

# Pregnancy outcomes among pregnant women infected with COVID-19 with and without underlying disease: A case-control study

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## ABSTRACT

Emerging infections have many effects on the health of pregnant mothers and their fetuses. Given the importance of coronavirus disease (COVID-19) during pregnancy, this study aims to evaluate the pregnancy and fetal outcomes in pregnant women with COVID-19 by using previous studies. To conduct this study, all studies related to the subject under discussion during the years 2000–2021 were checked out by systematic search in internationally available databases, including Web of Science, Science Direct, Scopus, PubMed, and Google Scholar. Finally, 21 closely related studies were selected to investigate the main objective. The results showed that common symptoms of COVID-19 in pregnant women included fever, cough, and muscle aches. The most common laboratory results included decreased blood lymphocytes and increased blood CRP. Consequences of pregnancy and childbirth in pregnant women included increased preterm delivery and increased cesarean section. Based on the results of the reviewed study, it can be concluded that newborns of mothers with COVID-19 were negative for COVID-19. However, the most common outcome for infants born to mothers with COVID-19 was low birth weight. Clinical signs, laboratory results, and radiographic criteria in pregnant women with COVID-19 are similar to those in non-infected adults. However, it is recommended that precautions be taken to prevent transmission of the virus, as well as preventive health instructions, particularly masking.

**Keywords:** COVID-19, fetal outcomes, giving birth, pregnancy outcomes

## Introduction

Coronavirus (CoV) is a virus containing triple ribonucleic acid (RNA) and is isolated from the family Coronaviridae and belongs to the order Nidovirales, which generally causes respiratory and gastrointestinal infections that may range from mild to more severe such as viral pneumonia disorders with systemic disorders. In the last two decades, the coronavirus

has been responsible for two major epidemics: severe acute respiratory syndrome (SARS) (SARC), which killed 8098 people with a mortality rate of approximately 10.5%, and Middle East Respiratory Syndrome (MERS), which killed 2519 people.<sup>[1]</sup> After these two major epidemics, Coronavirus 2019 (COVID-19) was first detected in December 2019 and spread to Wuhan, Hubei Province, China.<sup>[2]</sup> The virus was initially named nCoV-2019 and subsequently renamed SARS-COV-2, and eventually the associated disease was renamed COVID-19.<sup>[3]</sup>

In a pandemic of infectious diseases, pregnant women and their fetuses are considered high-risk populations.<sup>[2]</sup> Pregnant women are more susceptible to infectious diseases than the

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general population and are particularly vulnerable to low immune systems. In addition, their upper respiratory tract is swollen with high levels of estrogen and progesterone, and lung levels are limited. Therefore, in this way, pregnant women are prone to such diseases.<sup>[2,4-6]</sup>

Also, changes in physiological adaptation during pregnancy (e.g., increased diaphragm level, increased oxygen consumption, and edema of the mucous membranes of the respiratory tract) cause intolerance to hypoxia.<sup>[2,5,7]</sup> It should be noted that the potential risks of cytokine storm due to infection of pregnant women may be severe complications and even death.<sup>[5]</sup> These factors make pregnant women, their fetuses, and their newborns vulnerable to infectious diseases.<sup>[2]</sup> For example, the influenza pandemic of 1918 killed 2.6% of the population, but in pregnant women, the mortality rate was 37%. It was also reported that in the 2009 H1N1 flu epidemic, pregnant women were four times more likely to be hospitalized than other patients.<sup>[2]</sup> In addition, in the epidemic of infectious diseases, special attention should be paid to newborns as infants with infections may be asymptomatic and present with mild or severe symptoms. Body temperature in infected infants may rise, but temperature instability may also occur frequently in premature infants. The presence of tachypnea, apnea, and cough is very important in identifying the infection in adults, but these symptoms may not be a specialized sign of the disease in infants.<sup>[8]</sup> In addition, other manifestations such as malnutrition, lethargy, vomiting, diarrhea, and bloating are common in any malignant baby. Not all of the above findings can be linked exclusively to a specific infection in infancy.<sup>[9]</sup>

