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IMPACT OF COVID-19 ON PREGNANCY (REVIEW)

SARS-CoV-2 infection during pregnancy is associated with a number of adverse pregnancy outcomes, including preeclampsia, preterm birth, and stillbirth, especially among pregnant women with severe COVID-19. Several fetal complications such as early pregnancy loss, delivery of a premature fetus, preeclampsia, fetal death, vertical transmission, intrauterine growth retardation, and congenital structural anomalies in association with COVID-19 disease have been investigated.

To review on the fetal adverse outcome that is likely to occur during COVID-19 disease. The fetal detrimental outcomes that have been widely studied in the literature include preterm birth, stillbirth, vertical transmission. The evidence in the literature supports that there is a higher rate of preterm birth and stillbirth in women who tested positive for SARS-CoV-2 but their association with the disease is not completely clear. Furthermore, the emergence of other possible outcomes is not conclusively stated. Hence more studies are required to establish their association with COVID-19 disease to decrease and mitigate the risk of detrimental fetal outcomes through early interventions and preventive measures.

Keywords: COVID-19, pregnancy, perinatal adverse outcome, vertical transmission, congenital malformation.

Introduction

The study of the effect of SARS CoV-2 infection on various organs and systems, including reproductive organs, is of scientific and practical interest. SARS-CoV-2 infection during pregnancy is associated with a number of adverse pregnancy outcomes, including preeclampsia, preterm birth, and stillbirth, especially among pregnant women with severe COVID-19. In addition to the direct impact of COVID-19 on pregnancy outcomes, it is also of interest to study in the long term the impact of SARS-CoV-2 on the gestation process.

Members of coronaviruses (SARS-CoV, SARS-CoV-2, and MERS-CoV) have been known to have maternal-fetal complications during pregnancy. However, the detrimental maternal-fetal outcomes of MERS-CoV were more hazardous among all of them [1]. Maternal adaptations and physiologic changes in systems particularly immunological alteration during pregnancy make both mother and fetus susceptible to SARS-CoV-2 [2]. The risk of obtaining infection with SARS-CoV-2 in pregnant women is 15 times more likely than in non-pregnant women [3] and high-risk pregnancies are almost 3 times more prone rather than low-risk pregnancies [4]. According to a report published by CDC (Center for Disease Control and Prevention) in 2020, the risk of ICU admission, mechanical ventilation, and death were 3, 2.9, and 1.7 times higher in pregnant women than in their non-pregnant counterparts, respectively [5].

The Fetus can be affected during different stages of intrauterine life [6]. However, the level of detrimental fetal outcomes is related to the age of the fetus [7]. In addition, the severity of adverse perinatal outcomes is relevant to the severity of the maternal disease. The rate of severe maternal-fetal outcome is 4 times higher in severe-critical cases that required ICU admission and maternal respiratory support rather than in mild-moderate or asymptomatic cases [8,9].

The potential mechanisms responsible for fetal complications in pregnant women with SARS-Cov-2 are not fully understood. However published literature demonstrated that persistent expression of angiotensin converting enzyme-2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) receptors during the entire pregnancy facilitated the entry of the virus to the placental cells [10], abnormal placental inflammatory histopathologic changes including feto-maternal vascular malperfusion, intervillous fibrin deposition and villitis of unknown etiology were associated with the disease [11,12]. Furthermore, triggered pro-inflammatory and anti-inflammatory states of pregnancy (cytokine storm) throughout different stages of intrauterine life contribute to Th1/Th2 imbalance, and supra-physiologic levels of cytokines are involved in the

adverse perinatal outcome of the disease [10, 13]. In addition to the direct effect of SARS-Cov-2, the lockdown rules during the pandemic such as reducing or virtual pattern of medical services and late attending of the pregnant woman to the hospitals, fear of exposure to or spreading the infection, allocation of nearly all health facilities for COVID-19 patients, reducing public transport can indirectly impact the outcome of pregnancies, particularly for high-risk patients that need increased antenatal services [14, 15].

