Review Article

Swayam Swaroop Misra, Ashok Kumar Ahirwar*, Apurva Sakarde, Kirti Kaim, Pradeep Ahirwar, Mohd. Jahid, Smita R Sorte, Suryabhan Lahanu Lokhande, Amar Preet kaur and Rajani Kumawat

COVID-19 infection in pregnancy: a review of existing knowledge

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Abstract: The world has been coping up with the grave pandemic of COVID-19 since its inception into the human race in December, 2019. By entering the host through the spike (S) glycoprotein, it paves way for its own survival and multiplication. Respiratory tract being the point of entry causes pulmonary compromise and leads to development of ARDS. Having non-specific clinical features that resemble flu makes the clinical diagnosis much more

difficult. Pregnancy being an immunocompromised and a hypercoagulable state is prone to be a high-risk group for COVID-19. This study is an attempt to understand the maternal and fetal outcomes in COVID-19 and the vertical transmissibility of the virus. Evidence suggests that the contribution of COVID-19 is not very significant in maternal morbidity and mortality. However, due to some factors such as the immunological response in the mother, certain complications may arise in the neonate in the post-natal period. No vertical transmission of the virus has been reported yet. However, the management remains crucial as two lives are at stake. Some of the precautionary measures that can be implemented to prevent COVID-19 can be segregation of medical services from that of the general population in settings of outpatient care, inpatient care and labor room care. Also, triaging the patients into low risk, moderate risk and high risk can aid in faster delivery of health-care facilities to the pregnant and the newborn.

***Corresponding author: Ashok Kumar Ahirwar**, MD, DNB, Assistant Professor, Department of Biochemistry, University College of Medical Sciences, New Delhi, 110095, India, Mobile: +919654210832, E-mail: drashoklhmc@gmail.com. <https://orcid.org/0000-0003-3371-378X>

Swayam Swaroop Misra, All India Institute of Medical Sciences, Nagpur, Maharashtra, India, E-mail: swayam.swaroop@hotmail.com
Apurva Sakarde, Department of Biochemistry, All India Institute of Medical Sciences, Nagpur, Maharashtra, India, E-mail: aforapurva@gmail.com. <https://orcid.org/0000-0003-0645-1227>

Kirti Kaim, ESI Hospital, New Delhi, India, E-mail: kirti.kaim@gmail.com

Pradeep Ahirwar, Department of Radio-diagnosis, Index Medical College Hospital & Research Centre, Indore, Madhya Pradesh, India, E-mail: pradeepahirwar21@gmail.com

Mohd. Jahid, Department of Biochemistry, University College of Medical Sciences, New Delhi, India, E-mail: zahidkhan780@gmail.com

Smita R Sorte, Department of Physiology, All India Institute of Medical Sciences, Nagpur, Maharashtra, India, E-mail: drsmyta@gmail.com

Suryabhan Lahanu Lokhande, Department of Biochemistry, All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, India, E-mail: lokhandesuryabhan@gmail.com

Amar Preet kaur, Department of Biochemistry, All India Institute of Medical Sciences, Gorakhpur, Uttar Pradesh, India, E-mail: amar_0044@yahoo.com

Rajani Kumawat, Department of Biochemistry, All India Institute of Medical Sciences, Bathinda, Punjab, India, E-mail: dr.rajanikumawat@gmail.com

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Introduction

The world is experiencing yet another pandemic called COVID-19 caused by the Novel Corona Virus (nCoV) or SARS-CoV-2. The virus is enveloped having positive-sense ssRNA. It belongs to the family coronaviridae and there are 4 genera of coronaviruses: Alpha, Beta, Gamma and Delta. The nCoV belongs to Betacoronaviruses [1, 2]. Viral genome analysis has shown some phylogenetic similarity to SARS-CoV, MERS-CoV, SARS-CoV [2, 3], and thus named SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV).

