# COVID-19's Effect in Pregnancy and Vertical Transmission: A Systematic Review




## Abstract

The COVID-19 pandemic has significantly impacted public health and the global economy. It has also been found to have potential effects on pregnancy, neonatal outcomes, and mother-to-infant transmission. This systematic review aims to provide an overview of the maternal and perinatal outcomes associated with pregnancy. A systematic review study was conducted by searching the PubMed, MEDLINE, Embase, and Web of Science databases according to PRISMA guidelines from December 1, 2019, to December 23, 2022. The results indicate that there was an increase in the rate of cesarean delivery among mothers infected with SARS-CoV-2. However, the study found that the mode of delivery for pregnant women infected with SARS-CoV-2 did not increase or decrease the risk of infection for newborns. During the COVID-19 pandemic, there has been an increase in maternal and infant mortality rates, as well as stillbirths and ruptured ectopic pregnancies. Research has shown that SARS-CoV-2 can potentially be transmitted during pregnancy, although vertical transmission is rare. However, additional data are needed to investigate this adverse effect, especially regarding reports of disease recurrence in mothers infected with SARS-CoV-2.


**Keywords:** *COVID-19, pregnancy, systematic review, vertical transmission*


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## Introduction

Since the outbreak of COVID-19 (SARS-CoV-2), which rapidly became a global pandemic, numerous studies have been conducted on this disease.[1] Previous experience with coronaviruses in 2002 and 2012[2-4] has shown that pregnant females are at risk due to the physiological adjustments of their immune system during pregnancy, requiring particular attention during this situation.[5,6]

During pregnancy, due to increased uterine size reducing lung volumes, pregnant females may be more susceptible to rapid clinical deterioration with COVID-19, which increases the risk of adverse pregnancy outcomes.[7] The studies have demonstrated that COVID-19 in pregnant females is associated with intrauterine growth restriction, increased abortion, and premature birth.[8]

Pregnant females who contract COVID-19 and their neonates are at a higher risk of suffering from severe health issues or even death. They are also more likely to require admission into the intensive care unit. Furthermore, their newborns are at an increased risk of being born prematurely, having a low birth weight, and being admitted into the neonatal intensive care unit.[9] Some of the complications that can arise as a result of contracting COVID-19 during pregnancy include preterm delivery, C-section requirements, anxiety, and depression. In addition, COVID-19 infection during pregnancy can lead to an increased incidence of cesarean section, stillbirth, ICU admission, pre-eclampsia/eclampsia, and higher mortality rates. Pregnant females with COVID-19 often experience emotional distress, which can harm their well-being.[10] The symptoms of COVID-19 in pregnant females are similar to those experienced by non-pregnant females, but pregnant females are at a higher risk of requiring ICU admission and ventilatory support. The virus can be transmitted from the mother to the fetus through the placenta, and females with moderate-to-severe COVID-19 are more likely to have preterm births.[11]

COVID-19 vaccination is safe and effective for pregnant women and does not increase the likelihood of complications. Pregnant women who have received the vaccine



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have shown reliable immune responses, successful transfer of antibodies across the placenta, and potential benefits for neonatal immunity. Vaccination has also been found to prevent SARS-CoV-2 infection and COVID-19-related hospitalization in pregnant women. It is strongly recommended that pregnant women, those considering pregnancy, and breastfeeding women get vaccinated against COVID-19 to safeguard themselves and their infants from severe COVID-19 disease.[12]

Despite numerous studies, there is still insufficient information on the effects of COVID-19 on pregnancy, delivery, and infant outcomes. The scattered reports in the COVID-19 pandemic of the complications caused in pregnant females have drawn much attention.[13] Therefore, it is crucial to acquire knowledge about pregnancy outcomes such as the likelihood of vertical transmission, severity of symptoms in pregnant females, and potential complications during pregnancy, making systematic review necessary to demonstrate the effects of COVID-19 on pregnant females and the possibility of vertical transmission.

