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Coronavirus infection and pregnancy

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Abstract
After its first outbreak in 2019, SARS-CoV2 quickly attained pandemic status and has caused unprecedented deaths throughout the world. However, being a Coronavirus, it shares its genome with SARS1 and MERS whose first outbreak occurred in 2002 and 2012 respectively. These Coronaviruses causing disease in human beings, also posses' potential threat to the pregnant woman and the newborn progeny. Comparative study of the three different Coronavirus diseases in this group shows that a lot of similarities in symptoms and the outcome exists. To date, the therapy to treat Coronavirus disease in such cases also basically requires symptomatic treatment as the most potential safe option for the healthcare workers to be practiced.

Keywords: Coronavirus infection, pregnancy, SARS1, MERS

Introduction
The various diseases *viz.* the plague, rabies, Ebola, Zika virus infection, Nipah virus infection, *etc.* have created havoc situation in the past, however, the novel coronavirus COVID-19 (SARS coronavirus 2/SARS-CoV 2) have gained a noteworthy relevance worldwide even much more than that of the Spanish flu outbreak in the year 1918 because of the rapid worldwide spread, the unavailability of reliable theranostics and the questionable immunological memory issue of existing vaccines. In the current scenario, viral outbreaks are more frequent rather than bacteria or fungus. Moreover, the world had already faced a Spanish flu epidemic so the next pandemic of a flu virus (like the bird flu or the swine flu) was expected as flu viruses can adapt to different kinds of environments and can also undergo the trans-species switch involving the rapid mutations in their genome by the means of antigenic shift and antigenic drift. But it is also true that all the speculations went blank and instead coronavirus (CoV) became a major disease in 2020.

Hudson and Beaudette isolated coronavirus in the 1930s for the first time (Hudson and Beaudette 1932) [41]. It is well-known fact that domestic and wild animals serve as a reservoir for the coronaviruses. However, it becomes highlight after its first outbreak (SARS1 CoV) report in humans as a severe acute respiratory syndrome (SARS) in Guangdong province, China in the year 2002 (WHO, 2003a and 2003d) [42-43]. The SARS1 cases from 32 countries *viz.* Vietnam, Canada, Singapore, etc, and around 800 deaths with a total of more than 8000 infected persons in a very short time albeit WHO had issued early alarming global warnings about the disease (WHO, 2003e) [44]. However, the quick response of WHO and the governments of the affected countries restrict somewhat the incurred loss. This spread established the ability of the coronavirus (CoV) to cause potential pandemic disease.

Another trans-species switch of CoV in 2012 led to Middle East respiratory syndrome (MERS) outbreak in the Middle East, some parts of North Africa and South Korea, recognized as MERS-CoV (Mackay and Arden 2012; Fehr and Pearlman 2015; Cowling *et al*. 2015) [39, 40, 38]. One crucial difference among them has been the rate of spread, SARS (both SARS1 and SARS2) being more rapid in its response to cover a large area on the globe in comparison to MERS. Conversely, the comparative sequence and phylogenetic studies have portrayed them to be distinct from each other. MERS-CoV is supposed to be originated from an animal species probably bat because of the very high genomic similarity of MERS-CoV with the genome of CoV isolated from bats of the Middle East region (Kandeel *et al*. 2014) [29]. Camels may be one of the probable (animal to human) infection sources as the high antibody titer against MERS-CoV in both symptomatic and asymptomatic camel-handling persons as well as camels of Saudi Arabia has been documented (Choi *et al*. 2017) [30]. It has also been suspected that the reservoir for MERS-CoV is bat and camel (Cowling *et al*. 2015) [38], whereas for SARS-CoV is bat or pangolin (Zhou *et al*. 2020; Zhang *et al*. 2020) [34, 8-35].

