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The effect of corona virus on pregnant women and pregnancy

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Abstract

There are many unknowns for pregnant women during the coronavirus disease 2019 (COVID-19) pandemic and the effect of this virus on the pregnancy. Clinical experience of pregnancies complicated with infection by other coronaviruses e.g., Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS), has led to pregnant woman being considered potentially vulnerable to severe SARS-CoV-2 infection. Pregnancy is characterized by some changes involving both the immune system and the pulmonary physiology, exposing the pregnant woman to a greater susceptibility to viral infections and more serious complications. The impact of SARS-CoV-2 in pregnancy remains to be determined, and a concerted, global effort is required to determine the effects on implantation, fetal growth and development, labor, and neonatal health. Asymptomatic infection presents a further challenge regarding service provision, prevention, and management. Besides the direct impacts of the disease, a plethora of indirect consequences of the pandemic adversely affect maternal health, including reduced access to reproductive health services, increased mental health strain, and increased socioeconomic deprivation. In this review, we explore the current knowledge of COVID-19 in pregnancy and highlight areas for further research to minimize its impact for women and their children.

Keywords
COVID-19, Pregnant women, Pregnancy.

1. Introduction

The novel coronavirus was first detected in Hubei province in December of 2019 and quickly spread throughout China, then worldwide [1]. Epidemiological studies indicated that people of any age were at risk of infection, and the severity was associated with age and comorbidities. For example, cancer patients infected with SARS-CoV-2 have shown a higher risk of severe events and mortality rate compared with those without cancer, and COVID-19 patients with pre-existing digestive diseases were associated with more complications [2]. The higher vulnerability of these patients is likely to be caused by a suppressed immune system due to the underlying diseases or the side-effects from treatments, including surgery, chemotherapy, and immunosuppressive agents. Pregnant women develop a special immunological adaptation, which is necessary for maintaining tolerance of the fetal semi-allograft. This state of transient suppressed immunity is modulated by suppressing T cell activity, and hence predisposes pregnant women to viral infections. In addition, the physiological changes occurring in the respiratory and circulatory systems might worsen clinical outcomes when infected with a virus during pregnancy [3] also the levels of the hormones estrogen and progesterone go up during pregnancy, causing the upper respiratory tract to get more easily infected [4]. Besides, there were robust evidences that COVID-19 outbreak as an acute life-threating stressor to pregnant women is harmful to the course of pregnancy and their baby, such as lower infant birth weight, increase the risk of having complications related to the pregnancy, has higher level of depressive, anxiety, dissociative symptoms [5]. This article reviews focus on the effect of corona virus on pregnant women and the pregnancy

2. The Virus:

SARS-CoV-2 belongs to the family Coronaviridae, order Nidovirales. Coronaviruses are enveloped, nonsegmented, positive-sense ribonucleic acid (RNA) viruses. These viruses were called coronaviruses because of the crown-like appearance of their surface projections. Four types of coronaviruses have been identified (α, β, gamma, and delta) [6] They are classified according to their tropism and pathogenicity. The β viruses display great pathogenicity; they cause pneumonia and SARS and were responsible for the SARS-CoV and MERS-CoV outbreaks. Conversely, the α viruses usually present as mild to moderate upper respiratory tract infections.[11] The recently identified SARS-CoV-2 presents a similarity between 20 and 60% to MERS-CoV and a similarity between 45 and 90% to SARS-CoV. However, it also presents great similarity with the genome of coronaviruses found in bats 96% [7].

3. Immune system during normal pregnancy:

In pregnancy an alteration of cell-mediated immunity and lung physiology normally occur, the latter summed up in three main events: the onset of edema affecting the mucosa of the airways, that can be traced back to the high levels of circulating estrogen and progesterone, this consists of an attenuation of the Th1 type response with shift toward the Th2 type. Th1-type cytokines have a microbicidal and pro-inflammatory function, and include for example IFN-γ, IL-1α, IL-1β, IL-6, and IL-12; while Th2 type ones are anti-inflammatory and include IL-4, IL-10, IL-13, and TGF-β. The purpose of this shift is therefore to induce a state of immunological tolerance toward the fetus and placenta through the inhibition of the physiological rejection of something foreign in the body. [8]. an increased oxygen consumption, secondary to both the state of anemia that can occur physiologically during gestation and increased maternal metabolic activities by virtue of fetal oxygen demands; finally an elevation of the diaphragm due to the increase in the size of the pregnant uterus. The latter, in turn, involves a variation in the different lung volumes resulting in particular in a decrease in the functional residual capacity (FRC = volume of air present in the lungs at the end of a normal exhalation), in the residual volume (RV = volume of air that remains in the lungs at the end of a maximum exhalation), and finally of the total lung capacity (TLC = volume of air present in the lungs at the end of a maximum inspiration) [9].