## Methods

### Search strategy, study selection, and data extraction

A systematic search was conducted in the DisasterLit, Cochrane Library, Ovid Medline, Ovid Embase, LitCovid, Google Scholar, PubMed, Scopus, MedRxiv, and Web of Science Core Collection databases to find relevant literature published from the beginning of COVID-19 in 2019 to the end of 2022, to identify studies, reporting information regarding pregnancy and COVID-19. The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA) for reporting systematic reviews.[14]

The systematic search of databases was performed using a combination of keywords and free-text terms. Search terms used across all databases included: "SARS-CoV-2," "coronavirus," "COVID-19," "Coronaviridae," "fetus," "pregnancy," "mother-to-child," "infant," "maternal-fetal," "virus transmission," "mother-to-infant," "vertical transmission," and "disease transmission. "

Primary results were cross-referenced in order to identify additional relevant studies. English-language articles that focused on the effect of COVID-19 infection on pregnancy and fetus and neonate development were included. Citations were independently managed by using the EndNote 20 library.

### Eligibility criteria

All original studies, including observational studies (cohort studies, case-control studies, case series, and case reports), randomized and controlled studies, various laboratory studies, and clinical studies, including maternal and neonatal outcomes, were included in this review.

Studies with inconclusive results, unpublished reports, studies suspected of including duplicate reporting, review studies, guidelines, opinions, and comments were excluded.

### Study selection

First, duplicate documents were removed from the EndNote, decreasing the initial list of 18,991 citations to 13,746 citations. The title and abstract screening were performed by two independent screeners (Naeiji, Nazari), relevant studies were then read in full text and selected according to the eligibility criteria, and conflicts were resolved by consensus between the third screener (Abbasi). The quality of the studies was evaluated according to Murad and colleagues.[15]

We selected and extracted studies based on the general characteristics of the inclusion criteria (study type, sample size, study subject characteristics, and maternal and neonatal outcomes). Two authors (Khanjani and Abbasi) extracted the data independently and in duplicate. Finally, the differences were resolved through dialogue, and a consensus was reached. Finally, among the selected full texts, (Movahedi, Mousavi Seresht, Nazari, Naeiji, and Arbabzadeh) fulfilled the eligibility criteria for inclusion in the review [Figure 1].

## Results

In total, 18,982 articles were identified through the electronic search of the databases (8,922, PubMed; 1,530, Scopus; and 8,538 Web of Science). There were 5,246 studies left after duplicates were removed. Eventually, 1,883 studies that satisfied the eligibility criteria were included. Among these, 336 studies were case reports and case series.

### COVID-19 and changes in the immune system of pregnancy

The body's immune system adapts during pregnancy to the growth of the fetus.[16] During pregnancy, among other effects regulating the immune system, there is a change in the balance between T helper 2 (Th2) and helper 1 (Th1) cytokines, which decreases the Th1 cellular immune response and increases the Th2 humoral immune response, and these changes enable the immune resistance of the growing fetus but also increase the susceptibility to viral infections, especially respiratory pathogens.[17-19] These immune changes can affect the severity of COVID-19.[17] A Th1-mediated immune response plays a crucial role in lung injury in patients with COVID-19, and the increase in Th1-related cytokines such as interleukin-6 is associated with a poorer prognosis in patients with COVID-19. In this regard, a dominant Th2 immune response in pregnancy can help reduce the severity of COVID-19 in pregnant females.[17,18]

Also, due to fluctuating immune system regulation during pregnancy, pregnant females are in a pro-inflammatory state