Coronavirus Structure and Entry into Host

Coronaviruses (order-Nidovirales, family-Coronaviridae, and subfamily-Coronavirinae) have been broadly classified in four different subdivisions (genus), alpha-coronaviruses, beta-coronaviruses, gamma-coronaviruses, and delta-coronaviruses (Ujike and Taguchi 2015) [3]. Humans get infected by seven types of coronaviruses, out of which two are alpha-coronaviruses while the rest five are beta-coronaviruses. Both SARS (SARS1 and SARS2) and MERS coronavirus belong to the beta-coronavirus genera (CDC 2020). Enveloped coronaviruses with characteristic glycoproteins of sizes 80 to 120 nm usually assume a spherical shape but can also be pleiomorphic. The positive-sense single-stranded RNA is 5' capped and has a length of 26 and 32 kb with six open reading frames (ORFs) and also with a 3' poly-A tail makes it the longest genome among all RNA viruses (Ujike and Taguchi 2015; Perlman and Netland 2009) [3, 31]. The proximal two-thirds of the genome (*i.e.* ORF1a and ORF1b) encodes the replicase-transcriptase proteins, whereas the genes of the remaining one-third portion arranged in a predetermined order encode for the virus structural protein starting with spike (S) protein, followed by an envelope (E) protein, membrane (M) protein and finally ends in a nucleocapsid (NC) protein (Gorbalenya *et al*. 2006*)*. Additionally, the genes encoding accessory proteins are also present somewhere in between the major genes. This genomic structure remains wrapped initially by a helical NC protein and finally by a host-derived lipid bilayer along with S, M, and E proteins (Belouzard *et al*. 2012) [26]. Apart from aforesaid proteins, some coronaviruses also carry a hemagglutinin esterase protein.

The virus entry in the host cell depends on the usual phenomenon *viz*. virus and host cell interaction but by a specific mechanism which may vary species-wise. The virus spike (S) protein binds with a specific cell receptor through which the virus fuses its envelope with the target cell membrane and consequences their nucleocapsid release into the host cell (Li 2015) [17]. The S protein is comprised of a large ectodomain having two [S1 (for receptor binding) and S2 (for membrane fusion)] segments/subunits, a single-pass transmembrane anchor, and a short intracellular tail. (Li 2016; Agrawal *et al.* 2021) [48]. Different coronaviruses target a variety of receptors and initiate fusion activation (Li 2015) [17]. SARS-CoV uses angiotensin-converting enzyme 2 (ACE2) present in lungs for entering human cells (Li *et al*. 2003) [37], whereas MERS-CoV uses dipeptidyl peptidase 4 (DPP4) for the entry into human cells (Doremlen *et al*. 2014) [36]. Consequently, the receptor density-based diverse disease outcomes have been noticed. The present SARS-CoV2/COVID-19 pandemic accentuates the exploration of coronaviruses-mediated health predicaments and the extension of the research area as the information's about COVID-19 is not completely unearthed. Hence, the pregnancy-associated complications with MERS-CoV and SARS-CoV have complied in this review.

Effect of MERS-CoV infection on pregnancy

MERS-CoV has an affinity for serine peptidase DPP4 (Doremlen *et al*. 2014) [36] a glycoprotein of 110 kDa which is ubiquitously expressed on the surface of a variety of cells (Röhrborn *et al*. 2015). MERS-CoV infected person may be asymptomatic or may show characteristics respiratory illness with presence or absence of cough, acute respiratory distress syndrome, sore throat, muscle pain, abdominal pain, nausea, chest pain, rash fatigue, diarrhea, acute renal failure, shock, immune-suppression, etc (Drosten *et al*. 2013; Oboho *et al*. 2014; Payne *et al*. 2014) [28, 27, 25]. The pregnancy-related complications of MERS-CoV had also been explored.

The five MERS-CoV-positive pregnant women of Saudi Arabia were identified as critical and were admitted to ICU from November 2012 to February 2016. Two out of five born infants died although the transfer of MERS-CoV from mother to infants had not been witnessed. One was stillbirth at 34th week but completely recovered mother from MERS-CoV infection was discharged. Another one delivered surgically at 24th week died after four hours of delivery and mother died after several days. The mother who delivered a healthy neonate died after some days due to MERS-CoV (Assiri *et al*. 2016) [23]. The stillbirth case by a 5th-month pregnant MERS-CoV-positive woman in Jordan had also been reported (Payne *et al*. 2014) [25]. The pregnant woman showed acute respiratory symptoms accompanied by fever, rhinorrhea, fatigue, headache, and cough during the infection. On the seventh day of illness, vaginal bleeding and abdominal pain led to the spontaneous delivery of a stillborn infant.

