

SARS-CoV-2: an imperative maternal-fetal concern

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ABSTRACT

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is a newly emerged virus which belongs to *Coronaviridae* family within the betacoronavirus genus. Previous reports demonstrated that other betacoronaviruses were responsible for adverse outcomes during pregnancy in human. Due to inadequate data, the consequences of a SARS-CoV-2 infection during pregnancy is still a public health concern in the second year of SARS-CoV-2 circulation in human population. Herein, we aimed to review the probable risk of intrauterine vertical transmission of SARS-CoV-2 infection to the fetus, its adverse outcomes during pregnancy for both mother and the fetus and maternal risk factors which affect the severity Coronavirus disease 2019 (COVID-19).

Keywords: COVID-19; SARS-CoV-2; Pregnancy; Fetus; Vertical transmission

INTRODUCTION

A novel 2019 coronavirus, known as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), causes coronavirus disease 2019 (COVID-19) which emerged in Wuhan, China and quickly spread globally. As of February 14, 2021, World Health Organization (WHO) confirmed 108,246,992 cases of COVID-19 infections in the world with 2,386,717 deaths. SARS-CoV-2 is a member of *Coronaviridae* family within the betacoronavirus genus. Previous reports demonstrated that other betacoronaviruses such as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) were responsible for adverse outcomes during pregnancy (1, 2). It was

reported that the rate of preterm delivery in pregnant women infected with SARS-CoV and MERS-CoV was 28.9% and 32.1%, respectively. Moreover, the rate of miscarriage in SARS-CoV infected cases was 39.1% (3). For SARS-CoV-2 infection, due to the special immunological condition during pregnancy, adverse obstetric outcomes in pregnant women are a matter of concern, as people with immunocompromised condition and underlying diseases have a higher risk of disease development (4). In the second year of SARS-CoV-2 circulation in human population, still due to inadequate data on the consequences of a SARS-CoV-2 infection during pregnancy and vertical transmission to the fetus, all pregnant women with confirmed SARS-CoV-2 infection should be followed up and screened. Herein, we aimed to review the severity of COVID-19 and maternal risk factors, intrauterine vertical transmission of SARS-CoV-2 infection to the fetus and the probable risk of adverse outcomes of pregnancy. To reach these goals we searched papers in PubMed: ((SARS-CoV-2) OR (2019-nCoV)) OR (severe acute respiratory syn-

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drome corona virus 2)) OR (COVID-19)) OR (Coronavirus Disease 2019)) OR (novel coronavirus)) OR (Wuhan coronavirus)) AND (pregnancy)) AND (vertical transmission)) AND (adverse maternal outcomes)). Furthermore, the following search keywords combinations were used to search in Google scholar database: “SARS-CoV-2” OR “2019-nCoV” OR “severe acute respiratory syndrome corona virus 2” OR “COVID-19” OR “Coronavirus Disease 2019” OR “novel coronavirus” OR “Wuhan coronavirus” AND “pregnancy” AND “vertical transmission” AND “adverse maternal outcomes” AND “risk factors” AND “pregnancy complications” AND “persistence in placenta”. Inclusion criteria included case reports, original and review articles about pregnant women with a confirmed SARS-CoV-2 infection. We

excluded articles reported in a language other than English. The flowchart outlining the study identification and selection process were shown in Fig. 1. Following careful article assessment and execution of inclusion/exclusion criteria, 39 relevant papers retained for full-text evaluation. The information of included studies was summarized in Table 1.

Severity of SARS-CoV-2 infection in pregnant women. So far, different studies have shown that signs, symptoms, laboratory results and imaging findings in pregnant woman infected with SARS-CoV-2 were similar to non-pregnant individuals (5). Otherwise, it was shown that some patients with severe COVID-19 had inflammatory response (cytokine storm), which was correlated with critical