COVID-19 affects all age groups, and pregnant women may be more susceptible to the disease. It should be noted that COVID-19 may alter immune responses in both the mother and fetus and affect the well-being of mothers and infants.<sup>[5]</sup>

Pregnant women with SARC experienced worse results than non-pregnant women of the same age. Spontaneous abortion has been reported in women infected with SARC and MERC in the first trimester of pregnancy. Also, intrauterine growth restriction and preterm delivery have been reported in pregnancies in the second and third trimesters affected by SARC and MERC in the first trimester of pregnancy. Restriction of intrauterine growth and preterm delivery have also been observed in pregnancies affected by SARC and MERC in the second and third trimesters. In addition, intensive care for infants and endotracheal intubation, renal failure and maternal mortality have been reported in these patients.<sup>[3,6,10]</sup> However, no evidence of vertical transmission of SARC and MERC from mother to fetus has been reported.<sup>[3,11]</sup> Also, the studies by Yu *et al.* (2020)<sup>[4]</sup> and Schmid *et al.* (2020)<sup>[12]</sup> did not show any evidence of perinatal SARC and MERC infection in infants born to mothers who were infected during pregnancy. It is important to note that a number of pregnancies have had good results despite maternal infection with SARC or MERC.<sup>[6]</sup> Given the importance of this topic, the main purpose of this study was to investigate the possible effects of COVID-19 on pregnant women and their infants.

## Materials and Methods

The aim of this study was to investigate the possible effects of COVID-19 on pregnant women and their infants. For this purpose, systematic searches of internationally available databases including Web of Science, Science Direct, Scopus, PubMed, and Google Scholar were performed between 2020 and 2022. A systematic review by using the Mesh terms “Pregnancy outcomes,” “Women,” “Coronavirus disease,” “COVID-19,” “Newborn,” “Infant,” “Embryonic consequences,” “Fetal consequences,” “Mother,” “Outcome,” “Symptoms,” “Patients,” “Giving birth,” “Childbirth,” “Complications,” “Preterm delivery,” and other similar keywords was performed. For other databases, the same Mesh terms were used. To ensure the completeness of the search, the references of the found studies were evaluated (reference checking) to minimize the possibility of not entering the studies. Citation tracing was also reviewed. According to Figure 1, the search for literature review, especially articles, was done according to the PRISMA guidelines.<sup>[13]</sup> In addition, unofficial reports, articles in letter to editor format, and unpublished articles and content posted on Internet sites were removed from the list of downloaded files. Finally, the results of 21 published articles were investigated for the present review.