Emerging with the first case in the city of Wuhan, China in December 2019, the virus globally has now 263,563,622 confirmed cases, including 5,232,562 deaths as on 3 December 2021 as reported on the WHO COVID dashboard. Since the outbreak of COVID-19, a number of

studies have been conducted on the effects of the virus on pregnant women and the neonate. 118 pregnant women had been reported from Wuhan city, China between 8 December 2019 and 20 March 2020 [4]. Many cases in the pregnant have been reported in India as well including a few deaths.

Pregnancy being a state of altered physiological and immunological function has high risk of acquiring the infection. There are adaptive changes in respiratory system like decrease in respiratory volumes, increased oxygen consumption, elevated diaphragm and edema of the respiratory tract which contribute in abbreviating intolerance to hypoxia. Also, there is hypercoagulable state which renders the pregnant more susceptible to severe disease. Previous studies in SARS and MERS on the state of pregnancy have been known to cause many complications in pregnancy [5]. Vertical transmission has not been reported yet and many more studies are underway.

Structure and pathogenesis

The SARS-CoV-2 has a spike protein (S), hemagglutinin-esterase dimer (HE), a membrane glycoprotein (M), an envelope protein (E), a nucleocapsid protein (N) and RNA [6]. The spike protein (S) has two subunits S1 & S2 [3] and is heavily glycosylated with 23 glycosylation sites. By using an N-terminal signal sequence, it mediates attachment to host receptors. The SARS-CoV-2 enters the cell by binding to ACE2 receptor through its envelope spike (S) protein [7]. However, there has to be prior activation of spike protein i.e. priming by a cellular serine protease TMPRSS2 [8]. The SARS-CoV-2 spike protein has a strong binding affinity to human ACE2 receptor due to mutations in the receptor-binding domain (RBD) as compared to other viruses of the family [3, 9–11]. The binding of the RBD of the SARS-CoV-2 triggers a series of events leading to fusion of the viral membrane with that of cell for its entry. Studies have shown that, on binding there is dissociation of the S1 subunit which paves way for the S2 subunit to go for a hinge like movement and form a more stable state post-fusion [3, 12]. About 83% of ACE2-expressing cells are alveolar epithelial type II cells, though there is expression in extra pulmonary tissues like heart, ileum, kidney and endothelium as well. In the intestines, ACE2 is highly expressed on the luminal surface of intestinal epithelial cells [8]. As ACE2 has also been found to be expressed on innate lymphoid cells ILC2 and ILC3, the virus can attack these cells as well. The lung epithelial cells which have been infected by the virus have shown to release IL-6 and

IL-8. IL-8 is a chemo attractant, attracting both neutrophils and T cells. Neutrophils, on the other hand can act as double-edged sword by inducing lung injury, leading to severe pneumonia. Hence the pathogenesis is not entirely due to direct attack through virus, but through immunological mechanisms that lead to the pathogenesis of COVID-19 associated complications. *In vitro* studies have shown a delayed release of cytokines and chemokines from the cells of innate immunity at the lung epithelium, i.e. dendritic cells and macrophages in early stages of infection. Later, these cells secrete antiviral interferons (IFNs) and proinflammatory cytokines like IL-1 β , IL-6, IL-8, TNF and chemokines CCL-2, CCL-3 and CCL-5. So, nCoV-19 infects airway epithelial cells, macrophages and dendritic cells and induces a delayed release of proinflammatory cytokines and chemokines. Based on the severity of the disease condition, there has been demonstration of increased levels of IL-1 β , IFN γ , CXCL-10 and CCL2 which is indicating probably more towards TH1 cell activation. The “cytokine storm” might be the main factor leading to a more severe manifestation of the disease course. This can be attributed to the observation that the COVID-19 patients requiring more intensive care had higher concentrations of CXCL10, CCL2 and TNF α . Also, these patients were found to have cytokines like IL-4 and IL-10 which are anti-inflammatory and are released due to the activation of TH2 cells. So, unequivocally, there is a cytokine storm resulting from release of large amounts of proinflammatory cytokines (IFN α , IFN γ , IL-1 β , IL-6, IL-8, IL-10, IL-12, IL-18, IL-33, TNF α , TGF β) and chemokines (CXCL10, CXCL8, CXCL9, CCL2, CCL3, CCL5) which aggravates and maintains the abnormal inflammatory response. This cytokine storm along with rapid viral multiplication induces apoptosis in the lung epithelial and endothelial cells. The interferons signal inflammatory cell infiltration by involving Fas ligand and death receptor 5 (DR 5) and cause apoptosis of endothelial and epithelial cells. This damages the micro vasculature of the lungs and causes vascular leakage and edema which presents as hypoxia. So, the immune mediated mechanisms play a key role in ARDS and multi-organ failure.