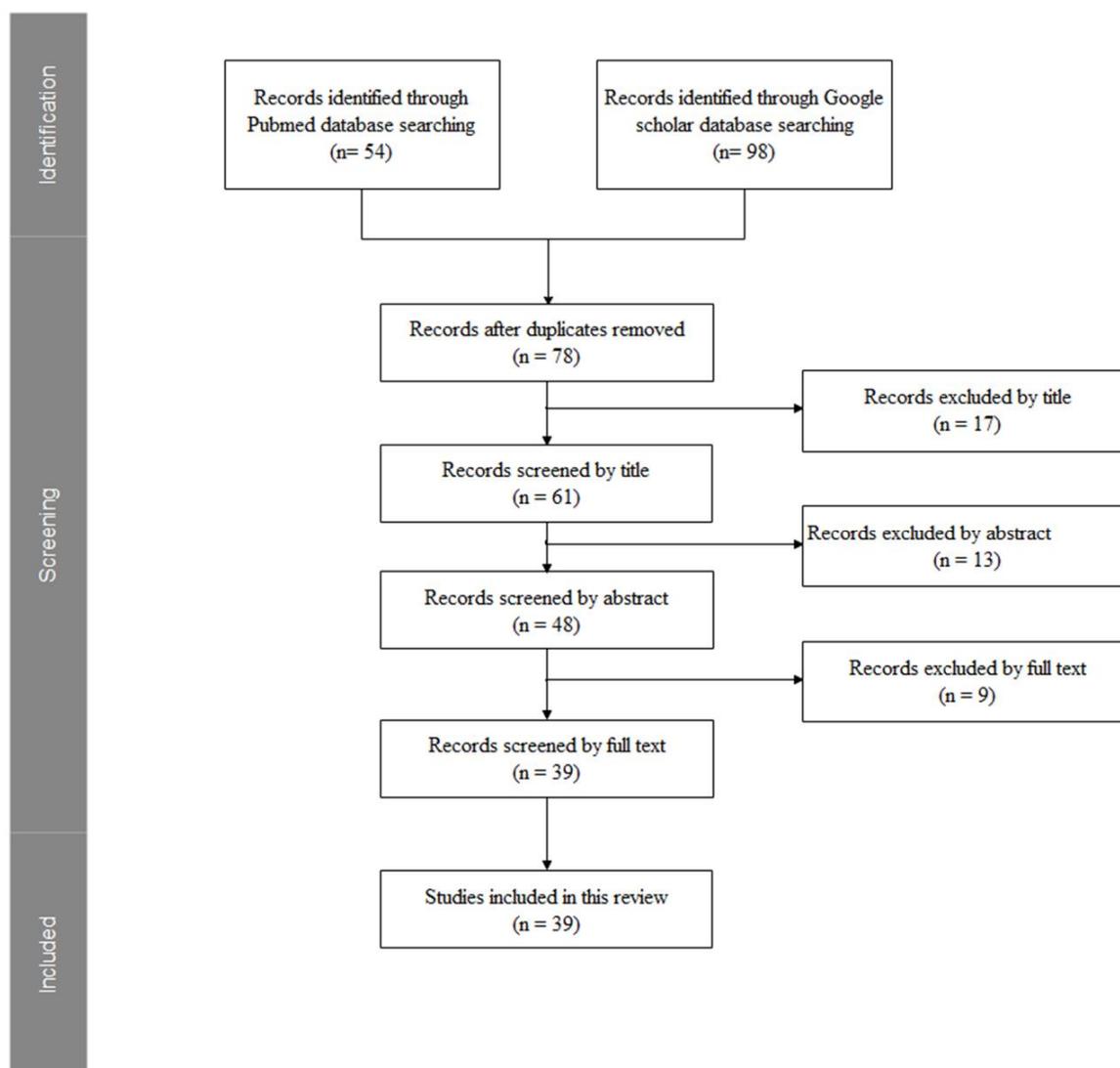


Fig. 1. Flowchart of the paper selection process based on keywords.

and fatal illnesses (6). However, whether the normal immunosuppression during pregnancy might affect the occurrence and intensity of this response still is obscure. Available data suggested that pregnancy and childbirth did not worsen the clinical symptom of COVID-19 dramatically, and most infected mothers recovered without adverse complications (7). Siyu Chen et al. described clinical features in five pregnant women infected with SARS-CoV-2. They showed all five cases after delivery had unusual chest imaging with general signs of respiratory tract infection including fatigue and low-grade fever which were not observed before delivery. These patients had no symptoms of hemoptysis, dyspnea, shortness of breath, nausea, and vomiting, it should be noted that all newborns delivered by these infected mothers had good conditions (8). Another study which was performed on 13 pregnant women with SARS-CoV-2 infection, showed 10 (77%) cases presented fever accompanied with dyspnea in 3 (23%) of them (9).