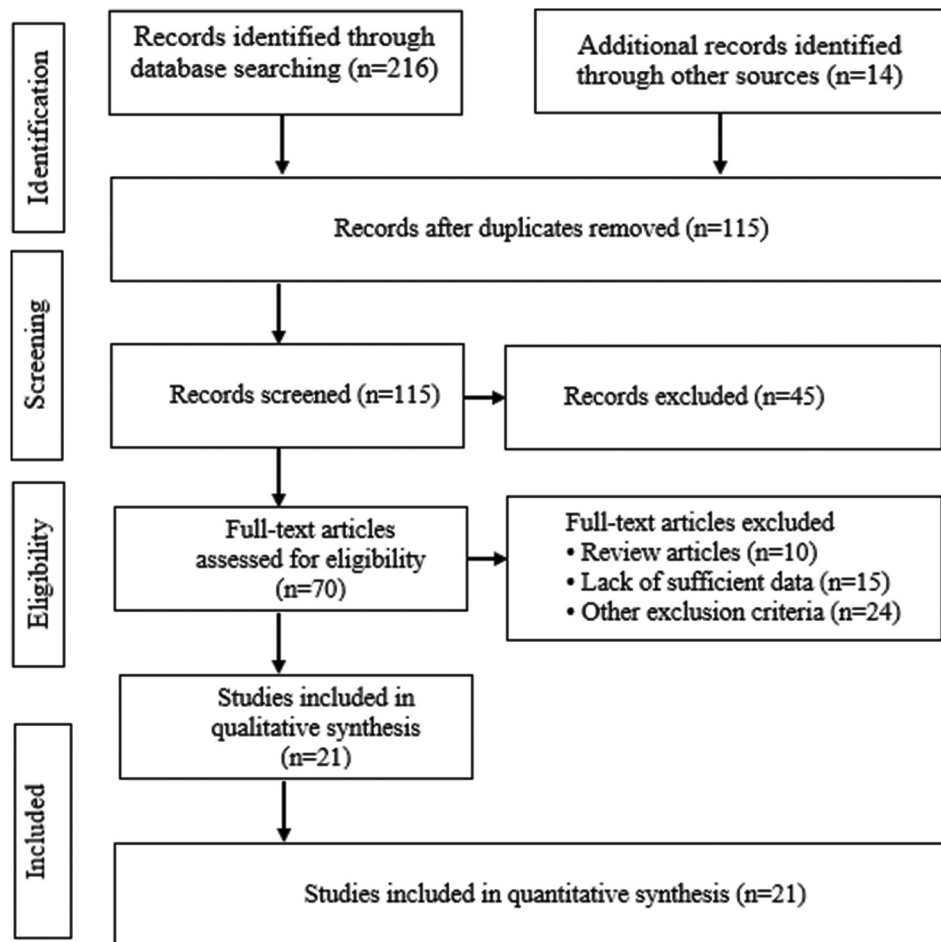
## Results

It is vital that life-saving interventions for infectious diseases be performed for pregnant women unless there is a compelling reason to eliminate them. Like all treatment decisions during pregnancy, it is important to carefully consider the benefits of interventions for both mother and fetus in terms of potential risks. Because monitoring systems have been developed for COVID-19 cases, it is important to gather and report information on pregnancy status as well as maternal and fetal outcomes, and some basic evidence to guide the treatment of pregnant women with COVID-19 should be presented. The clinical signs of the disease in pregnant mothers, radiographic criteria, pregnancy outcomes (including maternal and fetal outcomes), and vertical transmission of coronavirus from mother to fetus are presented in Table 1.

## Discussion

In various studies, no specific symptoms were observed for pregnant women with COVID-19 compared with non-pregnant adults. However, the COVID-19 pandemic has caused stress and anxiety for pregnant women around the world. Anxiety and stress in pregnancy are associated with side effects such as preeclampsia, depression, increased nausea and vomiting during pregnancy, premature birth, and low birth weight.<sup>[29]</sup>

Various studies have shown that viral infections and physiological changes in pregnant women with COVID-19 often cause complications, with preterm labor being the most common complication of pregnancy. However, it should be noted that the time and method of delivery should be chosen according to



**Figure 1:** Flow diagram of study identification according to PRISMA

clinical conditions or delivery factors as usual (not just during the COVID-19 pandemic). According to studies, COVID-19 was not detected in the patient's breast milk.<sup>[2,22,25]</sup> However, in some studies, breast milk was contraindicated for infants. Delayed umbilical cord closure and the presence of vernix caseosa on the infant's body also play a role in COVID-19 transmission. For the diagnosis of COVID-19 from IgM assay, it is not possible to make a definitive diagnosis because this diagnostic method can be prone to false-positive and false-negative results and is usually less reliable than molecular diagnostic tests based on nucleic acid diagnosis.<sup>[15]</sup> Regarding the uterine transmission of COVID-19 virus from an infected mother to the fetus, various studies have shown that although the RT-PCR test was positive in a number of newborns, given that the amniotic fluid viral nucleic acid test, breast milk, placenta, umbilical cord blood, and vaginal secretions of infected women are negative, vertical intrauterine transmission may not have occurred. There is also no evidence of vertical transmission of COVID-19 so far, and further study is needed. Even if the results of RT-PCR are negative for fetal COVID-19 infection, the mother's disease may cause secondary neonatal complications such as effects on brain development. For this reason, continuous awareness of the condition of the mother and fetus with their close management and supervision is essential.<sup>[30]</sup>

