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The impacts of COVID-19 on mother health and pregnancy, Mini-review

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Abstract

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread across the world causing a global pandemic. During a pandemic, it becomes increasing important to evaluate the effects on specific populations at risk. In this narrative review, we analyzed the literature regarding COVID-19 infection on the pregnant population as they are at increased risk of infection. COVID-19 did seem to significantly increase the risk of obstetric complications, specifically in underserved and marginalized populations. In general, COVID-19 rarely directly infected the fetus and placenta, apart from a very rare complication called COVID placentitis. In actuality, the mothers were at greatest direct risk due to COVID-19 infection. The most important takeaway from this pandemic is the prospective lesson and effect it had on social determinants of health. Women did not have safe access to antenatal care, leading to a plethora of indirect obstetric complications due to COVID-19. In conclusion, it was women who suffered from the pandemic, not the placenta nor the fetus. It is our duty as physicians to protect pregnant women, allowing the placenta to protect the fetus.

Keywords: COVID-19; COVID placentitis; Pregnancy; Maternal health; SARS-CoV-2

1. Introduction

The novel coronavirus disease 2019 (COVID-19) was first reported in Wuhan city, Hubei province, China, in late December 2019 [1]. The causative agent of this novel disease was identified on January 7th 2020, from throat swab samples taken from patients by the Chinese Centre for Disease Control. They subsequently named the disease based on its symptoms, severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2 [2]. After a few months, the World Health Organisation (WHO) named the disease COVID-19.To date, most COVID-19 infected individuals have developed mild symptoms that persist for periods ranging from days to weeks, such as fever, malaise, sore throat, dry cough, and shortness of breath [3]. The majority of patients have spontaneously recovered without the need for special treatment. However, some patients have developed serious complications, including septic shock, organ failure, severe pneumonia, pulmonary edema, and acute respiratory distress syndrome [4]. Various global studies have consistently shown that more than 80% of the total number of COVID-19-related deaths have been reported among older age individuals who suffer from other chronic diseases. Only 0.1% of deaths have occurred in individuals under 19 years of age [5].

Several physiological and immunological changes occur in a woman's body during pregnancy. These changes may predispose pregnant women towards significant health complications from respiratory infections, such as an increased risk of miscarriage, preterm birth, or even fetal mortality and morbidity [6]. Worldwide concerns were raised following the first reported cases of COVID-19, as previous similar diseases such as the severe acute respiratory syndrome-related coronavirus (SARS-CoV) and the Middle East respiratory syndrome-related coronavirus (MERS-CoV) were known to lead to adverse outcomes for pregnant women. Namely, pregnant women who contracted these diseases had greater mortality rates than non-pregnant individuals [7]. On March 11th, 2020, WHO characterized COVID-19 as a global pandemic. This decision was based on the previous coronavirus outbreaks that led to the loss of millions of lives, such

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as the Spanish flu (H1N1), which resulted in the highest number of deaths (approximately 50 million worldwide) and the Asian flu (H2N2), which resulted in between 1 – 4 million deaths [8]. Figure 1 presents the recent pandemics caused by coronaviruses worldwide, with the approximate number of deaths caused by each. Few previous studies have classified pregnant women as not significantly immune-compromised**.**Various immunological changes have recently been found to occur during pregnancy, which may, therefore, increase the susceptibility of pregnant women to certain intracellular pathogens, such as COVID-19**.** This, in turn, may render them more susceptible to infection and increase the risk of them being adversely affected when compared to the non-pregnant individuals.