Clinical features and laboratory findings

SARS-CoV 2 usually affects the respiratory system presenting with an array of symptoms from mild in the form of common flu-like symptoms like fever, rhinitis, shortness of

breath, cough, loss of sensation of smell and taste, sore throat, body ache to severe acute respiratory syndrome, pneumonia and death. The incubation period ranges from 2–14 days and the spread of the virus more commonly is known to be through droplet transmission or direct contact of contaminated surface. Some studies have shown the presence of the virus in the stools of infected patients suggesting a possible faeco-oral route of transmission.

It is not unknown of the fact that any outbreak will have some targeted population of high risk who will face more morbidity and mortality. In this case, it has been found that elderly (age > 60), people suffering from cardiovascular diseases, diabetes and having other comorbidities are at a higher risk of adverse outcome. Patients with more severe forms of the disease who require admission to the intensive care unit present with ARDS, multi-organ failure with shock etc.

COVID-19 in pregnancy

Most pregnant females with COVID-19 have been seen to develop milder symptoms including fever, cough and dyspnea and are diagnosed as mild pneumonia. Although few cases with multiorgan failure, ARDS requiring ICU admission with renal failure and hepatic failure and septic shock have also been reported. Almost all of them show increased or normal (near upper limits) WBC counts with lymphopenia. Some cases with thrombocytopenia have also been reported. In comparison to non-pregnant women, pregnant women were found to have higher levels of serum C-reactive protein (CRP). The baseline haemoglobin levels and albumin levels were lower which may be ascribed to hemodilution of pregnancy. A small number of pregnant females with COVID-19 had elevated levels of serum creatinine, LDH, AST, CK-MB and ESR. A rise in fibrinogen and D-dimers was also seen; D-dimer being a procoagulant marker which may be elevated in viral infections. A variable degrees of fibrin deposition in and around the chorionic villi was also noted in some cases [5]. These rise in inflammatory markers support the cytokine storm theory for possible pathogenesis, whereas the lymphopenia suggests the involvement of T-lymphocytes. It has also been observed that there is a rise in these markers post-partum [13]. A significant change in number of the immune cells including macrophages, NK cells, T cells during post-partum period is seen. This can be supported by the fact that there is a sudden decrease in steroid hormone concentrations post-partum, contrary to the

progressive trend through the course of pregnancy. Both these may trigger the onset of COVID-19 symptoms following partum. The chest CT scans have shown bilateral typical patchy ground glass opacity showing features of pneumonia [13]. No aggravation of pneumonia was seen following delivery. However, in these studies, the state of pregnancy did not suggest any relation with the severity of the disease experienced as most of the pregnancies went uncomplicated and COVID-19 was in milder forms [4, 14–20].

Complications of COVID-19 in pregnancy

With hormonal changes, respiratory adaptations, immunologic adaptations, fluid overload, there has always been an increased susceptibility to viral infections particularly respiratory viruses, as evident from previous respiratory viral outbreaks in pregnancy (e.g., influenza) [14]. This is further followed by complications along with a possible threat to the developing fetus [15, 16]. With regards to pre-eclampsia, the SARS-CoV-2 infection has not shown to increase the risk of pre-eclampsia nor pre-eclampsia was found to affect the disease progression and outcome. The premature rupture of membranes does not seem to occur at higher rates than the general population. A case series showed high rate of complications requiring emergency caesarean section due to fetal distress, premature rupture of membranes and still birth although the COVID-19 symptoms present were mild to moderate [17, 18]. Another study showed that there was no increased risk of perinatal complications in women suffering from COVID-19 including severe preeclampsia such as premature rupture of membranes, fetal distress, meconium staining, premature delivery, neonatal asphyxia and postpartum hemorrhage [4, 19, 20]. This can be attributed to the smaller sample sizes taken in the studies and the selection bias. Further studies need to be conducted in this regard. The comorbid pregnant population though suffered complications of pregnancy, the rate of occurrence of complications were similar to that of pregnant population without COVID-19 [4, 15–20].