Properly, rather than a state of constant immunosuppression, during pregnancy the immune response is tuned according to the different gestational phases: in fact, from a pro-inflammatory response in the first trimester (it is necessary for implantation of the embryo and for placentation), there is a switch toward an anti-inflammatory condition in the second trimester (a fundamental situation to allow fetal growth), finally a return to a pro-inflammatory state takes place in the last trimester and in preparation for childbirth [10].Summing up, therefore, the dynamic of the immune response in pregnancy and the adaptation of the pulmonary physiology are risk factors for greater susceptibility to infections – mainly by respiratory pathogens – and lower tolerance to hypoxia. These aspects make pregnant women more vulnerable to pneumonia and to a more severe course of the disease than non-pregnant women [11].

4. Pregnancy and Respiratory Viruses

Pregnancy presents characteristics that make pregnant women more susceptible to respiratory pathogens and severe pneumonia. These changes include increased oxygen consumption, elevated diaphragm, and edema of the respiratory

tract mucosa, which cause pregnant women to have an intolerance to hypoxia. This was noted during the H1N1 outbreak in 2009, in which pregnant women were four times more likely to be admitted to a hospital than the general population [12]. Pneumonia is one of the more prevalent nonobstetric infections of pregnant women. It is the third most common indirect cause of maternal death and requires ventilatory support in 25% of cases [13] Despite the therapeutic options available for pulmonary infection, during pregnancy, the morbidity and mortality of viral infections are more severe than those from bacterial pneumonia [14].

5. Pregnancy and Corona virus:

In general, it is accepted that pregnant women are at increased risk of severe morbidity and mortality from specific respiratory infections, such as H1N1 and varicella pneumonia. This includes a higher risk of severe illness when infected with viruses from the same family as COVID-19 and other viral respiratory infections, such as influenza. With regard to COVID-19, the limited data currently available do not indicate that pregnant individuals are at an increased risk of infection or severe morbidity (e.g., need for intensive care unit [ICU] admission or mortality) compared with non-pregnant individuals in the general population. An intense inflammatory response has been reported as one of the key features of severe COVID-19, and as there is relative immunosuppression in pregnancy this may partly explain, why many pregnant women do not develop severe respiratory symptoms. However, pregnant patients with comorbidities may be at increased risk for severe illness consistent with the general population with similar comorbidities [15].

Similar to nonpregnant patients, the predominant features of COVID-19 in pregnancy are fever, cough, dyspnea, lymphopenia, and Shortness of breath. In some cases, this may be difficult to discern from physiologic dyspnea due to increased maternal oxygen demands from heightened metabolism, gestational anemia and fetal oxygen consumption, which are common in pregnancy [16], and women present with a spectrum of clinical manifestations that range from mild symptoms and signs to severe illness, including pneumonia with or without acute respiratory distress syndrome (ARDS), renal failure and multi-organ dysfunction may require immediate advanced critical care support. As a result, those affected are typically described as having mild, severe or critical disease. Early reports suggest that the percentages in the pregnant population are similar to those described for non pregnant adults with COVID-19 infections (approximately 80% mild, 15% severe and 5% critical disease)[17]. A New York study applying similar COVID-19 disease severity characteristics as described by Wu *et al*.,[18] observed that 37 (86%) of women possessed mild disease, 4 (9.3%) exhibited severe disease and 2 (4.7%) developed a

critical disease, and these statistics have been reported in further reviews on the topic.**10** US study also described the development of viral myocarditis and cardiomyopathy in 33% of critically ill non pregnant cases [19].

6. Placental Responses to corona virus:

6.1. Physiology of the placenta and viral interaction:

The placenta is usually an effective barrier that prevents maternal infection spreading to the fetus (vertical transmission). It is well recognized that certain pathogens can overcome this barrier, with sometimes devastating effects on the developing pregnancy [20]. Cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus, and Zika virus (ZIKV) can all cause congenital syndromes, with variable rates of transmission and severity of effects that depend, in part, on the stage of pregnancy that infection occurs. Of note, many of these infections may have only minor effects on the mother, and there is little recognized correlation between maternal symptomology and severity of fetal effects. Experience of viral infections in pregnancy has led to three other key observations regarding congenital infection, in general. First, the presence of the virus on the placental surface does not necessarily indicate placental infection—vertical transmission of viruses depends on some kind of breach of the placental barrier. Second, viral infection of placental cells does not necessarily mean that there is transmission to the fetus. Third, even when fetal infection occurs, responses are heterogeneous; thus, fetal infection does not always mean fetal damage. [21]

The human placenta is hemochorial, meaning that maternal blood is in direct contact with the placental chorionic villi. The placenta formed predominantly of specialized, fetally derived, cells called trophoblasts, of which there are three main types. Terminally differentiated multinuclear syncytiotrophoblast cells line the villus tree and are in direct contact with maternal blood. Progenitor villous cytotrophoblast cells underlie the syncytiotrophoblast. Invasive extravillous trophoblast cells anchor the chorionic villi to the uterus and modify its vasculature. A number of potential mechanisms may be involved in vertical transmission of viruses, including direct damage to the villous tree, with breaks in the protective syncytiotrophoblast layer; spread from virally infected maternal endothelium to extravillous trophoblast; traffic of infected maternal immune cells across the syncytiotrophoblast or paracellular or transcellular transport (e.g., immunoglobulin-mediated transcytosis) into fetal capillaries; and/or ascending infection from the vagina [22].