In pregnant women with suspected or definitive diagnosis of COVID-19, all care should be taken in the hospital until complete recovery.<sup>[31]</sup> Pregnant women with suspected/probable COVID-19 infection or individuals with asymptomatic confirmed infection, as well as individuals recovering from mild illness, should be monitored by ultrasound evaluation at 2–4 weeks of fetal growth and amniotic fluid volume. In addition, Doppler ultrasound is recommended.<sup>[32]</sup> A pregnant mother with COVID-19 should be admitted to an isolated room immediately and only medical care providers should be present. Continuous electronic monitoring of the fetal heart during labor is recommended. The gynecologist, anesthesiologist, pediatrician, and infant nurse should be present during the delivery of the mother with COVID-19 and should be placed at the patient's bedside if necessary. The mother's oxygen saturation should be controlled and should be more than 94%.<sup>[31]</sup> The mode of delivery depends on the gestational age and the condition of the fetus and mother,<sup>[32]</sup> and based on the results of some studies, there is currently no preference for the type of delivery (cesarean or normal) in mothers with COVID-19. There is also no clear evidence of optimal timing of delivery, safety of vaginal delivery, or whether cesarean section prevents vertical transmission at delivery. Therefore, the method of delivery and the time of delivery should be decided individually based on the symptoms of gynecology and the condition of the mother and

**Table 1: The summary of results from previous similar studies on pregnancy and fetal outcomes associated in patients with COVID-19**

Authors (Study year)	Studied group	Studied cases	Key results
Díaz <i>et al.</i> (2020) <sup>[14]</sup>	Evaluation of a pregnant woman with definitively -COVID-19 Evaluation of the infant of this infected mother	Evaluation of the infant with COVID-19.	The mother underwent immediate cesarean section due to severe preeclampsia.
Chen <i>et al.</i> (2020) <sup>[2]</sup>	9 pregnant women with definitive COVID-19 infection in the third trimester of pregnancy. 9 infants of these infected mothers.	Cord blood sample, amniotic fluid, breast milk sample, and neonatal sputum sample after delivery.	All infants with good Apgar scores were born by cesarean section. Cord blood samples, amniotic fluid, breast milk, and neonatal sputum samples were negative for the COVID-19 virus in this study.
Yu <i>et al.</i> (2020) <sup>[4]</sup>	Evaluation of 11 definitively pregnant women with COVID-19 Evaluation of 7 infants of these infected mothers	Mothers and infants.	10 mothers gave birth by cesarean section, and 1 mother gave birth by natural method with complete health. The most common symptom in 86% of them was fever, while the remaining 14% had symptoms such as cough, shortness of breath, and diarrhea.
Rasmussen <i>et al.</i> (2020) <sup>[11]</sup>	18 pregnant women with definitive COVID-19 infection in the third trimester of pregnancy. 18 infants of these infected mothers.	Mothers and infants.	16 mothers gave birth by cesarean section and 2 mothers gave birth by natural method with complete health. Neonates have been reported to be negative for COVID-19.
Chen <i>et al.</i> (2020) <sup>[15]</sup>	Evaluation of placenta in 3 mothers with definitive COVID-19. Evaluation of 3 infants born from these infected mothers.	Evaluation of neonatal throat sputum specimens after giving birth. Evaluation of placental tissue for COVID-19 nucleic acid.	Neonatal sputum samples and placenta samples were negatively reported in this study for COVID-19 virus.
Wang <i>et al.</i> (2020) <sup>[16]</sup>	Evaluation of a 30-week-old pregnant woman with definitive COVID -19 Evaluation the infant of this infected mother.	Evaluation of the infant for COVID-19.	The mother gave birth in perfect health, and the baby was reported to be negative for COVID-19.
Zhu <i>et al.</i> (2020) <sup>[17]</sup>	Evaluation of 9 definitively infected pregnant women. Evaluation of COVID-19 in infants (a case of twins) of these infected mothers.	Samples of neonatal throat sputum	7 mothers gave birth by cesarean section, and 2 mothers gave birth naturally by complete health. 10 infants were reported to be COVID-19 negative.
Mullins <i>et al.</i> (2020) <sup>[18]</sup>	19 pregnant women with definitive COVID-19 infection in the third trimester of pregnancy. 20 infants of these infected mothers.	Mothers and infants	7 mothers gave birth by cesarean section, and 2 mothers gave birth by natural method; 8 cases of preterm delivery, one case of infant death; 15 infants were tested and COVID-19 was negatively reported.
Mullins <i>et al.</i> (2020) <sup>[18]</sup>	In a review report, 32 definitively infected pregnant women with COVID-19 examined 30 infants of these infected mothers.	Mothers and infants	Cesarean delivery was performed in 27 cases and normal delivery in 2 cases and 15 people (47%) had preterm delivery. One stillbirth and one neonatal death were observed. In 25 infants, no cases of vertical transmission were observed.
Zhang <i>et al.</i> (2020) <sup>[19]</sup>	Comparison of 16 pregnant women with COVID-19 with 45 healthy pregnant women	Mothers and infants	There was no significant difference between pregnant women with COVID-19 and healthy pregnant women in terms of the type of delivery, gestational age, birth weight, preterm delivery, meconium excretion, fetal disturbance and asphyxia, but in pregnant women with COVID-19, preventive use of Eutrotonic drugs have been reported to reduce bleeding during cesarean section. In addition, all infants of mothers with COVID-19 were negative for COVID-19.
Li <i>et al.</i> (2020) <sup>[20]</sup>	Evaluation of a 35-week pregnant woman with definitively -COVID-19 Evaluation of the infant of this infected mother	Infants	The infant was reported to be COVID-19 negative.
Liu <i>et al.</i> (2020) <sup>[21]</sup>	Evaluation of 15 definitively pregnant women with COVID-19 Evaluation of the infants of this infected mothers	Mothers and infants	Eleven patients had a successful delivery (10 cesarean deliveries and one normal delivery) and at the end of the period of the study, four patients were still pregnant (three in the second trimester and another in the third trimester). No cases of neonatal asphyxia, neonatal death, stillbirth, or miscarriage were reported.