Fetal outcomes in COVID-19

The studies conducted so far suggest that vertical transmission of SARS-CoV-2 *in utero* has not occurred, as the amniotic fluid, umbilical cord blood, placenta, vaginal

swabs and breast milk tested negative for SARS-CoV-2 by RT-PCR [16]. Few neonates however have tested positive for SARS-CoV-2. Hence the mode of transmission remains an enigma in these cases [14, 16]. However, with the mother presenting with pneumonia and developing immunological responses to the virus, consequent effect on the fetus can definitely be attributed. Statistically significant risks of fetal distress, meconium stained liquor, premature delivery and neonatal asphyxia were not found [17]. Some infants born to COVID-19 infected mothers however presented with shortness of breath, febrile illness, tachycardia, gastric bleeding, bloating, feeding intolerance, thrombocytopenia, neonatal respiratory distress syndrome etc. [13]. Lymphocytopenia and thrombocytopenia along with deranged LFT was found in infants in most of the case studies of COVID-19 infection in pregnant females [14].

Detection and diagnosis of COVID-19 in pregnant female

The gold standard for detection and diagnosis remains the real time reverse transcriptase PCR to detect viral RNA. Respiratory tract specimens or blood specimens can be taken for testing. Since pneumonia is seen to develop in some cases, CT scans can be beneficial, which usually show typical ground glass opacities. Sequential organ failure assessment (SOFA) score can be used to assess severity of disease. However, to be beneficial in pregnant population, the score should be modified to compensate for the adaptations in pregnancy. Elevated D-dimers being a good marker cannot be used in pregnancy solely as the state of pregnancy itself is supposed to raise D-dimer levels. Cord blood, placenta, vaginal swabs, breast milk and amniotic fluid (if possible) should be tested for viral RNA to check for evidence of vertical transmission.

Management of COVID-19 in pregnancy

Prevention of COVID-19 is always the best strategy in any population. Refraining from travelling, maintenance of social distancing, use of N-95/surgical masks and regular sanitization of objects touched with the use of an alcohol-based solvent as well as frequent hand washing/sanitization before and after touching the face can play a vital role in preventing transmission of the virus. Triaging the pregnant as per history or disease as well as allocation of dedicated healthcare workers can help to ensure proper care as shown in Figures 1 and 2.

For patients having mild or no symptoms, symptomatic treatment wherever isolation is possible in the comforts of their homes may be recommended along with on call visits if required. For patients with co-morbidities like diabetes and hypertension, depending on the severity of the case, priority treatment should be provided. The mildly co-morbid may be provided with a glucometer or a digital sphygmomanometer for regular self-monitoring supplemented by on call visits as and when required. Patients requiring inpatient care should be closely monitored for their vitals and should be evaluated if SpO₂ is <95%, Respiratory rate >30 per minute and pulse >120 per minute. Fetal heart rate should be monitored and chest CT may be done with fetal shielding if necessary. Triaging the patients not only otherwise but also in labour wards may help in identifying early complications and efficient delivery of healthcare. Close monitoring of infant and the mother is an essentiality postpartum. Breast feeding has not been contra-indicated as the viral RNA has not been detected in breast milk; however, proper precautions should be taken so as to prevent transmission by aerosols by proper use of masks during breastfeeding and sanitization of breasts prior to latching [21–27].

Figure 1: Healthcare delivery segregation to aid in better delivery of healthcare facility to the public in the pandemic.

Figure 2: Triaging of pregnant for better delivery of healthcare facilities.

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