypochlorite.

Treatment is symptomatic in consultation with treating physician, for fever, running nose and/or cough. Adequate rest and hydration are a must. Warm water gargles and steam are helpful. Self-monitoring of oxygen saturation and temperature should be done every 4 hours or more frequently as required. One can maintain a chart with the parameters of time, temperature, pulse and saturation, and also note whether breathing and general well-being are same, better or worse. This serves as an early warning tool for planning hospitalisation.

During home isolation, if any of the following danger signs appear, urgent action including hospitalization is required: worsening shortness of breath, tachypnea, oxygen saturation  $\leq 94\%$ , persistent high grade fever despite anti-pyretics, confusion, lethargy, inability to tolerate oral medications, chest pain or cyanosis.

Any obstetrical concern like pain, bleeding or reduced fetal movements also require hospitalization. Other risk factors for hospital admission include: age  $> 35$  years, BMI  $> 25$  kg/m<sup>2</sup>, pre-pregnancy co-morbidity and poor socio-economic status.

All pregnant women with moderate and severe infection should be admitted in hospital or specialized Covid centre with joint management under chest physician and obstetrician.

**Management of severe Covid**

In pregnancy it should be multi-disciplinary. Obstetrical care providers should look for changes not only in measured oxygen saturation by pulse oximeter, but also the supplemental oxygen requirements required to maintain appropriate levels. Recommended saturation in pregnancy is greater than 95%. Oxygen therapy is given as per standard protocol in Covid infection and may be non-invasive ventilation, mechanical ventilation or ECMO depending on the severity and need.

**Investigations**

Generally, no investigations are required in mild disease. For moderate and severe disease following tests are done as baseline - CBC, absolute lymphocyte count, LFT, KFT and repeated every 24 - 48hrs depending on report and CRP, ESR, D-Dimer, Procalcitonin, IL6, LDH, Ferritin are done as baseline and repeated in 48 - 72hrs. Laboratory findings based on severity of disease are listed in table below.

Parameter	Mild	Moderate	Severe
NLR	< 3.5	> 3.5	> 5.2
CRP	< 20	20 - 50	> 50
Ferritin	< 500	> 500	> 800
D-Dimer	< 0.5	0.5 - 1.0	> 1.0
LDH	< 300	300 - 400	> 400
IL-6	< 5	5 - 50	> 50 or rising
LFT	Normal	Slight deranged	Moderate deranged

**Table**

### Drugs for treatment of Covid -19

**Steroids:** NIH Covid-19 treatment guidelines panel recommends against using Dexamethasone in patients who do not require supplemental oxygen. Use is recommended for those who are mechanically ventilated or those on supplemental oxygen but not ventilated. Inhalational Budesonide (with spacer) - 800 mcg twice daily for 5 - 7 days is useful if symptoms (fever, cough) persist beyond 5 days. Oral steroids are recommended if symptoms persist beyond 7 days or worsening fever and cough. Pregnant women who meet criteria for use of glucocorticoids for maternal treatment of Covid-19 can receive standard doses of steroids [28]. For those requiring steroids for fetal lung maturity, usual dose regimen is followed (6mg, 4 doses, 12 hours apart). Unlike dexamethasone, prednisolone and hydrocortisone are extensively metabolised in the placenta with minimal transfer to the fetus. Aside of dexamethasone for lung maturity, the preferred options are oral prednisolone 40 mg once a day, or IV hydrocortisone 80 mg twice daily, for 10 days or until discharge, whichever is sooner.

**Remdesivir:** It has emergency use approval for moderate-severe disease, requiring supplemental oxygen, within 10 days of symptom onset, with no renal or hepatic dysfunction. Dosage - 200 mg i.v. on D1, 100 mg i.v D2-D5. Safety of remdesivir in pregnancy is largely unknown, it is recommended that it should be avoided in pregnant women with COVID-19 unless clinicians believe the benefits of treatment outweigh the risks to the individual [4].