Contd...

Table 1: Contd...

Authors (Study year)	Studied group	Studied cases	Key results
Fan <i>et al.</i> (2020) <sup>[22]</sup>	Evaluation of 2 definitively pregnant women with COVID-19 (In the third trimester of pregnancy) Evaluation of the infants of these infected mothers	Complete evaluation of umbilical cord blood samples, amniotic fluid, placental tissue, maternal vagina samples, breast milk samples, and postpartum throat sputum samples.	Both mothers had a successful cesarean section and the baby was separated from the mother immediately after delivery. Cord blood samples, amniotic fluid, placental tissue, maternal vagina samples, breast milk samples, and neonatal throat sputum samples were reported to be COVID-19 negative.
Schwartz <i>et al.</i> (2020) <sup>[3]</sup>	Evaluation of 38 definitively pregnant women with COVID-19 Evaluation of the infants of these infected mothers	Complete evaluation of mothers and infants as well as postpartum placentas.	No deaths have been reported in infected mothers. No intrauterine transmission or infant infection were reported. Tested placenta samples were reported to be COVID-19 negative.
Qiao <i>et al.</i> (2020) <sup>[10]</sup>	A qualitative study about the effects of COVID-19 on pregnant women and infants		Pregnant women are more prone to respiratory illnesses and severe pneumonia, which may make them more susceptible to COVID-19 infection than the general population, especially if they have chronic illnesses or maternal complications. Therefore, pregnant women and newborns should be considered in strategies focused on the prevention and management of COVID-19 infection of high-risk populations.
Wen <i>et al.</i> (2020) <sup>[23]</sup>	Evaluation of a 30-week pregnant woman with definitively -COVID-19	Mothers	The mother had mild diarrhea (2-3 times) for one day.
Zeng <i>et al.</i> (2020) <sup>[24]</sup>	All infants born to mothers with COVID-19 from Children's Hospital Wuhan in Wuhan	Infants	The clinical signs of 33 infants at risk for COVID-19 were mild and the results were favorable. But three infants with the symptomatic COVID-19 were severely affected, with complications including prematurity, asphyxia, and sepsis.
Dong <i>et al.</i> (2020) <sup>[25]</sup>	Evaluation of a pregnant woman with definitively -COVID-19 Evaluation of the infant of this infected mother	Mother and infant	The cytokinin test result was abnormal at 2 hours after birth, but PCR-RT was repeatedly negative (for nasopharyngeal swabs). In addition, vaginal discharge and breast milk were negative for COVID-19.
Chen <i>et al.</i> (2020) <sup>[26]</sup>	Evaluation of 9 pregnant women with definitively -COVID-19	Mothers and infants	All 9 cases were delivered by cesarean section. Pregnancy hypertension, preeclampsia, PROM, and fetal distress were observed in 1, 1, 2, and 2 cases, respectively. Cough, shortness of breath, sore throat, diarrhea, chest pain, fever at admission and fever after childbirth were the most important symptoms. All newborns were negative for COVID-19. Fetal outcomes were including premature infancy (4 cases), SGA (1 case), and LBW (1 case).
Li <i>et al.</i> (2020) <sup>[27]</sup>	Evaluation of 3 pregnant women with definitively -COVID-19 Evaluation of the infants of these infected mothers	Mothers and infants	Hypothyroidism and gestational diabetes were the most important maternal outcomes. Premature delivery, intrauterine fetal distress, and LBS were among the most obvious fetal outcomes.
Khan <i>et al.</i> (2020) <sup>[28]</sup>	Evaluation of 3 pregnant women with definitively -COVID-19 Evaluation of the infants of these infected mothers	Mothers and infants	All three gave birth naturally (vaginally). Premature birth, fever, cough, and chest tightness were the most important maternal outcomes. The prematurity of an infant was one of the most obvious symptoms of fetal outcome.

