Review Article

The Effects of COVID-19/ACE2 on Pregnancy Events and Outcomes: A Systematic Review

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Abstract

Background & Objectives: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was confirmed as the cause of Coronavirus disease 2019 (COVID-19). The disease presents with a wide range of clinical signs and symptoms involving vital organs such as the lungs, heart, gastrointestinal tract, liver, central nervous system, blood, and kidneys. It also potentially affects other organs, including the placenta.The present systematic review aimed to evaluate effects of SARS-CoV-2 on pregnant women, fetuses, and infants born to infected mothers.
Material & Methods: The search fields used in this study were angiotensin-converting enzyme receptor (ACE2), fetus, pregnancy, and SARS-CoV-2. We reviewed articles published in 2020 and 2022. The inclusion criteria were articles on receptor expression, virus entry into the host cell, studies on the characteristics and outcomes of pregnant or recently pregnant women with SARS-CoV-2 infection who were approved and characteristics and outcomes of infants whose mothers were infected with SARS-CoV-2.
Results: The virus uses the ACE2 to enter the cell. The coronavirus can be expected to affect any cell or organ that expresses ACE2. Female reproductive system is one of the systems that express ACE2. The destructive effects of COVID-19 on maternal and fetal health are strongly influenced by the spatial-temporal distribution of ACE2.
Conclusion: The harmful role of COVID-19 in pregnancy is highly controversial, although maternal COVID-19 infection contributes to adverse consequences of pregnancy. There is a limited amount of information on the efficacy of COVID-19 on pregnants and their fetuses.

Keywords: COVID-19; Pregnant women; Fetus; ACE-2; SARS-CoV-2; Neonate

Introduction

Coronavirus disease 2019 (COVID-19), a zoonotic disease, is a recent developing intense communicable infection that, in December 2019, it was first identified in patients with pneumonia (1). On March 11, 2020, it was announced by the World Health Organization as the fifth registered epidemic (2). Various research is trying to develop knowledge about the adverse effect of the viruses on all human organs in the long term. The disease presents with a wide range of clinical signs and symptoms involving vital organs such as the lungs, heart, gastrointestinal tract, liver, central nervous

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system, blood, and kidneys. It also potentially affects other organs, including the placenta (3).

The possibility of cellular infection with SARS-CoV-2 is directly relevant to the expression of ACE-2 and TMPRSS2. SARS-CoV-2 proliferates in infected cells, then releases, eventually causing host cell pyroptosis (4). SARS-CoV-2 enters the cell using the ACE2 receptor, a feature that can cause adverse effects on maternal and fetal health (5). For example, an infection increases the risk of fetal distress, IUGR, hospitalized in the neonatal intensive care unit (ICU), miscarriage, stillbirth, and neonatal deatlh (6). The following can also be mentioned: increased ratio of PTB , premature rupture of fetal membranes (7), maternal death, and preterm birth (8).

According to recent guidelines from the American Society of Reproductive Medicine (ASRM, 2020a), delaying treatment for infertile couples can reduce the chances of getting pregnant. In addition, people who need gonadotoxic treatment for cancer or other diseases need to store reproductive cells to maintain fertility *(ESHRE 2020b)*, the effect of this disease on pregnancy is not well known (9). Therefore, we conducted a systematic review to improve the understanding of the influence of SARS-CoV-2 on pregnancy and fetus to reduce its adverse outcomes.

Materials & Methods

We conducted this systematic review to investigate the effects of COVID-19 / ACE2 on pregnancy events and outcomes. The search fields used in this study were ("ACE-2", "fetus" and "pregnancy") and ("coronavirus" or "COVID-19" or "SARS-CoV-19") with limited English language Summaries. We reviewed articles published in 2020 and 2021.