Another case in Abu Dhabi, UAE reported a 32-year old pregnant MERS-CoV positive woman showing more respiratory symptoms, hypotension with persistent hypoxemia emergency which was being shifted to ICU as she did not respond to initial antibiotic and supportive treatment well. The baby delivered via cesarean section was healthy. The mother died due to deteriorating condition and septic shock despite intensive support (Malik *et al*. 2013) [24].

A 33-year-old nurse contracted the MERS-CoV disease at 32 weeks of pregnancy after *in-contact* with a MERS-CoV positive patient and quickly developed respiratory symptoms accompanied by cough. She was admitted to ICU, recovered from MERS-CoV infection, and delivered a healthy infant. The recovery might be possible because of her young age, the difference in the immune system, and presentation during the last stage of pregnancy (Alserehi *et al*. 2016) [22].

An asymptomatic 29-year-old pregnant woman and 39-year-old pregnant woman with a history of end-stage renal disease and hypertension on hemolysis tested via RT-PCR and found to be positive for MERS-CoV. Subsequently, both patients recovered and were discharged as RT-PCR was negative. Both did not deliver at the time of hospitalization (Alfaraj *et al*. 2019) [21].

In 2015, the MERS-CoV virus spread in Korea, and a gravid woman was confirmed through the positive result of polymerase chain reaction. She was able to recover only with conservative treatment. The result was positive with the delivery of a healthy full-term newborn without any symptoms of MERS-CoV transmission. However, only placenta abruption was observed as a dark blood clot was formed on the maternal side of the placenta (Jeong *et al*. 2017) [5].

Effect of SARS-CoV infection on pregnancy

The spike (S) protein of SARS-CoV has an affinity for ACE2 present in the lungs (Li *et al*. 2003; Agrawal *et al*. 2021) [37, 48] and uses cellular transmembrane protease serine 2 (TMPRSS2) for its priming (Matsuyama *et al*. 2010; Glowacka *et al*. 2011; Shulla *et al*. 2011) [18, 20, 19]. The upregulation of ACE2 consequence the conversion of Angiotensin I into Angiotensin 1-7 (acts as a vasodilator) instead of Angiotensin II (acts as vasoconstrictor). Consequently, a relatively low blood pressure prevails despite the upregulation of other parts of the renin-angiotensin-

aldosterone system. When the binding of SARS-CoV-2 S protein with ACE2 consequence the unavailability of ACE2 for angiotensin I and consequently lower Angiotensin 1-7 level which in turn may result in vasoconstriction, pro-coagulopathic effects, and inflammation that occur in preeclampsia (Narang *et al*. 2020) [46]. Hence, the possible complications associated with pregnancy must be unearthed.

A pregnant 36-year-old woman (gravida 2, 19 weeks gestation) with a travel history from United States (US) to Hong Kong showed symptoms of illness *viz.* weakness, fever, anorexia, cough, and difficulty in breathing. She underwent treatment in Hong Kong but did not recover and came back to the US. In the US, her treatment resumed, oxygen was supplemented to deal with hypoxia and the treatment regime was continuously being modified to make it more effective and later her illness was identified as SARS due to the presence of a high level of SARS-CoV antibody in her serum. She readily recovered on account of proper treatment and was discharged from the hospital. Later on, she delivered a perfectly healthy infant without any complications. However, when samples from serum, cord blood, and breast milk were examined by enzyme immunoassay and indirect immune-fluorescence assay it showed the presence of antibodies to SARS-CoV (Robertson *et al*. 2004) [15].

A 33-year-old woman in gravida 2 was identified as fulfilling the World Health Organization case description for probable SARS. She was admitted to the hospital at 31 weeks of gestation and showed symptoms of fever and dry cough along with patchy infiltrates on a chest X-ray. The patient acquired SARS from close contact with an infected family member. Convalescent serology tests revealed positive results for the presence of antibodies to coronavirus. The patient was kept in hospital for 21 days. She did not require any intensive care admission or any ventilatory support. Labour occurred at the proper time and a healthy baby, free from infection was delivered (Yudin *et al*. 2004) [14].