fetus.<sup>[33]</sup> If the mother has a preterm delivery, the mother should be allowed to have a vaginal delivery.<sup>[32]</sup> No unnecessary intervention in the delivery process should be done unless the mother is in urgent need of respiratory support. At present, the results of studies show that no positive cases of vaginal discharge infection with the COVID-19 virus have been observed.<sup>[31]</sup> Shortening the second stage with vaginal delivery can be considered because active pressure with a mask can be difficult for a woman.

In septic shock, acute organ failure, or fetal distress, a cesarean section should be performed immediately. "Water delivery" should

be avoided to protect the medical team.<sup>[32]</sup> The use of epidural analgesia has been reported in safe studies at the request of the mother. If Antonox is used, the respiratory system must have a filter. In the case of cesarean section, general anesthesia should be avoided as much as possible and epidural or spinal anesthesia should be used. Precautions should be taken with regard to the use of prenatal steroids (dexamethasone or betamethasone) for fetal lung maturation in patients with critical condition COVID-19 as this can potentially worsen the clinical condition. A woman with COVID-19 who has a preterm delivery should not use Tawakulz to delay delivery (to prescribe prenatal steroids).<sup>[31]</sup>



In the management of infants in suspected, probable, and confirmed cases of maternal COVID-19 infection, the umbilical cord should be closed immediately. The infant should be resuscitated for evaluation by a pediatric team. There is insufficient evidence as to whether delayed umbilical cord closure increases the infant's risk of COVID-19 through direct contact.<sup>[32]</sup> There is currently insufficient evidence on the safety of breastfeeding and the need for mother/infant separation. If the mother's condition is severe, it is best to separate the baby from the mother and hand expression of breast milk to maintain milk production. Precautions should be taken to clean breast pumps. If the patient is asymptomatic or has a mild illness, breastfeeding by the mother should be considered.

Because the main concern is that the COVID-19 virus may be transmitted through respiratory droplets instead of milk droplets, breastfeeding mothers should wash their hands and use a mask before contacting the baby. If the patient's mother is in a special room, the baby's bed should be kept at least 2 m away.<sup>[32]</sup>

## Conclusion

Based on the results of the reviewed study, it can be concluded that clinical signs, laboratory results, and radiographic criteria in pregnant women with COVID-19 are similar to those in non-infected adults. Common manifestations of COVID-19 in pregnant women with the disease included fever, cough, and muscle aches. The most common laboratory results included decreased blood lymphocytes and increased blood CRP. Complications of pregnancy and childbirth in pregnant women included increased preterm delivery and increased cesarean section. Given that most of the studies are in China, there is a need for more studies in this area in other countries. In addition, it is suggested that mothers with COVID-19 should take precautions to prevent transmission of the virus and preventive health guidelines, particularly masking, should also be considered.

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## Conflicts of interest

There are no conflicts of interest.

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