Search strategy used to find the publications

Three independent reviewers searched the PubMed, Scopus, ScienceDirect and Google Scholar databases. The search fields used in this study were ("ACE-2", "fetus" and "pregnancy") and ("coronavirus" or "COVID-19" or "SARS-CoV-19") with limited English language Summaries. We reviewed articles spublished in 2020 and 2022. All collected journals were screened according to the entry and exit criteria. Reference lists of all potentially relevant articles and other reviews in this area were reviewed to identify any studies that were missed in the search for the electronic database.

Inclusion Criteria

All the publications found in the databases were preliminarily included in this systematic review. To meet the inclusion criteria, studies should include complete articles examining the effect of SARS-CoV-2 on pregnancy and the fetus or related conditions during the Covid-19 epidemic, 2020 and 2022.

Exclusion criteria

As exclusion criteria, publications: (I) not related to findings related to the effect of SARS-CoV-2 on pregnancy and the fetus and other conditions; (II) published in a language other than English; (III) editorials, letters, reviews, responses, abstracts or short communications; and (IV) other stages of the epidemic were eliminated.

Methodological quality, risk of bias and levels of evidence (LE) of the selected papers

The publications were independently appraised by one reviewer, cross-checked by a second reviewer and when there was disagreement, a third researcher was consulted, and the issue was discussed until consensus was reached.

Study selection and data extraction

All references found in the database were exported to a data management software program (Mendeley) and duplicates were removed by the two authors. The review was conducted by two judges who independently reviewed titles, abstracts, eligibility criteria, and selected studies to be included in the systematic review (researchers were blind to each other's decisions). Disagreements were resolved by analyzing the third author. Data include (I) study information (author and year), (II) participants / groups (sample size, age, sex), (III) virus, (IV) ACE2 expression spatially and temporally, (V) tests,

(VI) objectives and (VII) results were categorized and sorted through data management software. One researcher noticed the extract and another person reviewed the results. The dispute was resolved by the third arbitrator.

Studies Selection

For this systematic review, selected databases retrieved 103 titles. After entering the information management software and removing duplicates, 82 studies with the title and abstract were screened. The AC and AS judges conducted the first screening and the third reviewer worked on their differences. Following this procedure, 35 potentially related manuscripts were considered. Figure 1 shows the flow chart used in the selection of studies.