There is a wide range of fetal complications that have been studied with covid-19 disease including miscarriage, stillbirth, growth restriction, preterm labor, vertical transmission, and congenital malformation. The purpose of this review is to focus on their emerging, frequency likelihood mechanism of development, and their relation to the severity of the disease. Moreover, this literature review gives an overview of the available evidence, points up the controversies, and helps the researchers to understand where to put their efforts in further research. This review can be an informative document for health care providers practicing medicine in all fields and pregnant women themselves.

To carry out this literature review, a search was performed using different databases such as Google Scholar and PubMed. The most relevant and recent articles related to different complications were selected. Original articles and systematic reviews were prioritized. However, for some complications, there were only case reports and case series available. The review is organized in sections, each section is intended to give an overview of the outcome, their association with the covid-19 disease, and the possible mechanism that they can develop.

Miscarriage

The association between previous coronaviruses (SARS-Cov and MERS-Cov) and adverse pregnancy outcomes including spontaneous abortion (termination of pregnancy less than 20 weeks of gestation) has been previously demonstrated [16]. The reported rate of abortion that was related to SARS-Cov in the 2002-2003 years was 57% and the adverse outcome of MERS-COV was more crucial [17]. Hence some authors tried to study the impacts of COVID-19 disease on the rate of first-trimester pregnancy loss. Gestational age at the time of infection is an independent risk factor for adverse fetal outcomes. The rate of adverse fetal outcomes is significantly higher in the first 12 weeks of pregnancy compared to second and third trimesters (35.3 vs. 2%, $p<0.001$) [7]. Cavalcante et al concluded in their systemic review and meta-analysis that the rate of miscarriage in pregnant women infected with SARS-Cov-2 was estimated at 15% and 23% using fixed and random effect models, respectively. However, their findings were not compared with pregnant women without SARS-Cov-2 infection [8]. A retrospective cohort study conducted by Sacinti et al including 1269 pregnancies compared the rate of miscarriages between the years 2019 and 2020. These authors found that the rate of miscarriage was 25% higher in the year 2020 than in 2019, but the increase in the rate could be related to a reduced number of overall pregnancies during the pandemic than in the pre-pandemic period (542 vs 727) or reduced attending of pregnant women due to lockdown rules since only 4.7 of women with miscarriage tested positive for SARS-Cov-2 [18]. Accordingly, another systematic review concluded that the risk of early and late spontaneous abortions increased in pregnant women who tested positive for SARS-Cov-2 and had no comorbidities or risk factors for abortion. However, all the included studies were between case reports and case series that suggest larger studies [19].

Conversely, Cosma et al in a case-control study at St. Anna hospital in 2020 indicated that there were no significant differences in the rate of SARS-Cov-2 positivity in both cases and the control group (11% vs 9.6) [20].

Hence the ACE2 and TMPRSS2 receptors do not express or are low up to 24 weeks of pregnancy [21] it appears that SARS-Cov-2 similar to previous coronaviruses (SARS-Cov) may act in an indirect pattern and provoke immune responses. The secondary triggered pro-inflammatory state is accompanied by high levels of IL-6, IL-8, TNF-alpha, and other cytokines. The established cytokine storm interferes with trophectoderm-endometrium molecular signaling and disrupts decidualization and trophoblastic invasion resulting in implantation failure. Furthermore, the associated hypercoagulable state produces microvascular thrombus formation in a preterm undeveloped placenta that results in an inappropriate intrauterine environment for a developing vulnerable embryo in the first trimester of pregnancy [13]. However, there was a case of 13 weeks spontaneous abortion reported the existence of viral N protein and signals for viral replication, RNA genome synthesis and surface spike proteins in the placenta and fetal tissues detected by Immunofluorescence and electron microscopy [12].

Summary of characteristics and results from some studies on miscarriage was presented on table 1.

