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IMPACT OF COVID-19 ON NEONATAL OUTCOMES: A SYSTEMATIC REVIEW

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Abstract

The COVID-19 infection is a pandemic that is still continuing strong and is marked by significant morbidity and fatality rates. In order to make effective use of the resources that are available, it is imperative that clinical and biochemical predictors of the severity and mortality associated with COVID-19 infection be identified as quickly as possible. Although it is impossible to be certain, there is a possibility that the SARS-CoV-2 virus can be passed on from mother to child. This transmission, however, has not been confirmed. This relationship discusses the potential interpretation of these results in terms of the effects of SARS-CoV-2 on the placenta and the pathophysiology of pregnant women. It also shows the spectrum of pathological findings from pregnant women with COVID-19 based on the infection status of their infants. Significant variation may be seen in the spectrum of pathological abnormalities between the placentas of pregnant women infected with COVID-19 and those of newborns who were not infected. The severity of maternal sickness or foetal impairment does not entirely explain the high frequency of preterm births and caesarean deliveries as well as the low incidence of breastfeeding that was found in this study. The maternal and perinatal results of COVID-19 infection during pregnancy are not marked by a severe clinical course and are, in fact, rather favorable. At this time, there is no convincing evidence that COVID-19 can be passed from person to person by the vertical route.

Keyword: *COVID-19, Neonatal, Outcomes, Placenta, Transmitted*

INTRODUCTION

The World Health Organization (WHO) has classified the coronavirus outbreak that is occurring in 2019–20 as a Public Health Emergency of International Concern (PHEIC). As of the 7th of March in the year 2020, there was evidence of local disease transmission discovered in several countries throughout all six WHO regions.[1] The COVID-19 infection is a pandemic that is still continuing strong and is marked by significant morbidity and fatality rates. It is imperative that clinical and biological predictors of severity and mortality associated with COVID-19 infection be identified as quickly as possible in order to make efficient use of the resources that are available.[2]

The epidemic of COVID-19 is rapidly expanding in both the number of cases and deaths as well as the number of countries affected. During the outbreak of severe acute respiratory syndrome (SARS) in 2002-2003, the number of deaths caused by the virus that causes COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), exceeded the number of deaths caused by the severe acute respiratory syndrome coronavirus (SARS-CoV). There is a paucity of information currently accessible on pregnant women who have COVID-19.[3]

COVID-19 infection is an ongoing pandemic characterized by high morbidity and mortality. There is an urgent need to identify clinical and biological predictors of severity and mortality associated with COVID-19 infection for the judicious use of limited resources.[2] There have been more than 16 million cases of COVID-19 and more than 500,000 cases of death related to COVID-19 reported worldwide. The rate of new infections appears to be exceeding the scale of public health preparedness and response, especially in countries with limited economic capabilities.[4]

A literature published in China recorded the outcome of 55 pregnant women and 46 neonates without any evidence of vertical transmission where all the baby swab results were negative for Covid-19. Meanwhile, the literature published in Italy reported that there were 19 neonates who were confirmed positive for Covid-19 out of a total of 685 neonates born to mothers who confirmed positive cases. The impact of COVID-19 on neonatal outcomes is investigated in this research using a neonatal population to conduct the study.

METHODS

Protocol

The approach of this investigation was based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 criteria. These factors influenced the legislation that were passed.

Criteria for Eligibility

This review of the literature aims to demonstrate the impact of COVID-19 on neonatal outcomes by assessing or analyzing previous research on the subject. This is a significant concern raised in the current research. Researchers participate in research that meets the following criteria: 1) Articles must be written in English and highlight or focus on the impact of COVID-19 on neonatal outcomes to be considered for publication. 2) This evaluation took into account articles published after 2020, but before the period of this systematic review. Editorials, submissions without a DOI, review articles that have already been published, or entries that are very similar to those that have already been published in a journal, for example, will not be considered for publication.

