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PREGNANCY AND COVID 19- A VULNERABLE CONNECTION?

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ABSTRACT
The coronavirus-2 (SARS-CoV-2) is highly contagious. The COVID-19 infection to pregnant women and the potential risks of vertical transmission to the fetus have become a major issue. Since little is currently known about COVID-19 in pregnancy, the understanding of COVID-19 in this particular group will be updated in time, and a comprehensive review will be useful to evaluate the impact of COVID-19 in pregnancy. Physiological adaptations in the immune system, respiratory system and hematological functions during pregnancy may have a significant impact on the entry and progression of the infection by SARS-CoV-2 during this period. Pregnant subjects with asymptomatic infection present a further challenge with respect to the provision, prevention, and management of therapeutic approaches. The histological changes of placentas from pregnant women infected by SARS-CoV-2 were implicated by the expression of ACE2 receptors in the vascular endothelium. Pregnant women with COVID-19 pneumonia show similar clinical characteristics compared with non-pregnant counterparts. The cytokine storm triggered by the SARS-CoV-2 in the body, produce a series of immune responses, and cause changes in peripheral leukocytes and immune system cells leading to pregnancy complications that may be associated with viral infections. As the presence of virus in breast milk is not confirmed in most of the studies carried out, the experts encourage breastfeeding for neonatal acquisition of protective antibodies The infection and vertical transmission of SARS-CoV-2 in pregnancy remains to be determined to a large extent, and a global effort is required to determine the effects of this virus on implantation, fetal growth and development and neonatal health.

KEYWORDS: SARS-CoV-2, Pregnancy, Vertical Transmission, Placenta, Trophoblast.

BACKGROUND
The novel 2019 coronavirus, SARS-CoV-2, was officially recognized by the World Health Organization on February, 2020 and the disease was called COVID-19. Coronaviruses are genotypically classified into four genera: Alpha coronaviruses (a), Beta coronaviruses (b), Gamma coronaviruses (g), and Delta coronaviruses (d) according to their phylogenetic and genomic data. Coronaviruses are enveloped viruses containing non-segmented, positive-stranded genomic RNA. The diameter of these virus particles ranges from 80 to 220 nm in diameter. The genome size of coronaviruses is approximately from 26–32 kilobases. Coronavirus also has crown-shape spikes projecting from its surface (80–160 nm. in size), from which its name derived. The virus enters into the host cell through interaction between its own S protein and the receptor of the host cell. It will bind with the angiotensin-converting enzyme 2 (ACE 2) receptor of host cell to create a suitable habitation for viral replication. The COVID-19 pandemic has spread all across the globe since December 2019. The World Health Organization (WHO) acknowledged this coronavirus epidemic as a pandemic and declared the outbreak as a public health emergency of international concern. Pregnancy is a period in the lifetime when various physiological changes lead the individual to prone to microbial attacks. These include reduced functional residual volumes, diaphragm elevation, and altered cell immunity. Pregnant women are particularly susceptible to respiratory pathogens and severe pneumonia due to these changes and may even lead to higher maternal and fetal morbidity and mortality.[1] The risk of giving babies with LBW, Preterm and SGA conditions have been found to be higher for women who have suffered from pneumonia during pregnancy.[2] The effect of SARS-CoV-2 infection on pregnancy is not already clear. Infection, especially viral pneumonia is a significant factor contributing to rising morbidity and mortality among pregnant women.

IMMUNOLOGICAL ADAPTATION AND SARS-CoV-2 INFECTION
During pregnancy there is a drastic adaptation in the immune system of the mother that is necessary for the growth of the fetus[3] that results in the altered immune response to infection during pregnancy.[4] The alteration

of immune system during pregnancy that takes place in the mother's body involve such changes which makes her vulnerable to microbial attack. The T cell population shows a shift in the expression of Th2 phenotype compared to Th1 that favors an increased humoral immunity than the cellular immunity.[5] This change in the T cell phenotype result in an altered clearance of infected cells. There is a reduction in the number in the circulating of the NK cells during pregnancy. These cells are particularly important in the body's defense against viral attacks.[6] It is unclear whether this decrease in circulating NK cells has clinical implications for COVID-19. The number of circulating dendritic cells also decreased during pregnancy. These cells are responsible for the production of Interferon against the viral attack. Early study observed an attenuated inflammatory response to the novel influenza virus.[7] This explained the reports of attack of the pregnant women during the H1N1 pandemic in 2009.[8,9] The circulating level of progesterone increased during pregnancy. This hormone is reported to enhance lung repair after the attack of Influenza virus[10] and may prove beneficial in the recovery from lung damage after COVID-19 infection. Further studies are needed to understand the role of pregnancy-related changes in progesterone and other hormones, including estrogen and androgens, which may contribute to immunoregulation[11] in the response to COVID-19 infection. There is an alteration in the Toll-like receptors (TLRs) during pregnancy.[12] During COVID 19 infection damage of the host cells result in the release of Damage-associated molecular patterns which further enhance inflammation. The role that the innate immune system and TLRs play in the COVID-19 immune response still needs to be investigated to understand how pregnancy affects this particular aspect of the viral response. Studies are needed to conclude whether the adaptations of immune adaptations result in a higher susceptibility and/or morbidity or are, in fact, protective against COVID-19.