Table 1 – Summary of characteristics and results from some studies on miscarriage

Author	Type of study and population	Objectives	Main outcomes	Results
Sacinti et al. (2020)	retrospective cohort study 1269 pregnancy	Compare the risk of early fetal loss during the pandemic to the pre-pandemic period	Early pregnancy loss was increased during the pandemic period	IRR 1.25 (95% CI, 1.16–1.35, *P*<0.0001)
Cosma et al. (2020)	Case-control studies 225 first trimester pregnancies (100 cases of spontaneous abortions and 125 normal ongoing pregnancies)	Demonstrate whether SARS-Cov-2 is a risk factor for early pregnancy loss	Exposure to SARS-Cov-2 in early pregnancy does not predispose to early pregnancy loss	OR 1.28 (95%CI 0.53-3.08, P=0.73)

Stillbirth

Stillbirth (intrauterine death of the fetus after 28 weeks of pregnancy but before birth) and the correlation with SARS-Cov-2 infection throughout the pregnancy have been widely studied. Pieces of evidence indicated that the rate of stillbirth increased during the pandemic than the pre-pandemic epoch. De Sisto and colleagues concluded in their study that the risk of stillbirth was nearly 2 times higher in pregnant women with COVID-19 disease compared to the pregnant population not exposed to the infection, particularly during the period of the Delta wave the rate was 4 times higher in infected pregnant women [22].

When evaluating the risk of stillbirth in pregnant women with COVID-19 in England, Urganci et al explored that fetal death was almost 2.5 times more likely in laboratory-confirmed SARS-Cov-2 infected pregnant women with a rate of 8.5 per 1000 birth versus a rate of 3.4 per 1000 birth in pregnant women without the disease [23]. Likewise, Khalil and colleagues found in their study at St. George's University Hospital, London that the rate of stillbirth was 2.38 per 1000 births in the pre-pandemic period versus 9.31 per 1000 births in the pandemic period. Although there were no cases of COVID-19 disease among pregnant women with stillbirth, it seems that lockdown rules contributed to the increased rate, particularly in high-risk pregnancies that required early intervention [15]. This is in concordance with the result obtained from a study conducted in four Indian hospitals. The authors found that despite a 43.2% reduction in hospitalization rate and 66.4% reduction in referred emergency obstetric case rates in tertiary care centers during the lockdown period, there was an increased rate of stillbirth compared to the pre-lockdown period (3.15 vs 2.25%) [14].

Some authors tried to study the correlation between the severity of maternal disease and fetal adverse outcomes. In a large cohort study encompassing data from the Premier Healthcare Database (20% of US hospitalization) Jering et al concluded that the stillbirth rate was 1.5 times higher in women with the covid-19 disease who give birth. However, their finding was not statistically significant. They also demonstrated that the rate of stillbirth was 8 times more likely in cases that required mechanical ventilation or in-hospital maternal deaths cases [24].

Characteristics and results from studies about stillbirth were presented on table 2.

Table 2 – Characteristics and results from studies about stillbirth

Author	Type of study and population	Objectives	Main outcomes	Results
De Sisto et al 2021	Retrospective study 1,249,634 pregnancy	Compare the risk of stillbirth in pregnant women with and without COVID 19	Higher Stillbirth rates were strongly associated with the Delta variant of SARS-Cov-2	aRR, 4.04 (95% CI, 3.28–4.97)
Gurol-Urganci et al 2021	Population-based cohort study 3527 women	Study of the association of SARS-Cov-2 and perinatal adverse outcome at the time of birth	laboratory-confirmed SARS-Cov-2 infected pregnancies was associated with higher rates of fetal death	aOR 2.21 (95% CI, 1.58-3.1, P<.001)
Jering et al 2021	Retrospective cohort study 406446 women	Study the clinical characteristics and severity of the outcome of women with and without COVID 19	Stillbirth was higher in SARS-Cov-2 positive pregnant women The risk is even more in women with respiratory support	aOR 1.23 (95% CI, 0.87-1.75) OR 7.88 (95% CI, 2.39- 25.98)