In pregnant women who developed COVID-19 pneumonia, early data showed approximately the same rate of intensive care unit (ICU) admissions as in the non-pregnant individuals but an increased risk of preterm and cesarean delivery was seen due to mothers condition (7, 10). An initial report from the United States in February-March 2020 indicated that 4 out of 143 pregnant COVID-19 patients were admitted to ICU. This data have not demonstrated a higher risk for severe COVID-19 among pregnant women (11). In another report from New York City, five out of seven SARS-CoV-2 infected pregnant women presented with symptoms of COVID-19, including cough, myalgia, fever, chest pain, and headache. It should be noted that two of these women had asymptomatic infections at the time of admission to the hospital for labor induction, but they became symptomatic postpartum and required ICU admission (12). In a report from Hubei Province (China), among 16 pregnant women with COVID-19, fifteen cases had normal conditions and one case had severe complications. It is worth noting that no one had progressed to critical pneumonia (13). In a cohort study in USA, of 241 pregnant women who were positive for SARS-CoV-2 infection, 63 (26.1%) had severe disease, 12 (5%) had critical condition and others remained asymptomatic. Totally 17 women (7.1%) were admitted to ICU and 9 women (3.7%) intubated during their delivery. Maternal death wasn't reported during this study (14). In a case-control study among

Table 1. Characteristics of included studies evaluating possible vertical transmission of SARS-CoV2.

First author	Study location	Study design	Number of pregnant women	Maternal risk factor	Symptom / severity of COVID-19 in pregnant women	Pregnancy complications	Evidence for vertical transmission
Wang (30)	China	Case report	1	Hypothyroidism	Normal, just fever	Normal	Neonate swab was Positive 36 h after birth
Na Li (15)	China	Case/Control	16 / 18	18.2% had chronic conditions including hypertension, polycystic ovary syndrome and hepatitis B	Fever, pneumonia in case group	preterm delivery in 18.8% and 10.5% of confirmed and suspected COVID-19 cases	No evidence
Chen (8)	China	Case report	5	None	Low-grade fever, cough	Normal	No evidence
Zamanyan (10)	Iran	Case report	1	Hypothyroidism	dyspnea, myalgia, anorexia, nausea, nonproductive cough	Preterm delivery	Amniotic fluid was positive, neonate swab was negative
Zhang (13)	China	retrospective	16	None	1 case had severe infection	Normal	No evidence
Khoury (14)	USA	prospective cohort study	241	55% Obesity (BMI≥30)	61.4% were asymptomatic, 7.1%, and 3.7% were admitted to the ICU and intubated	14.6% preterm delivery	No evidence
Freiesleben (18)	Denmark	cohort study	18	None	Normal, no hospitalization	1 Pregnancy loss	No follow up
Baud (23)	Switzerland	Case report	1	Obesity	Fever, myalgia, fatigue, mild pain when swallowing, diarrhea, and dry cough	Miscarriage during the second trimester of pregnancy	Placenta was positive
Liu (7)	China	Case report	15	One patient had thalassemia	86% fever, 60% cough	66% cesarean delivery	No evidence
Chen (5)	China	Case report	3	None	fever	cesarean	Negative for neonate swab and placenta

pregnant women, preeclampsia has been shown in 12 (7.7%) of women who were positive for SARS-CoV-2 compared to 26 (4.3%) in control group. Although preeclampsia had a higher rate in infected women, no significant difference was found between the case and control group. In this study gestational diabetes was not reported statistically different between case and control groups (9% and 13%).

Another case-control study reported that pregnancy complications, such as gestational hypertension, gestational diabetes mellitus, premature rupture of membranes, preeclampsia, hypothyroidism and sinus tachycardia were observed in 68.5% of COVID-19 confirmed cases (who had a positive RT-PCR test), 72.2% of suspected cases (who had a typical chest CT imaging but negative RT-PCR tests) and in 31-33% of control group (who had a normal chest CT imaging and negative RT-PCR tests). In this study, it was claimed that pregnancy complications in two mentioned case groups were significantly higher than the control group (15).