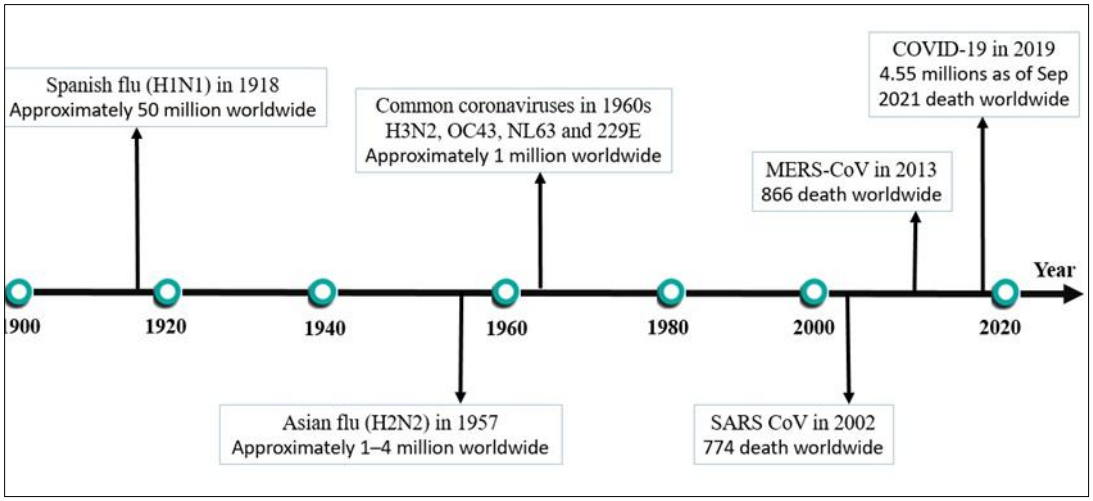

Figure 1 Presents the recent pandemics caused by coronaviruses worldwide, with the approximate number of deaths caused by each

Numerous research papers have been published regarding the clinical manifestation, characteristics, and symptoms of COVID-19, as well as on therapeutic clinical trials [9]. Systematic reviews examining its effect on women who are pregnant or in early maternal stags also have been published**.**However, most have been limited in the number of patients able to be examined due to the recency of the pandemic. Karimi-Zarchi *et al*.2020 [10] , examined the risk of COVID-19 being vertically transmitted from infected mothers to fetuses using published data in articles and official websites up till March 2020. Other reviews have further discussed the possibility of COVID-19 vertical transfer with controversial results **[**11]. The current review discusses the impact of COVID-19 on pregnant individuals, specifically in relation to its clinical manifestation and adverse maternal and fetal outcomes compared to non-pregnant individuals. Recent studies examining the mechanisms of vertical transmission of COVID-19 from infected mothers to newborns and/or fetuses have been used, in addition to the studies examining the placental pathology of infected mothers. Diagnostic approaches for COVID-19 and the therapeutic options that have been used are also highlighted, as well as the challenges pregnant women have faced during this pandemic.

2. Clinical characteristics of pregnant women infected with COVID-19

All genders and ages are susceptible to COVID-19 infection, including pregnant women and newborns**.**The clinical manifestation of COVID-19 among pregnant women has been characterized by mild and sometimes severe upper respiratory tract symptoms, such as dry cough and chest tightness, as well as other, less commonly observed symptoms such as high fever, fatigue, dyspnea, diarrhea, and headache [12]. Typically, severe upper respiratory tract infections are confirmed using chest computed tomography (CT images). China's case-control study revealed that 94% of pregnant women with confirmed COVID-19 infections had severe infections**.** However, another study reported that most pregnant women with COVID-19 were asymptomatic upon admission to hospital, and none experienced any severe respiratory failure during their hospital stay**.** This suggests that different stages of pregnancy and different immune responses in each case may affect the presenting symptoms of COVID-19 in pregnant women. A study by Yang *et al*.,2020 found that COVID-19 positive cases did not show any expectoration, dyspnea, or myalgia. However, CT images of their pulmonary systems resembled COVID-19 pneumonia. Furthermore, pleural effusion was significantly higher among COVID-19 positive cases in pregnant women compared to non-pregnant women. Figure 2.