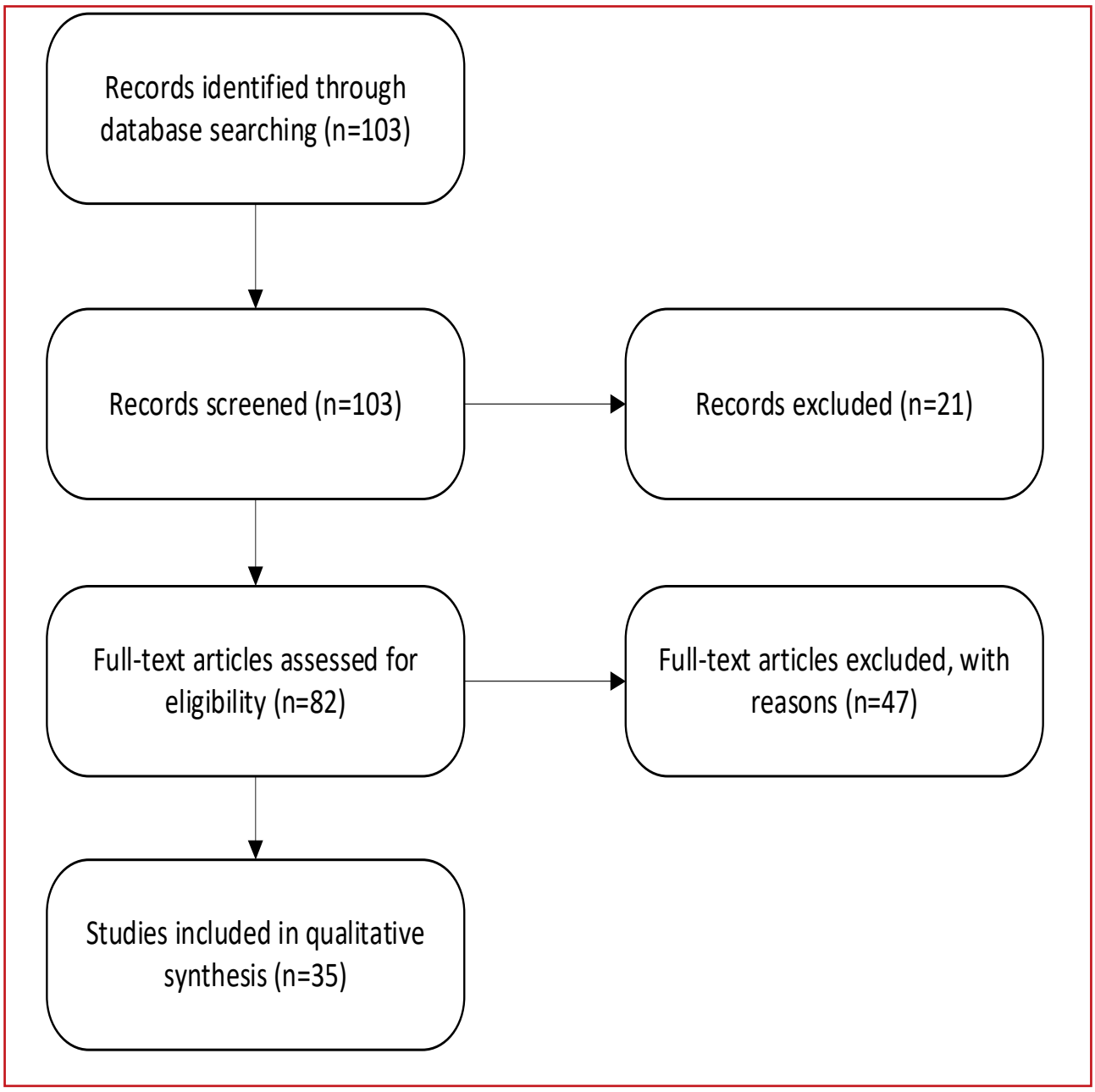


Figure 1. the flow chart used in the selection of studies

Result

The spatial-temporal distribution of ACE2 at different stages of pregnancy

Based on information from Bgee https://bgee.org/?page=gene&gene_id=(ENSG00000130234), the ACE2 expression is high in the oocytes (7). In zygotes, ACE2 expression is high, then decreases rapidly from the 4-cell stage to the morula stage. Subsequently; the expression of ACE2 increased in the blastocyst stage (10). Expression of ACE2 and TMPRSS2 is confirmed in the early stages of embryonic development, including blastocyst trophoblasts before implantation, syncytiotrophoblasts, and hypoblasts in the implantation stages (4). In addition, based on Lye and colleagues study, early pregnancy ACE2 has many expressions in endothelial/perivascular cells at the maternal-fetal interface (11). ACE2 express in the human placenta, mainly in the endothelium and smooth muscle of primary and secondary vascular vessels. Furthermore, ACE2 express in invasive and intravascular trophoblasts, decidual cells, arterial, and venous endothelium and umbilical cord smooth muscle (7).

Primary and secondary decidual zone, luminal and glandular cells of epithelium express ACE2 within early pregnancy, whereas the expression of ACE2 is detected in the epithelium of the yolk sac, the labyrinth placenta, and the amniotic during the late stage (12). Therefore, because ACE2 mRNA levels are high in the placenta in early pregnancy, it is likely that the placenta will be further damaged in the first trimester if infected with SARS-CoV-2 (13). In addition, co-expression of ACE2 and TMPRSS2 is highest on trophectoderm on day 6 as blastocysts are more likely to become infected with SARS-CoV-2, during peri-implantation embryo development on day 6 (10).