Clinical data of five pregnant inpatients in second and third trimesters infected with SARS were analyzed retrospectively. All five patients were primigravida (including 2 twins). Two women infected were in the second trimester. Rest three were in the third trimester. Most of them showed common symptoms of fever, chills or rigor, and cough. Two were detected with decreased lymphocyte, two with decreased platelet, three elevated alanine aminotransferase (ALT). All five showed abnormal chest radiographs. All five patients recovered completely with only one requiring intensive care. Five neonates born, including one twin, were followed up without evidence of SARS infections. Only in a twin pregnancy, a single fetus was lost while the pregnant mother situation was observed to be stable (Zhang *et al*. 2003) [13].

Twelve pregnant women suffering from SARS in Hong Kong were studied in 2003. Three deaths were reported among them. Four of the seven patients who were in their first trimester showed spontaneous miscarriage. Four of the five patients were delivered preterm who presented after 24 weeks. Two pregnant patients recovered without delivery. All the newborn infants were free from SARS (Wong *et al*. 2004) [12].

Effect of SARS-CoV2 infection on pregnancy

Three pregnant women (all in gravida 1, para 1, and in the third trimester of pregnancy) showed characteristic symptoms of SARS-CoV2 like fever, cough, etc. along with the history of contracted infection at Wuhan, Hubei province, China. All were diagnosed as SARS-CoV2 positive after the screening of nasopharyngeal swabs and subsequently, therapy (antibiotics, antivirals, and supportive medicines) was instituted. The live healthy babies were delivered vaginally who were SARS-CoV2 free. Out of the three, only one infant was delivered preterm, who tested negative for the infection. The infants were separated from their mothers and were observed under critical care at a pediatric center. The regular medicinal and intermittent oxygen therapies were continued until the complete recovery of mothers. (Khan *et al*. 2020) [11].

The researchers retrospectively reviewed clinical records of 116 pregnant women with SARS-CoV2 pneumonia from 25 hospitals in China from about mid-January to March 2020. The amniotic fluid, cord blood, and neonatal pharyngeal swab samples were screened for the presence of SARS-CoV2 as evidence of vertical transmission and concluded that SARS-CoV2 infection is not associated with an increase in the risk of sudden abortion and spontaneous preterm birth. Also, no evidence of vertical transmission was found when the infection achieves its peak in the third trimester of pregnancy during this study (Yan *et al*. 2020) [10].

Two SARS-CoV2 positive pregnant women in the last trimester of pregnancy (gravida 2 and gravida 1) were studied during their treatment and cesarean delivery at Wuhan, China. The nasopharyngeal swabs of both babies just after cesarean were tested and found negative for SARS-CoV2. Only one of the babies developed slight complications but readily recovered. Other samples obtained during delivery like the maternal serum, umbilical cord blood, placental tissues, amniotic fluid, breast milk, and vaginal swabs also tested negative for the presence of SARS-CoV2 (Fan *et al*. 2020).

A retrospective study was conducted by including 16 SARS-CoV2 positive and 45 SARS-CoV2 negative pregnant women at their last trimester in Hubei province, China. All delivered new-born via cesarean section. One newborn from SARS-CoV2 positive mother became somewhat severe. However, critical pneumonia was not reported in any case. A non-significant difference in the intraoperative blood loss or the birth weight of the newborns between the two groups was found. Ten infants who were tested for the presence of SARS-CoV2 were found to be all negative. Non-significant differences between the two groups were found for other parameters like fetal distress, meconium-stained amniotic fluid, preterm birth, and neonatal asphyxia (Zhang *et al*. 2020) [8-35].

Another retrospective study was carried on 46 pregnant women from about mid-January to mid-April in Washington state, USA. The SARS-CoV-positive women were included in the study regardless of the degree of symptoms. Nearly all included women in the study were symptomatic and the majority of them were either in the second or third trimester. Out of these only seven women were hospitalized and one was admitted to the intensive care unit. During the study, eight deliveries occurred in which one was preterm birth at 33rd week of gestation and one was stillbirth of unknown cause. The authors concluded that SARS-CoV2 infection occurred in approximately 15% of pregnant women. They found that overweight and obese women with underlying conditions are more susceptible to the occurrence of the infection which may result in complicated outcomes during pregnancy (Lokken *et al*. 2020) [7].