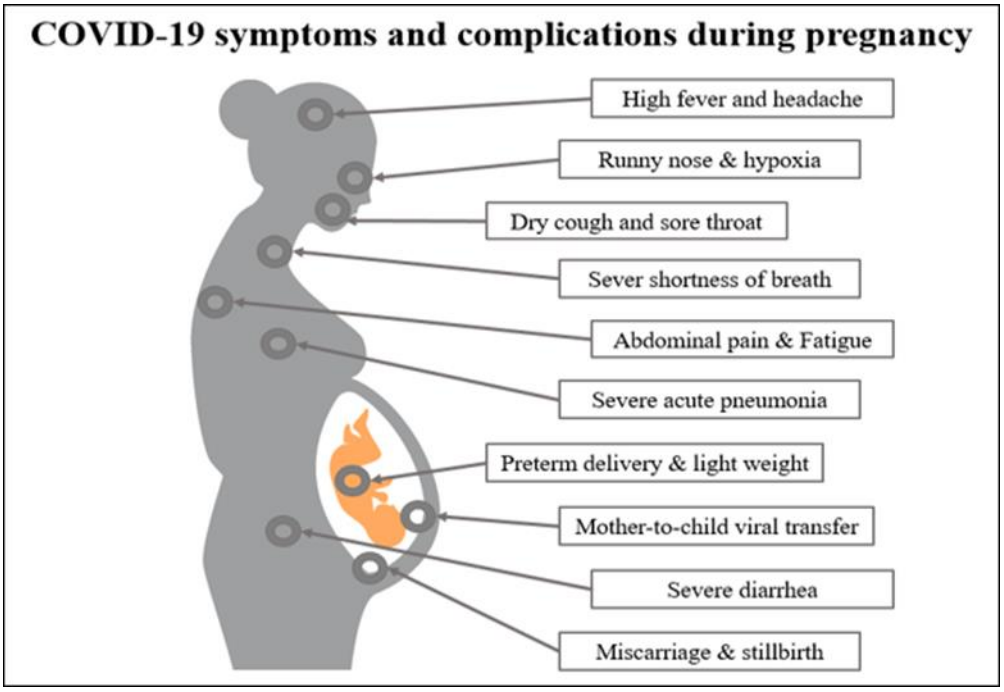

Figure 2 Presents a summary of the symptoms and potential complications that can occur in COVID-19-infected pregnant women

3. Adverse outcomes of COVID-19 among pregnant women

COVID-19 infection has been associated with maternal hypercoagulability and pyrexia (cytokine storm), which can lead to increased infarction, placental intervillous thrombosis, and maternal hypoxia**.**However, evidence regarding fetal morbidity and mortality due to COVID-19 infection is still limited. Still, maternal changes secondary to COVID-19-infected pregnant women may lead to hypoxia and fetal heart rate changes**.** In two recent studies by [13,14], it was found that in eighteen middle-aged pregnant women infected with COVID-19, all had at least one or more common clinical symptoms, such as a dry cough, fever, sore throat, chest pain, or diarrhea. A significant variation in newborn birth weight was observed in these mothers, with weights ranging from 1520 g to 3820 g. The authors reported that more than half of the pregnant women in the studies had preterm deliveries, which is a higher rate than seen in non-infected pregnant women. They also reported other obstetrical complications in these women, such as preeclampsia, irregular contractions, premature rupture of membrane, and stillbirth, indicating early pregnancy intervention. Anatomical changes during pregnancy, such as diaphragm elevation, increased thoracic cage transverse diameter, decreased maternal tolerance to hypoxia, put pregnant women at a higher risk from respiratory infections**.**[15] observed contractive abdominal pain and fever among pregnant women suffering from COVID-19. Fetal distress has also been reported in pregnant women; however, it remains unclear whether it is caused by the COVID-19 infection or pneumonia**.**A study from Iran reported that, out of nine COVID-19 infected pregnant women who were displaying initial symptoms of pneumonia, seven women died following a few days of hospitalization. Of the two who survived, one of them was critically sick and ventilator-dependent, while the other was successfully cured after prolonged hospitalization **[16].**

4. Fetal outcomes in COVID-19 infections

The first reported newborn infant delivered by a COVID-19 positive mother was on February 5th 2020. This was announced by the official Xinhua news agency. The infant had no fever or cough and stable vital signs but had observable shortness of breath, unusual chest radiographs, and abnormalities in liver function**.** Dashraath *et al*.,**2020** [17] observed numerous adverse neonatal outcomes from COVID-19 positive mothers, including fetal distress (43%), preterm birth (39%), intrauterine growth restriction (10%), perinatal death (7%), and miscarriage (2%). These outcomes were mainly dependent on the stage and complications during the pregnancy; increased effects of COVID-19 on pregnant women led to more adverse fetal outcomes. In their systematic review, Yang *et al*.,2020 reported that other COVID-19-related adverse fetal and neonatal outcomes had been observed, including fetal distress, stillbirth, neonatal death, and neonatal asphyxia. In a different study, the prognosis of infected infants was reported to be good, although preterm births with significantly low birth weights were observed, and many newborns suffered intrauterine fetal distress and

respiratory distress syndromes. Some newborns were immediately admitted to neonatal intensive care units as they had neonatal pneumonia, which requires neonatal mechanical ventilation**.** The placenta has been reported to execute and orchestrate the pathways of fetal growth. Some studies have revealed the ability of COVID-19 to induce placental gross pathological alterations**.** Vascular abnormalities that occur in the placentas of infected mothers included fetal vascular malformations and malperfusion in 50% of pregnancies**.** Chen *et al*.,**2020** [18] reported an increased incidence of spontaneous and induced abortions among infected mothers, suggesting the potential risks of abortion, premature gestational loss, and congenital defects in neonates in infected mothers.