Levels of ACE2 may not be expected in varied obstetric pathologies. In this regard, placental ACE2 mRNA levels are low in pregnancies that restrict the growth of the human fetus, and in contrast, in early-mid-pregnancy in women delivering intrauterine growth restriction (IUGR) babies, maternal plasma ACE2 levels are high (14). GeneCards data show high expression of ACE2 in the placenta to the lung, indicating the possibility of placental viral infection (7).

The function of the RAS system during pregnancy

COVID-19 promotes endothelial dysfunction in the placentas. These placentas have the same phenotype as observed in preeclampsia and IUGR. A preeclampsia-like syndrome has newly been observed in pregnant patients with COVID-19 (5). One study found that pregnant women with severe COVID-19 had symptoms similar to preeclampsia. In addition, the results of studies show that SARS-CoV-2 infection may cause a pro-inflammatory condition, resulting in systemic endothelial dysfunction and preeclampsia. A 2020 study in Sweden also confirmed that pregnant patients with Covid-19 are more likely to get preeclampsia (15).

According to Daclin et al, higher incidence of preeclampsia or "preeclampsia like" syndrome is clearly demonstrated and evaluated around 10.5–16.2% (16).

Risk of infection during pregnancy

The risk of severe Covid-19 in pregnant women is the same as in the general population, and the potential increased seriousness of COVID-19 in pregnancy has not been observed (17). Most pregnant women with COVID-19 have milder clinical manifestations and better recovery than others (18). In healthy pregnant women, overexpression of ACE-2 receptors causes higher expression of Ang- (1-7), and thus more dilation of arteries and anti-inflammatory response to SARS-CoV-2 infection. ACE-2 receptors up-regulate during pregnancy, a feature that may protect against severe COVID-19.

The gestational T-helper lymphocyte type-1- T-helper lymphocyte type-2 (Th1-Th2) immune alteration which has a potential role in the intensity of viral infections in pregnancy, are controlled by increased pregnancy-induced ACE-2-Ang- (1-7) expression, which may describe the observed improved outcomes of COVID-19 during pregnancy in comparison with prior viral prevalence in pregnant women (19).

Brandt et al. (2020) in US investigated 61 pregnant patients with Covid-19 and 2 uninfected pregnant women as a control group and illustrated that the odds of adverse maternal complications were 3.4 times higher than the control group. The probability of neonatal adverse events was 1.7

times as much as the control group (20). Also, pregnant women infected with SARS-CoV-2 with no mild symptoms have had good results (2).

The effect of SARS-CoV-2 on a fetus

Infants born to SARS-CoV-2 infected mothers were positively tested, and most of them did not have a negative outcome. Also, thirteen studies were performed to evaluate neonates with Covid-19, and only three studies tested positive. Even infants who tested positive had no or mild symptoms. Chi and colleagues (2021) in a systematic review indicated that the neonates were tested by PCR or serological testing and were approximately 8% positive for SARS-CoV-2 infection (21). Furthermore, Papapanou and colleagues (2021), in a systematic review, illustrated that 2.7% (292.8) of infants born vaginally and 5.3% (20/374) of those born through cesarean section (CS) were found positive (22). Also, Juan et al. (2020) in China reported that 155 neonates had nucleic-acid testing in throat swabs, and only three neonates were positive for SARS-CoV-2 infection (23).

So, embryos may be exposed to SARS-CoV-2 at vital stages of fetal development (15). Very small embryonic-like stem cells (VSELs) are precursors of oocytes, pluripotent embryonic stem cells, organoids, and some other stem cell types, including hematopoietic stem cells, and it is of concern that (potentially) infection or other adverse effects of SARS-CoV-2 on VSELs have been demonstrated (24). The most common symptom in patients with SARS-CoV-2 is fever. Fever increases the risk of congenital anomalies and may cause neural tube defects and miscarriage during the first trimester (18).