Search Strategy

The search for studies to be included in the systematic review was carried out from January, 21th 2023 using the PubMed and SagePub databases by inputting the words: "COVID-19" and "neonatal outcomes". Where *("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonatal"[All Fields] OR "neonate"[All Fields] OR "neonates"[All Fields] OR "neonatality"[All Fields] OR "neonatals"[All Fields] OR "neonate s"[All Fields]) AND ("outcome"[All Fields] OR "outcomes"[All Fields])* is used as search keywords.

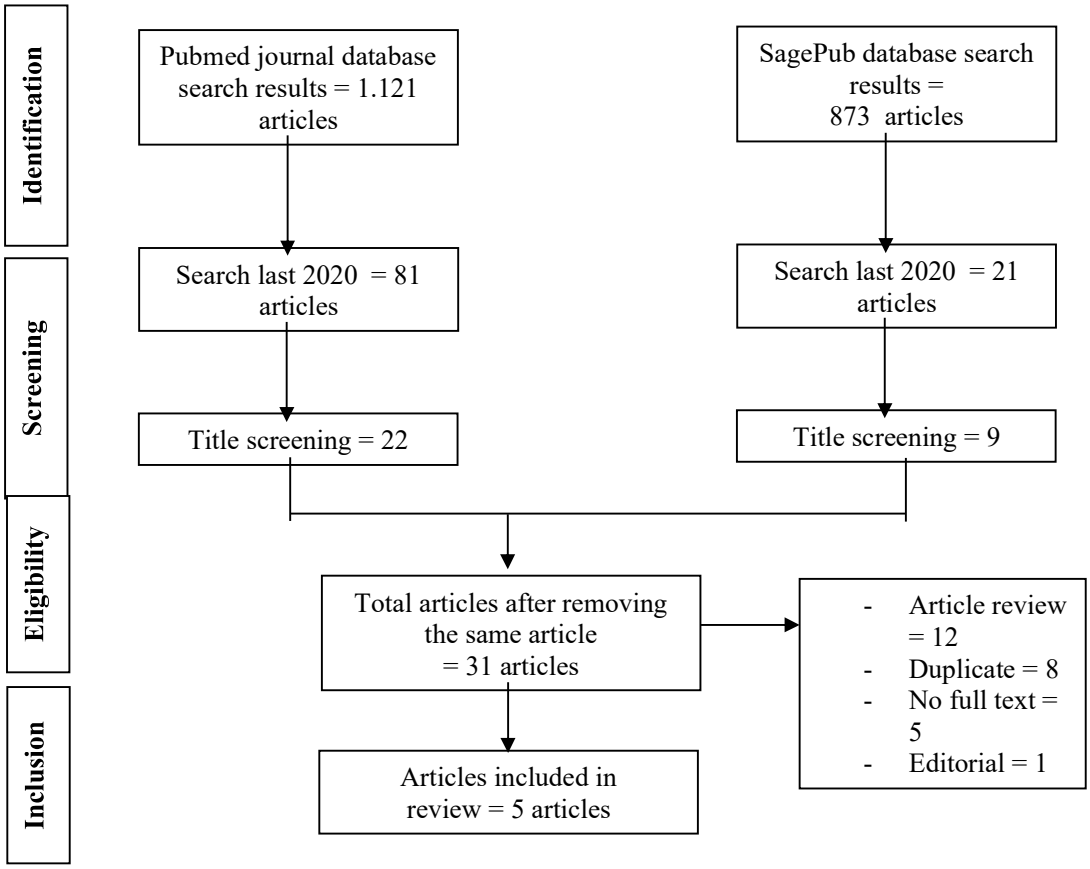

Figure 1. Article search flowchart

Data retrieval

The author modified the inclusion and exclusion criteria after conducting a literature review that included a review of the titles and abstracts of previous research. The revised criteria are included in the supplementary materials for the study. This clarified the scope of the problem and highlighted the aspects that need to be investigated further. After conducting research on additional studies with a similar format, the author came to this conclusion. During the systematic review process, only studies that met all of the inclusion criteria were considered.