5. Mechanisms of vascular damage of COVID-19 among pregnant women

The COVID-19 nucleocapsid proteins contain a highly complex RNA. However, as is typical of coronaviruses, the nucleocapsid is surrounded by a membrane containing three proteins: spike protein, small membrane protein E, and membrane protein M [19]. When the virus attaches to the respiratory tract, cell entry occurs via two pathways. One pathway is the direct plasma membrane route, which involves the transmembrane serine protease 2 and is used by most viruses**.**The other pathway is through viral spike proteins, which tightly attach to the ACE2 receptor (angiotensin-converting enzyme 2) and release the viral genome into the host cell. The viral genome is translated inside the host cell, replicating and producing more RNA genomes and viral proteins, and consequently, continuing the life cycle of the virus**.** Narang *et al*.,2020 [20] reported that the ACE2 enzyme plays an essential role in the conversion of many angiotensin compounds, including the conversion of angiotensin I to angiotensin-(1-9) and angiotensin II to angiotensin-(1-7), which causes antithrombotic, vasodilatory, and anti-inflammatory effects**.** During pregnancy, a women's hormonal profile changes, increasing the levels of renin-angiotensin-aldosterone system compounds, including ACE2.7. These changes put pregnant women at a greater risk of contracting and suffering adverse outcomes from COVID-19**.**Systemic vasodilator responses are maintained in pregnant women to balance their blood pressure. This occurs through the conversion of angiotensin II, resulting in increased levels of angiotensin-(1-7)**.**Garovic *et al*.2020 [21] reported that 3.5% of all pregnancies suffer from the pregnancy-specific hypertensive disorder, preeclampsia. Preeclampsia is characterized by multisystem involvement due to the loss of angiotensin regulation leading to imbalanced blood pressure. COVID-19 has been reported to down regulate the ACE2 receptor after it binds to it**.** This down regulation potentiates renin-angiotensin-aldosterone system abnormalities if the infection occurs during the pregnancy, and leads to an increase in the conversion of angiotensin II relative to the decreased angiotensin-(1-7) levels that are present in preeclampsia **[**22]. Coagulation abnormalities and endothelial cell dysfunction are two other common mechanisms shared between COVID-19 and preeclampsia, both of which cause vascular damage. Endothelial cells are known to express ACE2 receptors. Infection with COVID-19 during pregnancy may significantly mimic and/or initiate micro vascular dysfunction of endothelial cells by causing Endotheliitis. Endotheliitis has been reported to cause systemic inflammation and microcirculatory dysfunction. Some studies have reported that the induction of endothelial cell injury via an immune cell-mediated response is characterized by the resulting vasoconstriction and ischemia [23].

6. Vertical transmission of COVID-19 from mother-to-child

The transmission method of COVID-19 from mother to fetus has not yet been well-established**.**The possibility of vertical transmission has always been of great concern to obstetricians and neonatologists. Karimi *et al*.,2020 [24] collected data from published research articles and hospitals' official websites at the beginning of the pandemic and found that no COVID-19 infection had been detected in neonates or placentas. The authors reported two deaths of mothers after delivery from COVID-19-related respiratory complications. However, recent studies have reported three potential mechanisms of vertical transmission of the virus from mother to fetus, namely intrauterine transmission**,** placental blood transmission**,**and intrapartum transmission**,** Komine-Aizawa *et al*.,2020 [25] suggested four mechanisms for COVID-19 to cross the placental barrier, namely passaging from the maternal circulation to extravillous trophoblasts (placental cells) passaging through maternal immune cells, direct infection of syncytiotrophoblasts, and ascending infection through the maternal vaginal tract. Intrauterine transmission occurs during pregnancy at any time**.**Multiple findings suggest the possibility of intrauterine vertical transmission of COVID-19. Some studies have reported positive real-time PCR (RT-PCR) testing for COVID-19 of a neonate directly after birth, the elevation of specific immunoglobulins (Ig M), and the early onset of symptoms in neonates**(**Schwartz and Thomas,2023). However, other studies have revealed the opposite. Intrapartum transmission or transmission of COVID-19 from mother to baby during or directly after delivery have been reported to occur, despite initial negative test results, due to the incubation period of the virus being 14 days [26]. Intrapartum or early postnatal infection have also been reported to possibly occur through direct exposure of the newborn to COVID-19 infected maternal blood or other secretions**.**Placental blood transmission of COVID-19 may occur at different stages of pregnancy, which will result in different impacts depending on the developmental stage of the fetus**.**In a recent study by [27]. it was suggested that the diagnosis of intrauterine transplacental COVID-19 among infected mother-neonate dyads should be based on the identification of COVID-19 in fetal-derived cells, using advanced