Furthermore, infants born to mothers infected with SARS-CoV-2 had symptoms such as shortness of breath, fever, tachypnea, and vomiting (5). In addition Dashraath et al (2020) in US, reported other complications of the mother and fetus in pregnant women infected by COVID-19 as follows: fetal distress (8.8%), IUGR (9%), being hospitalized in the neonatal intensive care unit (ICU) (15%), miscarriage (2%), stillbirth (0.7%), and neonatal death (0.5%) (25). In a study by Prabhu (2020) in New York, swabs were collected in the first 24h of life in 71 newborns of infected pregnant women in which no SARS-CoV-2 virus was detected by RT-PCR. Placental pathology was performed in 28 infected and 99 non-infected parturients, with a greater presence of thrombi andmeconium in the placentas of women with Covid-19 (26). Therefore, more evidence is needed to investigate the risks of congenital COVID-19 infection.

Covid-19 infection and its complications during pregnancy can have a negative impact on the still-developing auditory system. Infants whose mothers had Covid-19 during pregnancy may have a normal cochlear function but may show significantly prolonged neural timing for acoustic stimuli at the level of the auditory brainstem. These neural delays could be due to atypical axonal and synaptic functions. Future studies are required to examine auditory system maturation in these infants (27).

The effect of SARS-CoV-2 on pregnancy

Previous studies have shown that pregnant patients with COVID-19 are more likely to give birth prematurely. Rates of preterm birth (PTB) in these pregnant women are between 23.8% to 39% or without an increase in the PTB rate (10). COVID-19 infection is a significant threat to pregnant women and their fetuses. Previous studies showed an increased ratio of fetal distress (26.7%), PTB (20.8%), premature rupture of fetal membranes (13.0%), and cesarean section (92.6%). The specific cesarean section rate is usually because of the worry about COVID-19 and obstetrical indications (7).

Histopathological findings illustrated that the placentas of COVID-19 patients indicate a greater prevalence of decidual arteriopathy, including atherosis and fibrinoid necrosis and mural hypertrophy of membrane arterioles; changes that cause a systemic inflammatory state of hypercoagulability; findings similar to placental changes in hypertensive disorders of pregnancy; and changes associated with oligohydramnios, fetal growth restriction, preterm birth, and stillbirth (28). In a large case-control study there were five reports from national registries (UK, Netherlands, China, France and Brazil), while the rest were regional reports from other countries (Italy, USA, Spain). In 2020, 2567 pregnant women with COVID-19 were examined with 746 deliveries. Most

women (73.9%) were in the third trimester. The ratio of Black, Asian, or minority ethnic group membership (50.8%), obesity (38.2%), and chronic co-morbidities (32.5%) was high. Fever (63.3%), cough (71.4%), and dyspnoea (34.4%) were the most clinical symptoms. C-reactive protein (CRP) or procalcitonin (54.0%), lymphopenia (34.2%), and high transaminases (16.0%) were raised. Maternal death (0.9%), preterm birth (before 37 weeks' gestations), primarily iatrogenic rather than spontaneous births (21.8%), and less than 1% perinatal death were observed. Neonatal nasopharyngeal swab RT-PCR was positive in 1.4% (8).

Azinheira et al., showed that pregnant women are less likely to present fever, myalgia, and dyspnea in comparison with non-pregnant women. However, fever and shortness of breathing among COVID-19 pregnant women are related to increased risk for acute maternal and fetal complications. Also, pregnant women infected with COVID-19 stayed 3.73 days longer in the ICU than women without COVID-19. Previous studies showed that maternal mortality due to COVID-19 was uncommon and less than <1% (5).

Ko et al (2021) in US collected data from the 703 hospitals with delivery hospitalizations.