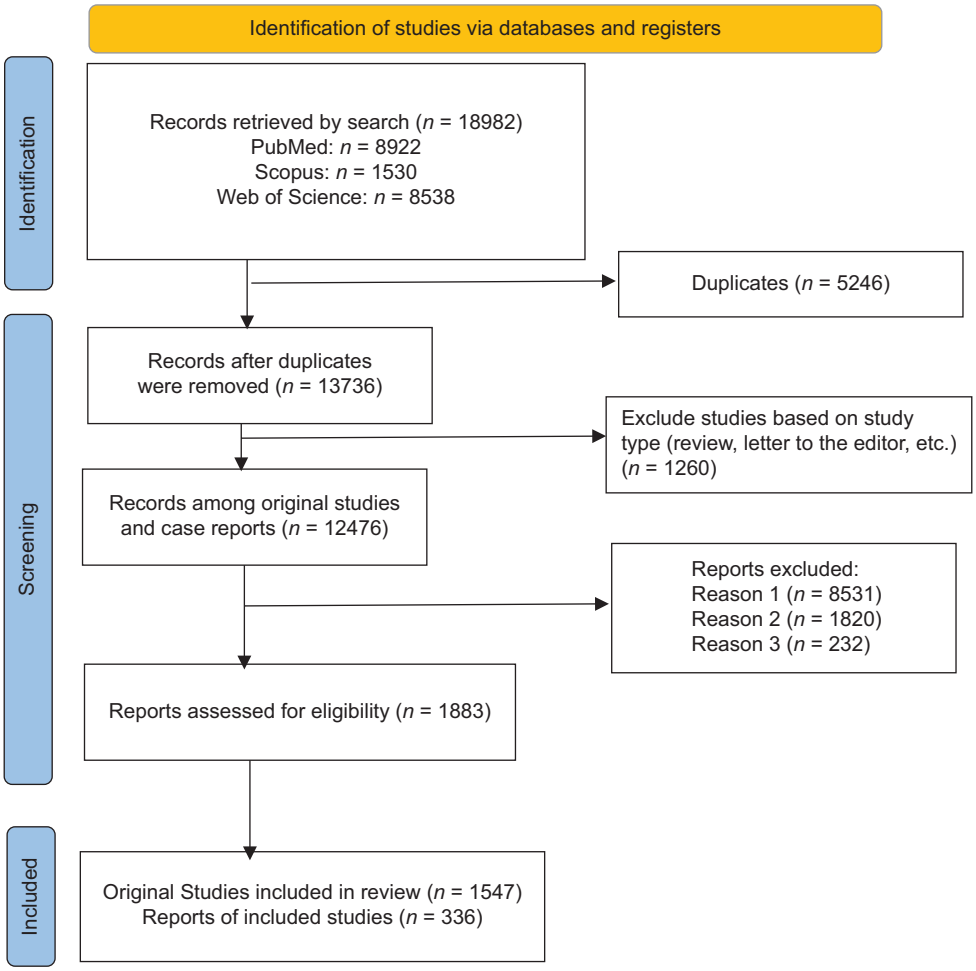


**Figure 1: PRISMA flow diagram showing the study selection process for the systematic review on COVID-19's effect on pregnancy and vertical transmission**

in the first and third trimesters. They can be more exposed to severe inflammation and cytokine storm of 2-CoV-SARS infection.[20,21] This excessive inflammation can increase the severity of the COVID-19 disease and increase its mortality rate.[22]

## COVID-19 and pregnancy

Due to the importance of the health of pregnant mothers and delivery results, many studies and reports have been published since the beginning of the COVID-19 pandemic. The study's results showed that the most common symptoms among pregnant mothers were fever, cough, shortness of breath, lymphopathy, and increased liver enzymes, which did not differ from other (non-pregnant) females in this regard.[23]

However, the most common complications reported in original studies and case reports were premature birth, fetal distress, premature rupture of membranes, low birth weight, chorioamnionitis, and stillbirth.[24]

Although different results have been reported regarding the risk of COVID-19 for pregnant females, most studies have been reassuring, and it seems that the risk of severe COVID-19 in pregnancy is not higher than in the general population.[25] However, we examined the most important results of the studies in several sections, which we will discuss in detail below.