**Tocilizumab:** It is an IL6 antagonist (off-label use) and recommended only in severe disease, within 24 - 48 hours of onset of severe disease or ICU admission, in women with significantly raised inflammatory markers (CRP, IL-6), no improvement despite steroids, and no active bacterial/fungal or tubercular infection. Although data for the use of tocilizumab in pregnancy in this situation are limited, there is currently no compelling evidence that tocilizumab is teratogenic or fetotoxic. For women meeting the criteria mentioned above (hypoxic with systemic inflammation), the use of tocilizumab should be considered.

Hydroxychloroquine, lopinavir- ritonavir and azithromycin have been shown to be ineffective in treating COVID-19 infection and should not be used for this purpose.

Magnesium sulfate therapy is recommended for neuroprotection of the neonate and should be offered to women up to 29<sup>+6</sup> weeks of gestation and considered up to 33<sup>+6</sup> weeks of gestation.

While most patients with severe COVID-19 infection will have normal or even high platelet counts, it can be associated with thrombocytopenia. When aspirin has been prescribed as prophylaxis for pre-eclampsia, it should be discontinued for the duration of the infection as this may increase the bleeding risk in thrombocytopenic women.

Thromboprophylaxis during pregnancy: Pregnancy being a hyper coagulable state, risk assessment for thromboembolism should be done, factoring Covid as a transient risk factor. In addition to hydration and mobility, Low Molecular Weight Heparin is prescribed based on risk assessment. Thromboprophylaxis that has been commenced for pregnant women who are self-isolating should be continued until they have recovered from the acute illness (between 7 and 14 days) [29]. All pregnant women admitted with confirmed or suspected COVID-19 should be offered prophylactic LMWH, unless birth is expected within 12 hours or there is significant risk of haemorrhage. All pregnant women who have been hospitalised and have had confirmed COVID-19 should be offered thromboprophylaxis for 10 days following hospital discharge. If women are admitted with confirmed or suspected COVID-19 within 6 weeks postpartum, they should be offered thromboprophylaxis for the duration of their admission and for at least 10 days after discharge<sup>4</sup>. Women who take LMWH thromboprophylaxis during pregnancy should discontinue this if their platelet count falls below  $50 \times 10^9/l$  and their care should be discussed with a haematologist.

### Obstetric management

Covid positive pregnant women should preferably be admitted in the Obstetric Unit with ICU facility. There should be capacity to isolate and provide oxygen and respiratory support for COVID positive women. There should also be facility for safe breast feeding/breast milk provision, KMC and sick and small newborn care [30].

Covid-19 positive status is not an indication for delivery [31,32]. In asymptomatic or mild symptomatic patients it is better to wait till woman becomes negative and induction of labour is avoided. However, medically indicated deliveries should not be delayed solely due to Covid-19 positive status. Between 37 - 39 weeks without other indications for delivery - expectant management is preferred until 14 days after PCR result or until 7 days after onset of symptoms or 3 days after resolution of symptoms. This allows for decreased exposure of health care worker and neonate and less PPE utilization. In women > 39 weeks, delivery can be considered to decrease risk of worsening maternal status.

For women presenting in spontaneous labour, all infection prevention measures should be in place. Pregnant women should wear a mask throughout labour, delivery and post-partum [33,34]. Mode of delivery is decided by obstetric indications. In women with symptomatic Covid-19, there may be an increased risk of fetal compromise in active labour, thus continuous fetal monitoring is recommended. There is no evidence that delayed cord clamping and skin-to-skin contact between woman and baby increases the transmission of SARS-CoV-2 to the neonate. The rate of neonatal COVID-19 infection is no greater when babies are born vaginally, breastfed or stay with their mother after birth [35]. Management of third stage of labour is not affected by Covid-19 infection. Post partum haemorrhage if occurs is managed as per standard protocol.

Delivery may be considered after 32 weeks in women with Covid pneumonia even if there is no obstetric indication as it will allow further optimization of care. It is unclear whether delivery provides substantial improvement in every case. However, mechanical ventilation improves and if there is severe hypoxemia, other options like prone positioning and ECMO can be easily provided.