Overall, 4.2% of all delivery hospitalizations had any adverse pregnancy outcomes of interest. Among all delivery hospitalizations, 0.8% had any maternal complication of interest, including 4.4% of individuals with a COVID-19 diagnosis and 0.7% of those who did not have a COVID-19 diagnosis. Indication of severe illness was observed in 1.6% of all hospitalizations, including 4.7% of individuals with COVID-19 and 1.6% of individuals without COVID-19. Those with a documented COVID-19 diagnosis were more likely to have concurrent documentation of acute respiratory distress syndrome (Adjusted risk ratios, 34.4), sepsis (aRR, 13.6), shock (aRR, 5.1), acute renal failure (aRR, 3.5), thromboembolic disease (aRR, 2.7), adverse cardiac event or outcome (aRR, 2.2), or preterm labor with pre-term delivery (aRR, 1.2) to require ICU admission (aRR, 3.6) or mechanical ventilation (aRR, 12.7) and to die (aRR, 17.0). Most (98.9%) patients were discharged home from the delivery hospitalization (29). In a recent metanalysis, diabetes was the most commonly associated comorbidity, found in 18% of pregnant women with COVID-19 infection (30). These comorbidities increase the risks of severity of the COVID-19 infection. The population of this study had a low rate of diabetes. According to Allotey et al., pregnant women had a lower risk of developing symptoms than non-pregnant women, but had a higher risk of serious complications if they had associated comorbidities. In our experience, COVID-19 patients were more likely symptomatic if they had associated comorbidities (16).

Discussion

In this study, we tried to describe the effects of COVID-19 on pregnant women and their fetuses during the SARS- COV-2 pandemic.

SARS-CoV-2 has several structural proteins, such as spike (S), membrane, envelope, and nucleocapsid proteins (31). S protein comprises two components: S1 and S2 (32). Initially, the S protein binds to the host receptor using the receptor-binding domain (RBD) in the S1 subunit, and then the viral and host membranes are integrated using the S2 subunit (33). Therefore, the determination of RBD in SARS-CoV-2 S protein is essential as the most likely target for the generation of neutralizing antibodies, virus-binding inhibitors, and vaccines. The reason for the great affinity of SARS-CoV-2 with human ACE2 is RBD (5). SARS-CoV-2 binds to ACE2 through its S protein and uses it as a host cell receptor (33). The trans-membrane protease serine protease-2 (TMPRSS-2) of the host cell is essential for priming the S protein, so that S protein can integrate the viral and host membranes via the S2 subunit. Thus, SARS-CoV-2 enters the cell via endocytosis, and viral RNA is released, then replicated, and transcribed by the host cell machinery, and more assembly occurs, and afterward, new viral particles are released during exocytosis (32).

How ACE2 distribution in the placenta during pregnancy is vital (4). ACE2 mRNA placental expression is dependent on gestational age. It has the most expression on the first days of pregnancy and the least to undiscoverable levels towards term (13, 14).

RAS system in pregnancy plays a vital role by regulating the electrolyte balance and subsequently contributes to the well-being of the mother and fetus. This system can also control maternal hypertension, embryo implantation, placental blood, nutrient

supply to fetuses, and fetal development during pregnancy (34). On the other hand, angiotensin II plays a role in stimulating trophoblast invasion. Also, ACE2 and Ang-(1-7) are necessitated in regulating angiogenesis, apoptosis, development, and uteroplacental circulation during pregnancy as local autocrine/paracrine regulators (7). SARS-CoV-2 binding decreases ACE2 bioavailability in the feto-maternal circulation and placentas (5) and further between the angiotensin-converting enzyme - angiotensin II- T-helper lymphocyte type-1 (ACE-AngII-AT1) axis, and the angiotensin-converting enzyme-2 - angiotensin-(1-7)-mitochondrial assembly 1 (ACE-2- Ang-(1-7)-MAS) axis causes an unbalanced dysregulation, therefore it contributes to the environment of progressive vasoconstriction, inflammation, fibrosis, and thromboembolic processes (19). Also, it may become a risk factor for placental vascular dysfunction, maternal hypertension, and adverse pregnancy-related consequences of placental dysfunction, exacerbating pregnancy complications (5).

In general, symptomatic infection in pregnant women seems to be of lower incidence compared to the general population. Nonetheless, in pregnant women with symptoms like fever and cough, adverse outcomes may be expected, especially after hospitalization due to the severity of the symptoms required.