*The effect of COVID-19 infection on the timing of pregnancy:* There is little evidence of the possible effect of COVID-19 on early pregnancy (up to 12 weeks of gestation). However, in late pregnancy (more than 24 weeks of pregnancy), SARS-CoV-19, like other viruses, can increase the rate of adverse pregnancy outcomes such as fetal growth restriction, premature birth, and perinatal mortality. These results indicate a lack of awareness of the infection in the first and second trimesters.[26]

*The effect of COVID-19 infection on preterm delivery:* Studies to examine the association between COVID-19 infection and preterm birth in pregnant females have provided unadjusted data. However, it does not seem that COVID-19 significantly affects premature birth.[27] Nevertheless, the point was that the disease's severity affected premature delivery.[28,29]

*The effect of COVID-19 infection on the mode of delivery:* Studies have shown that in mothers with COVID-19,

cesarean section[30,31] was performed in many cases due to the uncertainty of the risk of vertical transmission and to reduce abdominal pressure for better breathing.[32,33] Other causes, such as fetal distress, PROM, history of stillbirth, stillbirth, incomplete head rotation, chorioamnionitis, and amniotic fluid stained with meconium and pre-eclampsia, were also reported. However, several studies have emphasized that the risk of mother-to-child transmission is not dependent on the type of delivery (i.e., vaginal delivery or cesarean section).[7,34-37]

*The effect of COVID-19 infection on pre-eclampsia:* Pre-eclampsia in pregnancy is characterized by high blood pressure and proteinuria and is associated with critical maternal complications (stroke, cardiac arrest, kidney failure, and liver failure) and fetus (intrauterine growth restriction, premature birth, and stillbirth).[38] Studies have shown a higher rate of pre-eclampsia in hospitalized pregnant females with COVID-19.[39] Some studies considered pre-eclampsia in pregnant females who are infected with COVID-19 as a potential threat to the health of the mother and fetus.[40]

*The effect of COVID-19 infection on the mortality of pregnant mothers:* According to the scattered results that have been mentioned regarding the mortality of pregnant mothers, it is not possible to find a precise relationship between pregnancy and death among COVID-19 patients. The main reason is mainly because the results of the studies were obtained from small samples or case series, which reported very different clinical results.

Although the mortality rate was higher in pregnant females with COVID-19 compared to non-pregnant females with COVID-19,[41-43] pregnancy did not increase the risk of death compared to non-pregnant females with COVID-19. However, due to the physiological nature of pregnancy, many issues, such as the multiple effects of inflammation on the cardiovascular system, should also be considered.[44] A study also considered geographical performance patterns to be involved in the results.[45]

*COVID-19 infection and other complications:* The most significant complications reported in the form of cases were the activity and exacerbation of autoimmune diseases[46-49] and the acute activation of viral diseases, especially liver diseases, whose mechanisms are not fully known. Regarding liver diseases, mainly with acute activity of hepatitis and increased liver enzymes, most reports followed.[48,50]

The binding of SARS-CoV-2 to the receptor of angiotensin-converting enzyme 2 (ACE2) is the first mechanism of liver damage in patients with COVID-19, which is characterized by high expression of choanocytes and leads to bile duct damage.[51]

Some studies also show that this virus can cause liver ischemia through acute multiple organ failure and respiratory distress syndrome injuries.[52,53] Although, according to the evidence, the pathogenesis of COVID-19 patients seems to be multifactorial, the extent and basic mechanisms of liver damage in these patients are not fully known.

As a result of alterations in liver structure and function, including elevated basal metabolic rate and the deactivation of substantial quantities of estrogen and harmful metabolites in the liver, pregnant individuals are at an increased risk of liver injury. Therefore, it is imperative to acquire knowledge regarding pregnancy outcomes, such as the probability of vertical transmission, severity of symptoms in pregnant females, and potential complications during pregnancy amidst the COVID-19 pandemic. As mentioned at the beginning of the discussion, changes in the immune system led to inflammatory and anti-inflammatory responses that have resulted in these reports, and it seems that the need for more studies on the immune system can answer all these questions arising from these reports.

## The effect of COVID-19 infection on placenta and infant

Physiological and immunological changes during pregnancy in response to infection are associated with a high level of inflammation, which can have different effects on the fetus and the baby.[54] However, the critical issue addressed during the COVID era is the effects on the placenta and birth weight, which will be discussed further. Let us talk about it.