REPIRATORY CHANGES AND COVID-19

Anatomical and physiological changes take place in the respiratory structure and functions during pregnancy. Physiological alterations to the chest shape and elevation of the diaphragm due to diaphragmatic splinting by the gravid uterus cause changes to the respiratory function. There is an increase in the tidal volume although a reduction in functional residual capacity, expiratory and residual volumes have been observed. The reduction in total lung capacity and inability to clear secretions can make pregnant women more susceptible to severe respiratory infections.[13]

HEMATOLOGICAL CHANGES AND COVID-19

During pregnancy increased production of thrombin and higher circulating levels of coagulation and fibrinolytic factors, such as plasmin results in a hypercoagulable state that is also implicated in the pathogenesis of SARS-CoV-2 infection.[14] Therefore, pregnant women with COVID-19 may have additive or synergistic risk factors for thrombosis. There is a report of the mortality of a pregnant woman with COVID-19 due to embolism in pulmonary and basilar arteries.[15] Now it is recommended that all pregnant women with confirmed COVID-19 should have thromboprophylaxis until 10 days postnatal and that their clinicians have a low threshold for investigation of possible thromboembolism.[16]

Vascular adaptation to pregnancy results in the reshaping of specialized uterine spiral arterioles to form sinuses that become placental villi. There is an increase in blood volume, heart rate and stroke volume and cardiac output and a decrease in vascular resistance. Preeclampsia during pregnancy is associated with significant maternal and fetal complications.[17] Pregnant women with COVID-19 are more susceptible to develop preeclampsia as found in a review.[18]

Placenta and Sars-Cov-2 Infection

The placenta is the organ for communication between mother and her fetus. In the placenta maternal blood is in direct contact with the placental chorionic villi. It also creates an effective barrier that prevents maternal infection spreading to the fetus. However congenital abnormalities caused by various viruses such as CMV, HSV, varicella zoster virus, Zika virus etc. expressed the non-efficacy of this barrier organ. The mechanisms which helps in the vertical transmission of the maternal to fetal body may involve damage to the villous tree, from maternal endothelium to extra villous trophoblast, spread of infected maternal immune cells across the syncytiotrophoblast etc.[19] Various observations have been reported for the expression of COVID-19 in the placental tissue, though it is not clear whether the infection with COVID-19 was a primary one or due to damage of the placental tissue. One study observed SARS-CoV-2 localized predominantly to syncytiotrophoblast cells at the materno-fetal interface of the placenta and highlighting the potential for severe morbidity among pregnant women with COVID-19.[20] Electron microscopy revealed presence of virus-like particles in the cytosol of placental cells in this case and the result was termination of pregnancy with maternal preeclampsia with thrombocytopenia and coagulopathy.[20] Another case of miscarriage during the second trimester of pregnancy in a woman with COVID-19 appears related to placental infection with SARS-CoV-2, supported by virological findings in the placenta has been reported.[21] The placentae from the subjects were found to be COVID positive and showed signs of vascular perfusion of the virus and fetal vascular thrombosis.[22] However, since there were no control groups, signs observed could be related to other etiologies. Placentae from 16 pregnant women who were COVID-19 positive, were examined in another study and it was found that majority of the placentae signs of maternal vascular malperfusion namely villous infarctions, villous agglutination, or decidual

arteriopathy.[23] To obtain a more definite picture further research is required involving standardized examination of placental samples from women with SARSCoV-2 and matched negative controls, by pathologists unaware of SARSCoV-2 status.

Presence of signs of viral infection of placental cells does not obviously indicate fetal infection or fetal harm. So far, very few reports were obtained with a positive result among various studies with tissues of pregnant mothers and fetal samples.[24,25,26] The cases of neonatal respiratory diseases were reported even rarely in these positive cases. Use of antibody tests in various studies supported the vertical transmission theory of SARSCoV-2. This is evident from the fact that higher levels of immunoglobulin (Ig)M and IgG for SARS-CoV-2 were found in the blood of babies with COVID-19 positive mothers.[27,28] Since IgM is larger molecule, its presence in the blood of the neonate obviously indicate a vertical transmission of SARSCoV-2. However, all the infants in reports so far have been asymptomatic and tested negative for SARS-CoV-2 viral RNA at birth.[27,28] Mechanism of viral invasion through the human placenta is yet to be clearly established.

ACE2 gene expression was reported in first-trimester decidual stromal and perivascular cells and in the villous cytotrophoblast and syncytiotrophoblast in both first trimester and term samples.[29]

Expression of ACE2 and co-expression of TMPRSS2 in the trophoblast, the blastocyst, and the hypoblast of human embryo was found in another study suggesting routes of fetal infection by SARS-CoV-2.[30] The lack of ACE2 and TMPRSS2 co-expression in the placenta suggested an alternative mechanism for infection to the fetus. This is further indicated by the expression of proteases like DPP4 and CD147 in the placenta.[31] In some studies, the SARS-Cov-2 viral RNA has been detected in the amniotic fluid.[20,25,32]

BREASTFEEDING AND SARS-CoV-2 INFECTION

The transmission of SARS-CoV-2 through breast milk is uncertain. There has been one case study in which breast milk tested positive for SARS-CoV-2 on four different occasions.[33] On the other extreme, samples of breast milk of nine SARS-CoV-2-positive mothers were tested, and none were found positive.[34] The WHO guidance is for SARS-CoV-2-positive mothers is to continue breastfeeding even if they have tested positive during birth and the postpartum period. Basic hygiene advice and handwashing should be followed, and women with confirmed COVID-19 should wear a medical mask while feeding, if available.[35]

CONCLUSION

The present knowledge regarding the risk factor of SARS-CoV-2 attack pregnant women and its vertical transmission to her fetus makes it difficult to draw absolute conclusions. Most women who were included in the study experienced mild or asymptomatic disease with no lasting consequences; however, some centers have seen increased rates of ICU admission, and the need for mechanical ventilation in pregnant women. There is a probability for vertical transmission, but it appears rare, and in the majority of neonates, it has minimal impact. Researchers should be urged to consider inclusion of pregnant women to create a balanced and informed evidence base with data from a representative population.

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