SARS-CoV-2 infection may cause a pro-inflammatory condition, resulting in systemic endothelial dysfunction and preeclampsia (15). Factors that increase the severity of the disease in pregnant patients include aging, diabetes, obesity, and non-white ethnicity (2). Infants born to SARS-CoV-2 infected mothers were positively tested, and most of them did not have a negative outcome. Infants who tested positive had no or mild symptoms. COVID-19 infection increases the ratio of fetal distress (26.7%), PTB (20.8%), premature rupture of fetal membranes (13.0%), and cesarean section (92.6%). Due to the high proportion of preterm births in pregnant patients with Covid-19, it is difficult to determine whether the symptoms are due to premature complications or directly to Covid-19 (5). In a systematic study of 324 pregnant women with Covid-19, Juan et al. (2020) in China reported that up to 14% of mothers with severe pneumonia required critical care, with a total of 9 cases of maternal deaths, 4 cases of spontaneous abortion, 4 cases of intrauterine fetal deaths, and 3 cases of neonatal death (23). There are conflicting results about the effects of COVID-19 on pregnant women and their fetuses. In women who develop COVID-19 after 33 weeks of gestation, the mother's condition worsens, and the percentage of PTB increases. Although most cases of PTB are iatrogenic, PTB in COVID-19 pregnant women may range up to 63.8%. Also, COVID-19 can increase fetal death, since five fetal deaths related to acute chorioamnionitis from COVID-19 infected pregnant at 21–38 weeks have been reported. Moreover, the introduction of SARS-CoV-2 into syncytiotrophoblasts may adversely affect the transport efficiency of nutrients and drugs, hormonal output, and cause cellular changes, resulting in robust inflammatory response and disruption of the syncytiotrophoblast barrier (13). Pathological findings of the placenta of pregnant women with COVID-19 have varied, some reports show no considerable change, some show either fetal or maternal vascular malperfusion or both, and others illustrate inflammatory lesions including chronic histiocytic intervillositis, villitis, funisitis, and chorioamnionitis, most coming from non-infected placentas (11). A more restriction to the data is that in most studies, only women with COVID-19 symptoms are tested, while one study tested all pregnant women on the labor ward and found that only 11.1% of women with COVID-19 were symptomatic. On the other hand, universal testing showed that 44-82% of pregnant who tested positive for SARS-CoV-2 had no symptoms (5). Conflict findings may be due to differences in obstetric intervention practices across populations and geography, our outcome of preterm labor with preterm delivery (not preterm birth), and our ability to adjust for underlying medical conditions (29). To date, it is well known that placentas are susceptible and can be infected by SARS-CoV-2. It is also known that in these cases, placental ACE2 is down-regulated, which can potentially contribute to altering key physiological processes during placental development and vascularization. This is supported by the fact that a preeclampsia-like syndrome can

emerge in cases of COVID-19 infection during pregnancy. However, the gestational age at exposure may also be an important factor determining placental vascular responses or outcomes (5).

Risk factors like obesity and pre-existing cardiovascular disease, including hypertension and diabetes, play a significant role in increasing the chances of a more severe disease presentation and evolution (35).

Major risk factors for associated morbidity were Black and Hispanic race, advanced maternal age, medical comorbidities, and antepartum admissions related to COVID- 19 (20).

Conclusions

In this study, according to the studies performed, the effects of coronary artery disease on maternal and fetal health were investigated and it was found that SARS-CoV-2 infection in pregnancy risks such as preeclampsia, stillbirth, preterm delivery, hospitalization in NICU and others increases adverse outcomes for mother and infant. Further studies on pregnancy events and outcomes are needed to evaluate the impact of the coronavirus on maternal and fetal health and to identify effective strategies to prevent adverse outcomes in pregnancy with Covid-19 and its embryos.

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Conflict of interest

The authors have nothing to disclose. There is no conflict of interest in this article.

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