*COVID-19 and placenta:* Studies have investigated pregnant mothers with COVID-19. The studies were often in the form of case reports and different weeks of pregnancy. It is often in spontaneous abortions that the resulting investigation showed virus-like particles in the cytosol of placental cells. The severity of virus expression was higher in higher weeks.[55,56] However, some studies also reported that although virus particles were seen, no viral expression was observed in the tested fetal tissues.[55] In both case reports,[55,57] macrophage infiltration and fibrin

**Table 1: Perinatal birth weight of pregnant females with COVID-19**

| Studies | Gestational age | Mode of delivery | Birth weight (Mean) |
|---|---|---|---|
| Chen *et al*. 2020[33] | 37w | All cases of cesarean section (9 cases) | ~2,970 g (Min: 1880g) |
| Lee *et al*. 2020[61] | 37w | In one case, it was a cesarean section | 3,130g |
| Zhu *et al*. 2020[62] | 34w | 6 cases were cesarean section, and 1 case was Vaginal Delivery | ~2,300g (Min: 1,520g) |
| Yu *et al*. 2020[63] | ~38w | All cases of cesarean section (7 cases) | ~3,250g (Min: 3,000g) |
| Chen *et al*. 2020[64] | 39w | 2 cases were cesarean section, and 3 cases were vaginal delivery | 3,700g (Min: 3,235g) |

**Table 2: Maternal and neonate characteristics and outcomes among pregnant females with COVID-19 infection**

| Studies | Mode of delivery | Assessment of vertical transmission | Complication | Mother sequel | Infant sequel | Preterm delivery |
|---|---|---|---|---|---|---|
| Zamaniyan *et al*.[75] | CS | Nasopharyngeal swab (+)<br>amniotic fluid (+)<br>cord blood (−) | No | Died | Alive | Yes |
| Zhu *et al*.[62] | 7 cases CS<br>2 cases NVD | Nasopharyngeal swab (+) | 6 cases: Fetal distress<br>3 cases: PROM | Alive | 8 cases alive<br>1 case died | 5 cases: Yes<br>4 cases: No |
| Gidlöf *et al*.[76] | CS | Nasopharyngeal swab (-) | No | Alive | Alive | Yes |
| Hwan *et al*.[77] | CS | Nasopharyngeal swab (-)<br>amniotic fluid (-)<br>cord blood (−) | | | | |
| Huang *et al*.[78] | CS | Nasopharyngeal swab (-) | Fetal distress | Alive | Alive | Yes |
| Li *et al*.[79] | CS | Nasopharyngeal swab (-)<br>Placenta (-)<br>cord blood (-)<br>amniotic fluid (-)<br>neonate urine and feces (-)<br>breast milk (-) | Fetal distress | Alive | Alive | Yes |
| Khan *et al*.[80] | NVD | Nasopharyngeal swab (-) | No | ? | Alive | 1 case: Yes<br>2 cases: No |
| Chen *et al*.[24] | CS | Nasopharyngeal swab (-)<br>Amniotic fluid (-)<br>Cord blood (-)<br>Breast milk sample (-) | 2 cases: Fetal distress<br>2 cases: PROM | Alive | Alive | 4 cases: Yes<br>5 cases: No |
| Wang *et al*.[81] | CS | Nasopharyngeal swab (-) | No | Alive | Alive | Yes |
| Iqbal *et al*.[82] | NVD | Nasopharyngeal (-)<br>amniotic fluid (-) | No | Alive | Alive | No |
| Liu *et al*.[83] | 2 cases CS<br>1 case NVD | Nasopharyngeal swab (-)<br>Placenta (-)<br>Cord blood (-)<br>Neonatal urine (-)<br>Breast milk (-)<br>Vaginal mucus (-)<br>Neonate blood (-) | 1 case: Fetal distress<br>1 case: Chorioamnionitis | Alive | Alive | No |
| Dong *et al*.[69] | CS | Nasopharyngeal swab (-)<br>Breast milk (-) | No | Alive | Alive | No |
| Li *et al*.[84] | NVD | Nasopharyngeal swab (-)<br>Amniotic fluid (-)<br>Breast milk (-)<br>Rectal swab (-) | No | Alive | Alive | No |
| Zeng *et al*.[72] | CS | Nasopharyngeal swab (-) | No | Alive | Alive | No |
| Wang *et al*.[85] | CS | Nasopharyngeal swab (-)<br>Placenta (-)<br>Amniotic fluid (-)<br>Neonatal blood (-) | No | Alive | Alive | Yes |
| Khan *et al*.[67] | CS | Nasopharyngeal swab (-) | No | Alive | Alive | 3 cases: Yes<br>14 cases: No |
| Chen *et al*.[86] | 1 case CS<br>1 case NVD | Nasopharyngeal swab (-) | No | Alive | Alive | No |