This ensured that only relevant information was discovered. We did not consider any research proposals that did not meet all of our requirements. This ensured that a thorough examination would take place. This effort produced information relevant to the studies, such as their titles, authors, publication dates, locations, research investigation types, and parameters. These are the item categories that are available. These are abilities that can be honed. Depending on the information source, these data can be presented in a variety of formats.

Quality Assessment and Data Synthesis

Before deciding which articles to investigate, each author conducted an independent investigation of a piece of research mentioned in the titles and abstracts of the papers. The full texts of publications that meet the systematic review's inclusion criteria will then be reviewed to determine which papers will be included in the review. This is done to determine which articles will be included in the review. To facilitate the selection of articles for the review. Which studies are of sufficient quality to be included in the review?

RESULT

Dehan, et al (2020) study with 11 patients had a healthy delivery during the course of the study (10 patients had successful cesarean deliveries and one patient had a successful vaginal delivery), and four patients were still pregnant at the conclusion of the study (three patients were in the second trimester and one patient was in the third trimester). There were no cases of stillbirth, abortion, infant asphyxia, or death reported during this time period. The ground-glass opacity was the most common finding in the early stages on chest CT (GGO). The advancement of the disease was accompanied by a crazy paving pattern on CT, as well as consolidations.[5]

At the conclusion of the trial period, all of the patients exhibited absorptive alterations caused by the anomalies. In pregnant women who were diagnosed with COVID-19 pneumonia, the first symptoms that manifested themselves were a fever (13/15 patients) and a cough (9/15 patients). Lymphocytopenia was the aberrant laboratory finding that occurred

in the majority of patients (12/15). CT scans that were performed both before and after delivery revealed no signs of an escalation in the patient's pneumonia after birth. The antiviral medications were not administered to the four patients who were still pregnant at the end of the research period but had made a full recovery despite not receiving treatment.[5]

Other study conducted with 16 pregnant women with confirmed COVID-19 and 18 suspected cases who were admitted to labor in the third trimester. Two had vaginal births, while the others had cesarean sections. On admission, only a few individuals showed respiratory symptoms, but the majority had classic chest CT pictures with COVID-19 pneumonia. COVID-19 pneumonia patients showed reduced numbers of WBC, neutrophils, CRP, and ALT on admission compared to controls.[6]

WBC, neutrophils, eosinophils, and CRP levels were observed to be elevated in pneumonia patients' postpartum blood tests. Preterm birth due to maternal difficulties occurred in three (18.8%) and three (16.7%) of the mothers with confirmed or suspected COVID-19 pneumonia, respectively, which was substantially greater than the control group. During their hospital stay, none of them had respiratory failure. COVID-19 infection was not discovered in the babies, and none of them suffered from serious neonatal problems.[6]

The tiny sample size of this case report study hampered its findings. A bigger sample size investigation investigating the likelihood of COVID-19 vertical transmission in the second and third trimesters of pregnancy and possible unfavorable pregnancy outcomes should be encouraged. As of March 1, 2020, none of the three women in this study has died from COVID-19 infection. There was no vertical transmission of COVID-19 in the third trimester of pregnancy among infants delivered vaginally. Furthermore, we found no indication of COVID-19 transfer from mother to fetus via vaginal delivery.[7]