Maternal risk factors correlated to severe COVID-19. A systematic review showed high body mass index (BMI), maternal age, non-white ethnicity, chronic hypertension and pre-existing diabetes were associated with exacerbation of COVID-19 during pregnancy. Furthermore, underlying health condition in pregnant women increased the rate of admission to ICU and the need for invasive ventilation 95% CI 1.53 (0.53 to 4.41) (3). In a cohort study in the USA and Sweden, it has been shown that pre-existing lung disease and diabetes were strongly associated with severe COVID-19 in pregnant women (16). It seems, like non-pregnant women, comorbidity during pregnancy can be associated with severity of disease.

COVID-19 outcome during first, second and third-trimester pregnancy. It has been declared that the first and the third trimester of pregnancy are pro-inflammatory phase, unlike the second trimester which is anti-inflammatory (17). Since COVID-19 is a pro-inflammatory disease, during the first and the third trimester of pregnancy, women are more susceptible to contracting the disease in comparison to the second trimester (17). A cohort study was done in Denmark on women with previous SARS-CoV-2 infection in early pregnancy that showed SARS-CoV-2 infection did not significantly increase the risk of pregnancy loss and those women did not have

a remarkably different nuchal translucency thickness measured at their first trimester scan compared to women without previous SARS-CoV-2 infection (18).

Data on ACE2 gene expression on placenta is controversial. In a study expression of ACE2 gene in the villous cytotrophoblast, syncytiotrophoblast, decidual stromal and perivascular cells in both first trimester and term samples has been reported, while in another study just a low level ACE2 expression was found in placental and fetal membranes in the third trimester (19).

COVID-19 and possible pregnancy complications. There is a hypothesis that hyperthermia-related to COVID-19 might increase the risk of congenital anomalies, especially neural tube defects, or miscarriage during organogenesis in the first trimester of pregnancy (20). It was indicated that pregnant women who had developed pneumonia related to COVID-19 showed an increased frequency of preterm labor, pre labor rupture of membranes and cesarean delivery because of abnormal fetal heart rate which was correlated to severe maternal disease (15, 21, 22). A systematic review showed among 32 COVID-19 pregnant patients, seven (22%) were asymptomatic and two (6%) were admitted to the ICU. Cesarean section, vaginal delivery and preterm delivery occurred in 27 (84.3%), 2 (6.25%) and 15 (47%) cases, respectively. Furthermore, one case of stillbirth and one case of neonatal death were reported (22). Moreover a case of miscarriage was reported in Switzerland during the second trimester of pregnancy in a woman with SARS-CoV-2 infection (23). Represented data showed that perinatal deaths were not directly due to the fetal or neonatal infection with the SARS-CoV-2 (22). A recent systematic review estimated that overall preterm birth was 17% (95% CI 13% to 21%) and spontaneous preterm birth rate was 6% (3% to 9%). They reported 18 stillbirths from 2837 offspring and 6 neonate deaths from 1728 neonates among pregnant women with COVID-19 (3).

SARS-CoV-2 could trigger preeclampsia through different mechanisms. On the one hand, systemic inflammation and microcirculatory dysfunction might cause vasoconstriction and ischemia. On the other hand, local inflammation subsequent to SARS-CoV-2 placental infection could result in lymphohistiocytic villitis, chronic histiocytic intervillitis and chronic deciduitis. Furthermore, endothelial cell dysfunction and coagulation abnormalities were in-

volved in preeclampsia development (24, 25).