Labour anesthesia - neuraxial block, provides good analgesia, reduces cardio-pulmonary stress from pain and anxiety and can be topped up in case emergency caesarean is required [36]. Nitrous oxide for pain relief is not preferred as per SOAP (Society of Obstetric Anesthesia and Perinatology), although there is no evidence that the use of Entonox is an aerosol-generating procedure. Intubation, required for GA, generates aerosols that significantly increase the risk of transmission of SARS-CoV-2 to attending staff.

### Post partum care

Evaluation of newborns: New-borns of Covid positive mothers should be treated as suspects. Ideally RT PCR naso-pharyngeal swab within 24 hrs of birth and repeat after 48 hrs [37]. This takes care of false positive result due to maternal contamination. Single test at discharge can be planned if there is heavy case load.

There is no recommendation for separating mothers and babies after birth in Covid suspects or positives except if mother and newborn are very sick. Rooming-in helps bonding and establishing breast feeding. New-born can be kept in the same room, but 6 feet apart on a separate bed with a healthy care giver who is tested negative and observes all precautions. Mother wears surgical mask and performs proper hand hygiene before breast feeding, skin to skin contact or routine care. Along with this, effective family education in infection prevention strategies should be given. These precautions should be continued after discharge for ten days after testing positive on routine screen in asymptomatic mothers and ten days post symptom onset in symptomatic being afebrile for at least 3 days.

There is no need to curtail breast feeding unless mother or baby is very sick. Breast milk does not spread the virus [38], however, all precautions need to be taken while breast feeding to prevent respiratory transmission. Hands should be washed before and after touching

the baby. Expressed milk feeding is also a safe option if help is available to mother, so that she does not handle the baby till she is negative on RT-PCR.

Hospital discharge for mothers is based on need for monitoring and hospital care, availability of home isolation facilities in symptomatic patients. For asymptomatic patients, discharge is planned as for non-covid patients (48 or 72 hrs after delivery based on mode of delivery). All households should self-isolate at home for 14 days after birth of a baby to a woman with COVID-19, to ensure a full period of isolation in case of incubation of the virus in the baby.

Post natal visits are as usual. All post partum women should be screened for depression [39] and contraception plus vaccination counselling is done during post natal visit.

### Vaccination

The Joint Committee on Vaccination and Immunisation (JCVI) published updated advice on the 30 December 2020 and confirmed the available data do not indicate any safety concerns or harm to pregnancy, and vaccination in pregnancy should be considered where the risk of exposure to SARS-CoV-2 infection is high or cannot be avoided [40]. Furthermore, the JCVI stated that vaccination should be considered where the woman has an underlying condition that puts her at very high risk of serious complications of COVID-19. Similar advice was issued for breastfeeding women.

The Centers for Disease Control and Prevention (CDC) recommended that people who are pregnant may choose to be vaccinated at their own discretion with their healthcare provider. However, pregnant and lactating women were not included in Phase 3 vaccine efficacy trials; thus, data on vaccine safety and immunogenicity in this population is limited [41].

Center for Virology and Vaccine Research evaluated the immunogenicity of COVID-19 mRNA vaccines in pregnant and lactating women who received either the Pfizer or Moderna COVID-19 vaccines. The researchers found that both vaccines triggered robust immune responses in pregnant and lactating women [42,43]. Maternal vaccine antibodies were also detected in cord blood and breast milk providing indirect protection to the newborn [44,45].

An exploratory, descriptive study of 103 women, ages 18 - 45, who received an mRNA COVID-19 vaccine (54 percent received Pfizer; 46 percent received Moderna), found similar levels of vaccine-induced antibody function and T cell responses in all non-pregnant, pregnant and lactating women after their second vaccine dose [46]. Additionally, both pregnant and non-pregnant women who received the mRNA vaccines developed cross-reactive immune responses against the COVID-19 variants of concern B.1.1.7 and B.1.351.

### Summary

There are guidelines by all international societies as well as country specific guidelines for management of COVID-19 infection during pregnancy. Most are based on current evidence as well as country specific scenario and are regularly updated. The article outlines the basic principles of management. Health care providers associated with COVID-19 management in pregnancy should refer to latest guidance specific to their area of work to provide optimal care.

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