Vertical transmission of SARS-Cov2

Transplacental transmission of the SARS-Cov-2 has not been conclusively stated. There are controversies in studies on vertical transmission of the disease. Placenta has an important role in protecting the fetus. The Syncytia-Capillary Barrier (SCB) in the placental villas prevents the entrance of the virus into the fetal circulation by having strong intercellular junctions. On the other hand, lack of Caveolins expressions (a plasma membrane protein in syncytiotrophoblasts responsible for activation of inflammatory pathways in the cells) prevents inflammatory mediated damage of the barrier by cells that were able to enter the syncytiotrophoblasts and vertical transmission of SARS-Cov-2 [21].

To assess the possibility of maternal-fetal transmission of SARS-Cov-2 Arora and colleagues found in their prospective pilot study that RT-PCR test of cord blood samples during vaginal delivery and test of amniotic fluid in addition to the cord blood sample in cesarean deliveries collected in a sterile manner were negative in all neonates born from SARS-Cov-2 positive mothers. Moreover, the authors repeated the throat and nasopharyngeal swab RT-PCR tests of newborns 24-48 hours after delivery, despite they were room in with their mothers the tests showed negative results [25]. The transmission of SARS-Cov-2 infection in midterm alive intrauterine pregnancies also have been studied. Yu et al reported 2 cases of second-trimester pregnancy with a history of COVID-19 disease that had undergone amniocentesis. The amniotic fluid sample RT-PCR test, as well as SARS-Cov-2 IgG and IgM, showed a negative result. [26] Similar to the above research, a retrospective cohort study conducted by Patberg et al at NYU Winthrop Hospital concluded that despite degrees of placental histopathological changes in pregnant women who tested positive for SARS-Cov-2 infection, the RT-PCR tests of their neonates were negative [27].

Considering the above studies maternal-fetal transmission is unlikely not only in the term but also in midterm pregnancies. However, there are some reported cases of SARS-Cov-2 vertical transmission. Transmission of the virus from the mother to the fetus may be dependent on fetal genetic factors, SARS-Cov-2 genetic variants, and high maternal viral load [28].

Vazquez et al studied a case of spontaneous abortion in a pregnant woman infected with SARS-Cov-2. The researchers detected viral N protein, signals for viral replication, RNA genome synthesis, and surface spike proteins in the placenta and fetal lungs and kidneys with the use of Immunofluorescence and electron microscopy analysis [12]. A similar case was reported by Facchetti et al studying 15 cases of SARS-Cov-2 infected mothers undergoing delivery where the authors identified only one case of neonatal RT-PCR positive test that progressed to pneumonia twenty-four hours after birth. In addition, viral N and S proteins were also detected in the placenta at the time of birth [28].

Preterm delivery

Prematurity is the primary contributor to mortality among children under 5 years of age. The short and long-term complications of preterm birth contribute to an estimated 1 million death of children each year [29]. Hence establishing the association between SARS-Cov-2 infection and the risk of preterm labor and prematurity is in high priority. Diriba and colleagues in their systematic review and meta-analysis including 25 studies in developed countries found that the rate of preterm birth at <37 weeks in pregnant women with the covid-19 disease increased to 14.3% [16]. Whereas the rate of preterm birth ranges from 5% in high-income countries to 18% in low-income countries [29]. A population-based cohort study in California showed that SARS-Cov-2 infection during pregnancy was associated with 40% increased odds of preterm birth, and 60% increased odds of very preterm birth. The rates of preterm birth and very preterm birth were even higher in pregnant women with the COVID-19 disease and maternal comorbidities. Furthermore, the COVID-19 disease was associated with a 50% increase in the rate of spontaneous preterm labor and a 30% increase in induced preterm labor [30]. However, a multinational cohort study demonstrates a different result with medically indicated preterm delivery the most common type of birth (83%) in pregnant women infected with SARS-Cov-2 rather than spontaneous preterm birth and hypertensive disorders of pregnancy constituted 24.7%, the leading cause of induction [31].