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Period	Measurement	Result
Dehan, 2020[5]	China	Cross sectional study	15 consecutive pregnant women with COVID-19 pneumonia	January 20, 2020, to February 10, 2020	Semiquantitative CT scoring system was used to estimate pulmonary involvement and the time course of changes on chest CT	Eleven patients delivered (10 cesareans and one vaginal) during the research, and four were still pregnant (three in the second trimester and one in the third) at the end. No newborn asphyxia, death, stillbirth, or abortion occurred. Ground-glass opacity was the most common early chest CT finding (GGO). CT showed erratic paving and consolidations as illness progressed. All patients had absorptive abnormalities at study's end. Fever (13/15) and cough (9/15) were the most common symptoms of COVID-19 pneumonia in pregnant women. 12/15 patients had lymphocytopenia. Post-delivery CT scans indicated no pneumonia worsening. Four pregnant patients who did not receive antiviral medications recovered well.
Li, 2020[6]	China	Case-control study	16 pregnant women with confirmed COVID-19 and 18 suspected cases who were admitted to labor in the third trimester.	January 24 to February 29, 2020	Semiquantitative CT scoring system was used to estimate pulmonary involvement and the time course of changes on chest CT	Two had vaginal births, while the others had cesarean sections. On admission, only a few individuals showed respiratory symptoms (fever and cough), but the majority had classic chest CT pictures with COVID-19 pneumonia. COVID-19 pneumonia patients showed reduced numbers of white blood cells (WBC), neutrophils, C-reactive protein (CRP), and alanine aminotransferase (ALT) on admission compared to controls. WBC, neutrophils, eosinophils, and CRP levels were observed to be elevated in pneumonia patients' postpartum blood tests. Preterm birth due to maternal difficulties occurred in three (18.8%) and three (16.7%) of the mothers with confirmed or suspected COVID-19 pneumonia, respectively, which was substantially greater than the control group.
Khan, 2020[7]	China	Case series	3 pregnant women infected with COVID-19	January 28 and March 1, 2020	qRT-PCR on specimens from the respiratory tract (nasal and pharyngeal swabs) and blood specimens	The tiny sample size of this case report study hampered its findings. A bigger sample size investigation investigating the likelihood of COVID-19 vertical transmission in the second and third trimesters of pregnancy and possible unfavorable pregnancy outcomes should be encouraged. As of March 1, 2020, none of the three women in this study has died from COVID-19 infection. There was no vertical transmission of COVID-19 in the third trimester of pregnancy among infants delivered vaginally. Furthermore, we found no indication of COVID-19 transfer from mother to fetus via vaginal delivery.
Cao, 2020[8]	China	Retrospective study	10 pregnant women confirmed with COVID-19	January 23 to February 23, 2020	qRT-PCR on specimens from the respiratory tract (nasal and pharyngeal swabs) and CT scan	The sample size for this case report study was modest. A bigger sample size investigation should be encouraged to evaluate the likelihood of COVID-19 vertical transmission in the second and third trimesters of pregnancy and possible poor pregnancy outcomes. In summary, as of March 1, 2020, none of the three women in this study had died from COVID-19 infection. There was no vertical transmission of COVID-19 in the third trimester of pregnancy among vaginally delivered newborns. Furthermore, we found no

						indication of maternal-to-neonatal intrapartum transmission of COVID-19 via vaginal birth.
Ferrazi, 2020[9]	Italy	Retrospective study	42 women with COVID-19 delivered	1 to 20 March 2020	Clinical records	An elective caesarean section was performed in 18/42 (42.9%, 95% CI 27.7–59.0) cases: in eight cases the indication was unrelated to COVID-19 infection. Pneumonia was diagnosed in 19/42 (45.2%, 95% CI 29.8–61.3) cases: of these, 7/19 (36.8%, 95% CI 16.3–61.6) required oxygen support and 4/19 (21.1%, 95% CI 6.1–45.6) were admitted to a critical care unit. Two women with COVID-19 breastfed without a mask because infection was diagnosed in the postpartum period: their newborns tested positive for SARS-Cov-2 infection. In one case, a newborn had a positive test after a vaginal operative delivery.
Chen, 2020[10]	China	Retrospective study	All nine patients had a caesarean section in their third trimester	Jan 20 to Jan 31, 2020	Clinical records, laboratory results, and chest CT scans	Seven patients had a fever. Other symptoms noticed included cough (4/6), myalgia (3), sore throat (2), and malaise (2). In two cases, fetal discomfort was tracked. Five of the nine patients showed lymphopenia. Three patients had elevated aminotransferase levels. As of February 4, 2020, no patients had developed severe COVID-19 pneumonia or died. There were nine livebirths recorded. There was no evidence of neonatal asphyxia in newborn newborns. All nine livebirths had an Apgar score of 8-9 at 1 minute and a 5-minute Apgar score of 9-10 at 5 minutes. Six patients' amniotic fluid, cord blood, neonatal throat swab, and breastfeeding samples were screened for SARS-CoV-2, and all proved negative.
Zhu, 2020[11]	China	Prospective study	of 10 neonates (including 2 twins) born to 9 mothers with confirmed 2019-nCoV infection	January 20 to February 5, 2020	Clinical features	In most cases, fever and a cough were the first symptoms experienced, and 1 patient also had diarrhea. Of the newborns born to these mothers, 8 were male and 2 were female; 4 were full-term infants and 6 were born premature; 2 were small-for-gestational-age (SGA) infants and 1 was a large-for-gestational-age (LGA) infant; there were 8 singletons and 2 twins. Of the neonates, 6 had a Pediatric Critical Illness Score (PCIS) score of less than 90. Clinically, the first symptom in the neonates was shortness of breath (n=6), but other initial symptoms such as fever (n=2), thrombocytopenia accompanied by abnormal liver function (n=2), rapid heart rate (n=1), vomiting (n=1), and pneumothorax (n=1) were observed. Up to now, 5 neonates have been cured and discharged, 1 has died, and 4 neonates remain in hospital in a stable condition. Pharyngeal swab specimens were collected from 9 of the 10 neonates 1 to 9 days after birth for nucleic acid amplification tests for 2019-nCoV, all of which showed negative results.