In a study, 23 SARS-CoV2 confirmed pregnant patients were hospitalized and observed between December 31, 2019, to March 7, 2020, in Wuhan, China. The clinical presentations

were analyzed retrospectively. The radiological findings of the lungs and other clinical characteristics in pregnant women with SARS-CoV2 infection were similar to those of non-pregnant women positive for SARS-CoV2. Also, it was found that median absorption time and length of hospitalization in asymptomatic patients were significantly less than in symptomatic patients (Wu *et al*. 2020) [6].

Khalil *et al*. 2020 meta-analyzed several databases for reports of pregnant women with positive RT-PCR results. The most common clinical symptoms identified were fever, cough, and dyspnoea. Common laboratory abnormalities observed during the infection were raised CRP or procalcitonin, lymphopenia, and elevated level of transaminases. Birth before 37 weeks gestation was quite common. Though maternal intensive care unit admission was required in some cases, maternal mortality was very uncommon (~1%). The authors believed that the chances of vertical transmission are rare but may be probable.

Tactics to minimize corona infections

Martens *et al*. 2016 [5] recommendations for MERS affected pregnant patients include: 1) Standard supportive therapy for severely ill patients with respiratory infection 2) Early delivery to permit better ventilation 3) Preventive measures at the time of delivery to reduce the viral load. Delivery by the help of Caesarean section is not encouraged 4) Isolation of the mother from the newborn for at least 14 days 5) Isolation will also lead to delay in breastfeeding until antibodies are detected in the mother's milk.

Standard supportive therapy is also recommended for SARS infection which can be supplemented with oxygen to overcome the hypoxic condition. COVID-19 Treatment Guidelines Panel of the National Institute of Health (NIH), USA does not recommend the use of chloroquine or hydroxychloroquine with or without azithromycin in both hospitalized as well as non-hospitalized patients suffering from COVID-19 infection. Also, the panel recommended against the use of both HIV protease inhibitor drugs like lopinavir/ritonavir and anti-parasitic drug ivermectin (https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/). In comparison to SARS-CoV, both MERS and SARS-CoV2 were found to be associated with the highest rate of preterm birth, perinatal death, and C-section deliveries (Mascio *et al*. 2020) [47].

Angiotensin-converting enzyme inhibitors and angiotensin receptors blockers are not considered safe in pregnancy (FDA 2020) [4]. Only Remdesivir is recommended by FDA for use in the treatment of COVID-19 infection. Remdesivir is generally found safe for pregnant women (Igbinosa *et al*. 2020) [3] but it is not completely supported by analysis of large-scale data. Only chances of transaminitis side-effects may prevail during remdesivir use (Goldman *et al*. 2020) [2]. According to NIH only corticosteroids like dexamethasone in different doses can be used in patients who are suffering from different degrees of hypoxia. Dexamethasone is considered a safe drug for pregnant women and helps in the improvement of lung maturation but may result in preterm birth (ACOG 2020) [4]. Convalescent plasma may not be used in COVID-19 affected pregnant women as sufficient data for its safety is not available (NIH 2020) [1].

Conclusion

All the three Coronaviruses studied in gravid patients, most probably rule out the chances of vertical transmission. However, the utmost care and symptomatic treatment can only help pregnant women who suffer from such infection to come out of the trauma caused by the uneasy symptoms. Out of the three only MERS infection in patients showed comparatively high chances of an unwanted outcome during pregnancy. However, further data recording and study into a large number of similar cases can only statistically confirm it. As far as the treatment aspect goes, only corticosteroid treatment seems to be effective especially during hypoxic conditions in gravid women but with a risk of preterm birth. Also, corticosteroids suppress the immune system of the individual making them susceptible to a large number of secondary infections generally of fungal and sometimes a bacterial origin. So, corticosteroids should always be used with care, and follow-up of the patients should be done for few days even after complete recovery from SARS/MERS infection.

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