techniques such as *in situ* hybridization, nucleic acid-based technique, or immunohistochemistry. The authors demonstrated that COVID-19 was able to enter the placenta and pass to the fetus prior to delivery. These findings confirm placental viral infection in different neonates.

7. Placental pathology in COVID-19-infected mothers

The RNA of COVID-19 has been proven to transfer through placental tissues, leading to adverse effects for developing fetuses**.**Numerous studies have confirmed the potential transmission of COVID-19 through the placenta. In a study by Yang *et al*.,**2020** e[28] vidence of COVID-19 infection was found in nine out of 83 neonates. Vascular malperfusion has been reported to be the most common placental pathology among COVID-19-positive mothers. Mulvey *et al.*,2020 [29] investigated the placentas of five COVID-19 infected mothers who delivered at term and reported that all showed fetal vascular malperfusion and multiple thrombosis. The evidence of thrombosis in all five mothers was seen in larger vessels in the fetal circulation. The presence of the spike protein and RNA of COVID-19 within the placentas of infected mothers was rare, indicating that COVID-19 did not directly infect the placentas, and thus the observed effects of thrombosis were a result of the systemic effects of the virus**.**Maternal and fetal tissues are known to be separated by syncytiotrophoblast layers, which act as a physical barrier against the vertical transmission of many pathogens, including viruses. However, Baergen *et al*.,2020 [30] reported nine cases of fetal vascular malperfusion among 20 cases of COVID-19 infected mothers.

8. Diagnostics and therapeutic options for COVID-19 in pregnancy

The COVID-19 pandemic spread globally at a rapid pace, causing a necessary and rapid adjustment in the fields of gynecology and obstetrics. RT-PCR has been described as the best diagnostic approach for detecting COVID-19 infection [31]. However, this technique is highly affected by the quality of the sampling process, Ali *et al*.,2021 used RT-PCR for scanning 11 asymptomatic pregnant women from China, who all tested negative for COVID-19. The authors also performed a CT scan and serum antigen-antibody (IgM and IgG) titers, revealing typical abnormalities related to COVID-19, indicating that infection lesions and ground-glass opacity had resulted from viral pneumonia. The authors also observed elevation in IgM and IgG antibody levels in the serum of patients that were determined to be pregnant following the CT scan, which is another indication of COVID-19 infection. This suggests that both CT imaging and serum antigen-antibody profiles are accurate markers for COVID-19 diagnosis, particularly in asymptomatic pregnant women. Consistency comparisons between CT and RT-PCR have been carried out. [30]**,** who reported similar results, suggested the requirement for longer RT-tests for COVID-19 detection. Zhang *et al*.,**2020** [32] suggested using serum antigen-antibody (IgM and IgG) for COVID-19 detection as a more accurate approach that is not limited by low-quality sampling like RT-PCR.

9. Conclusion

The present review investigated the impact of the COVID-19 pandemic on pregnancy, maternal and fetal health. Throughout this pandemic, pregnant women have had to ensure they follow the guidelines set out by organizations such as WHO, the Royal College of Obstetricians and Gynaecologists and the American College of Obstetricians & Gynecologists. Additionally, they have had to undergo frequent COVID-19 testing to prevent any possible transmission of the disease. As a global pandemic, COVID-19 continues to expand and spontaneously mutate and develop. Therefore, there will be a continuous need for additional information on the impact of COVID-19 on pregnant women, early-stage maternal women, and newborn infants. Many studies have confirmed the symptomatic, clinical, and physical pathogenicity of COVID-19. However, more genetic-based studies should be done to determine whether COVID-19 has a genetic or epigenetic impact on pregnant women that may affect future generations. The need to safeguard the growing fetus during prenatal, labor, and delivery adds to the challenges that face obstetricians and gynecologists in managing this disease. Despite the ability of SARS-CoV-2 to vertically transmit from infected mother to child and its presence in the breast milk of infected women, special precautions are always required to minimize the cross-infection of surrounding people, such as relatives, friends, and healthcare providers.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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