Other retrospective study conducted with sample size for this case report study was modest. A bigger sample size investigation should be encouraged to evaluate the likelihood of COVID-19 vertical transmission in the second and third trimesters of pregnancy and possible poor pregnancy outcomes. In summary, as of March 1, 2020, none of the three women in this study had died from COVID-19 infection. There was no vertical transmission of COVID-19 in the third trimester of pregnancy among vaginally delivered newborns. Furthermore, we found no indication of maternal-to-neonatal intrapartum transmission of COVID-19 via vaginal birth.[8]

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Zhu, et al (2020)[11] show the newborns born to these mothers, 8 were male and 2 were female; 4 were full-term infants and 6 were born premature; 2 were SGA infants and 1 was a LGA infant; there were 8 singletons and 2 twins. Of the neonates, 6 had a PCIS score of <90. Clinically, first symptom in neonates was shortness of breath (n=6), but other initial symptoms such as fever (n=2), thrombocytopenia accompanied by abnormal liver function (n=2), rapid heart rate (n=1), vomiting (n=1), and pneumothorax (n=1) were observed. Up to now, 5 neonates have been cured and discharged, 1 has

died, and 4 neonates remain in hospital in a stable condition. Pharyngeal swab specimens were collected from 9 of the 10 neonates 1 to 9 days after birth for nucleic acid amplification tests for 2019-nCoV, all of which showed negative results.

DISCUSSION

Corona Virus Disease 2019 (COVID-19) (formerly also known as the Wuhan Novel Coronavirus) is an infectious respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is closely related to the SARS virus. This virus first appeared in Wuhan, China and is now the cause of the 2019-20 coronavirus outbreak. The World Health Organization announced on 11 February 2020 that "COVID-19" will be the official name of this disease.[12] Overall infant and neonatal mortality and morbidity rates due to infection are not well established; while case fatality rates have changed over time in the current outbreak the proportion of infections that develop into a diagnosed disease is unclear.[13]

Pregnant women are especially vulnerable to respiratory infections and severe pneumonia because they are immunocompromised, and physiologic changes during pregnancy (e.g., diaphragm elevation, increased oxygen intake, and edema of respiratory tract mucosa) make them hypoxic intolerant. Pregnant women were four times more likely than the general population to be hospitalized to the hospital with 2009 swine-origin influenza A (H1N1). Furthermore, according to a prior report, around 50% of pregnant women with SARS were admitted to the ICU, approximately 33% required mechanical breathing, and the mortality rate for pregnant women with SARS was as high as 25%.[10,14]