Vertical transmission of SARS-CoV-2 to the fetus. Some studies reported that SARS-CoV-2 has not been detected in neonates delivered from infected pregnant women (5, 13, 26-29), however some studies found opposite results (30-32). The former studies have stated that ACE2 and TMPRSS2 as receptors for SARS-CoV-2 were presented on the placenta tissue which might help the virus to enter the cell (33). However low RNA expression of ACE2 in decidua and placenta tissues has been reported during the first trimester of pregnancy (34). Furthermore, detection of SARS-CoV-2 genome in umbilical cord blood and placenta tissue have been reported. Nevertheless, mechanism of vertical transmission has not been exactly understood (35). In a study performed on neonates born to mothers with confirmed COVID-19 infection, 4 out of 10 cases were full-term infants and 6 were born premature. For SARS-CoV-2 detection, pharyngeal swab specimens were collected from 9 of these 10 neonates 1 to 9 days after birth. All 9 cases had negative RT-PCR results (27). Contradictory to this report, another study described positive results for SARS-CoV-2 in nasopharyngeal swab samples of 3 (9%) out of 33 neonates delivered from mothers with confirmed infections (36). Analysis of three placenta specimens from pregnant women with confirmed SARS-CoV-2 infections showed various degrees of fibrin deposition inside and around the villi with local syncytial nodule without any pathological change of villitis and chorioamnionitis. Among these placenta tissues, one case had a concomitant morphology of chorionic hemangioma and another one showed massive placental infarction. All samples from three placentas were negative for SARS-CoV-2 (5). A review article on total of 31 infected pregnant women with SARS-CoV-2 (up to March 4, 2020) represented no vertical transmission of infection from infected mothers to their neonate or placentas. The study reported two cases of mothers death due to COVID-19-related respiratory problems after delivery (37). Dong L et al. reported one neonate with elevated IgM antibodies to SARS-CoV-2 after two hours of birth from a mother with COVID-19. The results of the Real Time RT-PCR tests for SARS-CoV-2 on nasopharyngeal swabs of this infant were repeatedly negative during 15 days after birth. Because PCR test was not performed on their amniotic fluid or placenta, they could not con-

firm vertical transmission of SARS-CoV-2 (38). In order to investigate the SARS-CoV-2 vertical transmission at the time of delivery, some researches were performed. In a study, on a neonate with cesarean delivery, SARS-CoV-2 genome was detected in the pharyngeal swab after 36 hours of birth. The infant had no contact with the mother after birth. However, SARS-CoV-2 was not detected in the cord blood and placenta, therefore its vertical intrauterine transmission remains unclear (30). Another case report, presented a pregnant woman with severe COVID-19 pneumonia with exacerbation of disease in the postpartum period. Unfortunately, she died from acute respiratory distress syndrome (ARDS). Her newborn was positive for SARS-CoV-2 twenty-four hours after preterm delivery until one week but she was in a good condition. The result of SARS-CoV-2 detection in the vaginal secretion and umbilical cord blood were negative but positive for amniotic fluid sample. The study pointed out the possibility of intrauterine infection of the fetus which raised the concerns of potential vertical transmission. Based on these studies, vertical transmission of SARS-CoV-2 from infected mother to her fetus has not been proved yet, but this risk should be considered.

Possible persistency of SARS-CoV-2 in the placenta. Persistent infection of SARS-CoV-2 had been reported from pneumocytes and endothelial cells of lung tissue as well as gastrointestinal tract (36, 39). Recently, a study showed that in a case of a mother who had asymptomatic SARS-CoV-2 infection, after five weeks since her throat swab tested negative, both RNA and spike protein of the virus were detected in the placental villi which suggested that SARS-CoV-2 could persist in the placenta. Moreover, histological examination revealed avascular villi with extensive perivascular fibrin deposition led to hydrops fetalis at 13 weeks of gestation (40). The study proposed that transplacental transmission of SARS-CoV-2 could occur and cause fetal death.

CONCLUSION

Herein clinical characteristics and probable complications of SARS-CoV-2 infection for infected mother and her fetus, also the possibility of vertical transmission to the fetus throughout pregnancy were described. Up to know, different studies showed that

clinical manifestations of COVID-19 in pregnant women are similar to non-pregnant adults but some maternal risk factors such as comorbidity, obesity, advanced maternal age, non-white ethnicity could increase severity of disease. Presumably, SARS-CoV-2 unlike other betacoronaviruses causes less adverse complications during pregnancy. However, it might cause some pregnancy complications including fetal distress, miscarriage, premature rupture of the membrane, stillbirth and preterm labor.

Preterm birth is the most common adverse pregnancy outcome during third trimester of pregnancy in women with SARS-CoV-2 infection. To date, the vertical transmission of SARS-CoV-2 during pregnancy has not been proved but more research in this field is needed.

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