*Contd...*

**Table 2: Contd...**

| Studies | Mode of delivery | Assessment of vertical transmission | Complication | Mother sequel | Infant sequel | Preterm delivery |
|---|---|---|---|---|---|---|
| Kalafat *et al*.[32] | CS | Nasopharyngeal swab (-)<br>Cord blood (-)<br>Placenta (-) | No | Intubation but alive! | Alive | Yes |
| Liao *et al*.[87] | CS | Serologic test (-) | 3 cases: Fetal distress<br>1 case: PROM | All of them are alive (someone has a bat situation) | All of them alive | 6 cases: Yes<br>4 cases: No |



deposits were observed in placental histology, which the authors attributed to most likely related to viral infection.

The histological studies did not have a correct and accurate method, and there was no control group for comparison, which made interpretation and conclusions difficult. The findings were mainly in such a way that they could be related to other causes. Therefore, it is impossible to give an opinion until detailed pathological studies are carried out.

*COVID-19 and birth weight:* In the review of case reports, it has been stated that pregnant females, especially females with moderate-to-severe COVID-19 multiple times, are at risk of lower birth weight,[58] but the summaries of the results of the studies show no significant relationship between birth weight and COVID-19 infection. However, the results of 19 studies of mothers did not indicate a relationship between birth weight and COVID-19 infection.[58-60] In Table 1, some studies with complete data are shown.

### COVID-19 and vertical transmission

In the studies that reported the result of vertical transmission as positive, one issue is that the authors did not report whether preventive measures were taken during delivery. Furthermore, some explained that vertical intrauterine transmission may not have occurred because viral nucleic acid tests of the placenta and umbilical cord blood in this patient were negative for the virus.[63] In studies with acceptable methodology, a few infants have been reported to test positive for SARS-Cov-2 shortly after birth, which may indicate the possibility of intrauterine vertical transmission.[65-71]

Other comprehensive reviews have also noted that viral infection of placental cells does not necessarily mean fetal infection or fetal damage.[25] Moreover, this transmission is rare in these rare cases due to the high concentration of immunoglobulin (Ig) M and IgG; it has been considered for SARS-CoV-2.[69,72] While IgG can be transferred from mother to fetus during pregnancy, IgM is too large to pass through the placenta. Therefore, the circulation of SARS-CoV-2 IgM in newborns may partially justify the vertical transmission of the virus.[69,72]

The mechanisms of viral invasion of the placenta are not yet clearly defined, but a series of cellular studies have shown that co-expression of ACE2 and TMPRSS2 does not occur in the placenta at the same time, so it seems likely that SARS-CoV-2 through an alternative mechanism to enter placental tissues,[73,74] which requires further studies. In general, comprehensive information about the process of childbirth and transmission of the disease to the baby is shown in Table 2, which is a complete summary of this study.

## Conclusions

This review study is an overview of pregnancy and neonatal outcomes of mothers infected with SARS-CoV-2. There is no significant difference in the clinical characteristics of pregnant females and non-pregnant patients with COVID-19. Also, the results showed that the mode of delivery (vaginal or cesarean section) for females infected with SARS-CoV-2 does not increase or decrease the risk of contracting COVID-19 for babies. Although the possibility of vertical transmission in pregnant females with COVID-19 infection is rare, there have been positive reports, but the evidence is still unclear, and the route of transmission should be appropriately investigated. Maternal mortality rates were higher in pregnant females infected with COVID-19 than in females without the disease, but the exact cause is still unclear.

However, multicenter or even international prospective studies with precise methodology are needed to clarify the real risk of mother and child SARS-CoV-2 infection and identify optimal prevention and control strategies.

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### Conflicts of interest

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