The risk of preterm birth is strongly associated with the severity of the maternal disease. Shu Qin Wei et al conducted a systematic review and meta-analysis on the effect of COVID-19 disease on pregnancy outcomes. The authors also compared the extent of adverse fetal outcomes according to the severity of SARS-Cov-2 infection. The results showed that the risk of preterm birth was 1.8 times higher in pregnant women with COVID-19 disease than in those without. In symptomatic pregnant women, the risk was 2.29 times more likely than in asymptomatic patients and the likelihood of preterm birth was elevated to 4 times in severe cases compared to mild COVID-19 cases [32].

Implementation of mitigation measures for the prevention of SARS-Cov-2 can reduce the incidence of preterm birth. Following a large national quasi-experimental study, Been and colleagues concluded that preventive measures for COVID-19 were associated with a significant reduction of preterm birth rate throughout all gestational ages with a more apparent, effective, and statistically significant for the gestational ages of 23 weeks-36 weeks ± 6 day [33]. Reduced exposure to infection and physical activity due to the changing work environment and pattern impacted the rate of preterm birth particularly very preterm birth and extremely very low birth preterm birth [33, 34].

The cause of preterm birth in pregnant women infected with SARS-Cov-2 is likely related to the exaggerated systemic inflammatory state [10], maternal vascular damage that contributes to preeclampsia, IUGR, and fetal distress as a consequence of medically initiated preterm birth [11,31], and fetal vascular injury damage [27].

Characteristics and results from some studies about preterm birth were presented on table 3.

Table 3 – Characteristics and results from some studies about preterm birth

Author	Type of study and population	Objectives	Main outcomes	Results
Shu Qin Wei	Meta-analysis including 42 studies	Study the association between SARS-Cov-2 and adverse pregnancy outcome	Preterm birth in SARS-Cov-2 infected pregnant women vs non-infected Symptomatic vs asymptomatic Severe cases vs mild cases	(OR 1.82, 95% CI 1.38 to 2.3) (OR 2.29, 95% CI 1.49 to 3.53) (OR 4.29, 95% CI 2.41 to 7.63)
Karasek et al	Population-based cohort study 240,157 pregnant women with live births	Study the effect of the covid-19 pandemic on the rate of preterm birth	Very preterm + comorbidities Preterm + comorbidities	aRR 1.6 (95% CI 1.3, 2.0) aRR 2.6 (2.1, 3.1) aRR 1.3(95% CI 1.2, 1.5) aRR 2.0 (1.8, 2.2)
Villar J et al	Prospective cohort study 2130 pregnant women	Evaluation of risks in pregnancy with COVID-19 compared with not-infected pregnant patients	Preterm birth	RR 1.59 (95% CI 1.30 to 1.94)

Intrauterine growth retardation

One of the adverse fetal outcomes of COVID-19 disease that have been investigated is intrauterine growth retardation. Fetal growth retardation is associated with stillbirth, neonatal death, and long-term neonatal complications. Maternal-fetal infections and placental diseases including placental insufficiency can account for fetal growth delay [35].

Eltemamy et al conducted a pilot case-control study to establish the correlation between SARS-Cov-2 exposure and the risk of both fetal growth retardation and structural anomaly. The authors found no significant differences in fetal growth parameters, Doppler study, and rate of gross structural anomalies in regular antenatal visits of the cases group (pregnant women with no risk factors, normal nuchal translucency, and history of confirmed positive SARS-Cov-2 in their first trimester) compared to controls group.[36] Similar results were found in a retrospective cohort study where Narang et al also concluded that there were no significant differences in the rate of intrauterine growth retardation rate in mild or asymptomatic SARS-Cov-2 infected pregnant women, irrespective of the timing of infection, compared to those with a negative infection result (3.4% vs 4.8%, p=0.36) [37].