The majority of those patients had fever, dry cough, dyspnea, and bilateral ground-glass opacities on a chest CT scan, and individuals with severe sickness develop acute respiratory distress syndrome and require intensive care unit admission. Nonetheless, COVID-19 patients exhibited little gastrointestinal symptoms, whereas approximately 20-25% of MERS-CoV or SARS-CoV patients had diarrhea. Study with 17 COVID-19 parturients displayed non-classical clinical features. There were only two incidences of chest pain and one case of dyspnea. Despite this, none of the patients were hypoxemic or required supplemental oxygen prior to the operation. Nine of the parturients did not exhibit conventional symptoms such as fever and cough; instead, the chest CT scan revealed abnormalities. These nine patients either had minor or no symptoms.[15–17]

According to the findings of Chen H et al. (2020), all nine pregnant women delivered their babies via cesarean section (CD). The researchers noted that the criteria for CD included severe pre-eclampsia, a history of CD, and fetal distress. During the course of our research, two of our patients had successful vaginal deliveries, two of our patients underwent intrapartum caesarean sections due to fetal distress, and the remaining six pregnant women underwent selected caesarean sections directly due to a history of caesarean section, pre-eclampsia, placenta abruption, or twin pregnancy. Although infection with COVID-19 is not one of the reasons for CD, given the unknowns associated with a new disease, we may be more likely to choose for CD given the circumstances.[10]

A report once examined a neonate who was positive for COVID-19, but the source of the infection was not yet known. Transmission of the causative agent, SARS-CoV-2 from mother to baby has been suspected although it is difficult to be certain. This relationship shows the spectrum of pathological findings from pregnant women with COVID-19 based on the infection status of their infants and discusses the potential interpretation of these results in terms of the effects of SARS-CoV-2 on the placenta and the pathophysiology of pregnant women. The placentas of pregnant women with COVID-19 and uninfected neonates show significant variability in the spectrum of pathological findings.[18]

In contrast, the placenta of an infected maternal-neonatal is characterized by the presence of inflammatory mononuclear cells in the intervillous space. This placenta showed prominent positivity of syncytiotrophoblast by SARS-CoV-2, meeting published criteria for transplacental viral transmission as confirmed in fetal cells through identification of viral antigen by immunohistochemistry or viral nucleic acid using RNA in situ hybridization. Trophoblastic necrosis appears to be a risk factor for placental infection with SARS-CoV-2 as well as for maternal-fetal viral transmission, and suggests a potential mechanism by which the coronavirus can penetrate the mother-fetal interface.[18]

During a SARS-CoV-2 pandemic, there are special dietary concerns that need to be made for newborns. Breast feeding from sick moms is still a contentious issue; although some institutions continue to advocate for it with the understanding that necessary safety measures must be taken, other institutions continue to advise using milk formula instead. Chen et al.[6] found no evidence of SARS-CoV-2 in breast milk samples taken from six moms who were infected with SARS; nevertheless, more research is required to rule out the possibility that this was a mode of transmission.[19–21]

The prognosis was favorable for newborns who were infected with SARS-CoV-2. After a median hospital stay of 10 days, all of the neonates were released from the hospital alive. Even while the median length of hospitalization was the same for neonates, children, and adults, the impact of the condition was significantly different in neonates and children as opposed to adults, who had a poorer prognosis. Several hypotheses have been proposed as potential explanations for this observation. These hypotheses include a lower expression of ACE2, which is the receptor that SARS-CoV-2 uses for host entry; a less proinflammatory cytokine response; a stronger innate immune response; and a higher proportion of total lymphocytes and absolute numbers of T and B cells.[22,23]

It is important to highlight that recent research has pointed to certain disparities in prognosis within the paediatric population. According to this research, there is a correlation between being younger than one month and a higher chance of admission to an intensive care unit. In addition, children may need less assistance from critical care providers than adults do, but it is expected that each kid would occupy the intensive care bed for an extended period of time, which has important repercussions for the planning of services.[22,23]

CONCLUSION

This article reveals a high risk of preterm births and caesarean deliveries, as well as a poor rate of breastfeeding, which cannot be explained entirely by the severity of maternal illness or foetal impairment. Indeed, the maternal and perinatal outcomes of COVID-19 throughout pregnancy are typically favorable, with no signs of a severe clinical course. There is presently no convincing evidence of COVID-19 vertical transmission.

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