6.2. SARS-CoV-2 and the placenta

There have been a series of case reports examining the placentas of women with COVID-19. SARS-CoV-2 expression has been detected in samples taken from midtrimester placentae, but it remains unclear whether the presence of virus was due to primary infection or facilitated by placental damage from other pathologies. SARS-CoV-2 was found on RT-PCR of swabs and biopsies following a spontaneous fetal loss at 19 wk gestation [23]. SARS-CoV-2 was also highly expressed in placental and umbilical cord biopsies following a termination of pregnancy at 22-wk gestation. The pregnancy was terminated as a result of placental abruption and severe maternal preeclampsia with thrombocytopenia and coagulopathy. In this case, electron microscopy revealed virus-like particles in the cytosol of placental cells; however, no viral expression was detected in fetal tissues tested. In both case reports, macrophage infiltrates and fibrin deposits were seen on placental histology, which the authors attributed to being most likely associated with viral infection. However, such intervillositis can also be idiopathic, autoimmune, or associated with other infections, and so could be unrelated to the presence of SARS-CoV-2. A further case study found both placental swabs and amniotic fluid were positive for SARS-CoV-2 PCR. On microscopic examination, the placenta also had evidence of perivillous fibrin deposition with infarction and intervillositis. In this case, the neonate tested positive on nasal and rectal swabs, and required NICU for respiratory support [24]. Two other publications report placental histological findings in women with SARS-CoV-2 infection. In a study of the placentae from 20 women found to be positive for SARS-CoV-2 on routine testing at the time of birth (32 to 40 wk gestation), 10 placentae showed signs of possible fetal vascular malperfusion or fetal vascular thrombosis. However, there was no control group for comparison, making interpretation of findings difficult. Findings were mainly low grade and could be related to other etiologies. Another study examined the placentas from 16 women with SARS-CoV-2 infection [25]. The placentas were from babies born between 16 to 40 wk gestation, with 11 of the maternal SARS-CoV-2 infections diagnosed around the time of birth, and five diagnosed earlier in pregnancy. Twelve of the 15 third-trimester placentas were reported as showing signs of maternal vascular malperfusion (villous infarctions, villous agglutination, or decidual arteriopathy), a statistically significant higher proportion when compared with pathology reports from historical controls (identified by natural language processing). However, pathologists performing the examination were not blind to the SARS-CoV-2 status of the mother. As the pathological examination was indicated by maternal SARS-CoV-2 infection in the majority of cases, and histological signs of placental vascular malperfusion are somewhat subjective, these findings need to be interpreted with caution. Further research is

required, including standardized examination of placental samples from women with SARS-CoV-2 and matched negative controls, by pathologists unaware of SARS-CoV-2 status, to verify these preliminary reports of potential vascular and thrombotic effects in the placenta associated with maternal COVID-19. In addition, these findings should be correlated to clinical status of the fetus, ideally with longer-term follow-up [26].

7. Conclusions and recommendations:

Coronaviruses constitute a large family of pathogenic microorganisms causing a wide range of clinical manifestations. Respiratory system represents the main target of coronaviruses, from mild involvement of upper airways to severe interstitial pneumonia. Balance between etiological agent and host's conditions influences the progression of the infection toward ARDS, MOF, shock, until fatal events. From newborns to elderly age, any people might be infected by coronaviruses, with milder disease in children. Pregnant women represent a risk group with particular characteristics. In fact, the physiological state of immunosuppression of pregnant women makes them more susceptible to viral infections and more severe course.

Our review evaluated literature regarding the relationship between known coronaviruses and pregnancy. Obviously, as far as SARS-CoV-2 is concerned, the recent outbreak of the epidemic necessarily makes preliminary and provisional any assessment, and it requires continuous updating of the available evidence. As far as pregnancy is concerned, on the basis of available data so far, COVID-19 appears neither more frequent nor more serious in pregnancy than in non-pregnant women. Currently there is no evidence for cesarean delivery in women with COVID-19. The method of the delivery should not be influenced by the positivity for SARS-CoV-2 but exclusively based on maternal and fetal clinical conditions.

Finally, infections in pregnancy are not only a risk for transmission of the pathogens, but infectious diseases also expose the fetus to inflammatory response. Better understanding about maternal immune activation (MIA) in COVID-19 is needed, since maternal cytokine storm (mainly, IL-6 and IL-17) and intra-uterine inflammation might disturb fetal epigenetic machinery, with long-term effects, detectable during child's development [27]. Future studies are required to optimize the diagnostic aspects through the combination of virological and serological tests and to better understand the pathogenetic aspects of COVID-19.

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9. Reference

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