Conversely, following a case-control study Anuk and colleagues found that the pulsatility index and resistance of umbilical artery and uterine artery of low-risk pregnant women with a history of COVID-19 disease 3 weeks after the quarantine was remarkably higher than women with no history of exposure to SARS-Cov-2 [38]. Whereas umbilical artery Doppler study is a strong assessment method for predicting IUGR in high-risk pregnancies [39]. The likelihood of intrauterine growth retardation manifestation in the later stage of pregnancy could not be excluded. Furthermore, Kumar et al found a case of intrauterine growth retardation associated

with severe oligohydramnios and loss of fetal movement in a term pregnancy with a history of positive SARS-Cov-2 at 32 weeks gestation. Hence the woman had no risk factors for fetal growth delay and the antenatal follow-ups were normal up to 32 weeks, SARS-Cov-2 was assumed to be the cause [40].

Despite the placental histopathologic changes contributing to placental ischemia in pregnant women with positive SARS-Cov-2 have been widely investigated. None of the studies has acknowledged the association between placental changes and fetal growth retardation [11,27].

Congenital anomalies

Viral infections in pregnancy are known to be associated with congenital malformations. It is still fully unknown whether SARS-Cov-2 infection, anti-COVID-19 therapy, or vaccination during pregnancy have an adverse effect on the growing fetus or not [41,42]. There is a lack of enough evidence to conclude the risk of structural malformation in women with a history of positive SARS-Cov-2 throughout their pregnancy. Perveen et al reported a case of limb structural deformation due to ischemia and gangrene in a preterm 33 weeks neonate born of a mother with a history of positive SARS-Cov-2. However, the author did not find any thromboembolic events in the placenta or neonatal vasculature, and also there were no risk factors in neonates for in utero thromboembolism and the skin tissue specimen was negative for infections thus the possible association between SARS-Cov-2 and limb gangrene could not be ruled out [43]. On the other hand, SARS-Cov-2 and the associated hyperinflammatory and hypercoagulable state may lead to ischemic limb injury in adults [44].

There is a hypothesis that exposure to SARS-Cov-2 during organogenesis may affect the developing fetus and increase the risk of structural anomalies and neural tube defects. ACE2 receptors that exist in the zygote and uterus facilitate the viral entry to the replicating cells. Moreover, placental vascular malperfusion with fetal hypoxia, [45] induced maternal systemic illness such as hyperthermia, and antiviral medication [42] might have a neurodevelopmental adverse effect on the growing fetus.

Some authors reported cases of organ injury in neonates born from mothers exposed to SARS-Cov-2 in utero [45]. While others did not find any congenital malformation even though there were the findings of viral particles and signs of viral replication in neonatal tissue examinations [12].

Almost all of the studies on the impact of COVID-19 disease on congenital anomalies are confined to the case reports and case series that recommend large studies to confirm the association between SARS-Cov-2 and the risk of congenital anomalies [43, 45, 46].

Preeclampsia

Several studies have reported an epidemiological association between COVID-19 and preeclampsia. Two recent meta-analyses found a higher incidence of preeclampsia, severe preeclampsia, eclampsia, and HELLP syndrome in pregnant women with SARS-CoV-2 than in the general pregnant population [47, 48, 49]. In the INTERCOVID study, preeclampsia was the only condition in women with asymptomatic SARS-CoV-2 infection [31].

Conclusion and recommendations for future research

To date, there is strong evidence for the adverse effects of SARS-Cov-2 on pregnancy, with a higher incidence of severe preeclampsia, miscarriage, preterm birth and stillbirth. Finding out the association between fetal adverse outcomes and the SARS-Cov-2 during pregnancy is crucial for predicting, early intervention, and preventing complications.

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