

SYSTEMATIC REVIEW

Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies

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Abstract

Introduction: The pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has exposed vulnerable populations to an unprecedented global health crisis. The knowledge gained from previous human coronavirus outbreaks suggests that pregnant women and their fetuses are particularly susceptible to poor outcomes. The objective of this study was to summarize the clinical manifestations and maternal and perinatal outcomes of COVID-19 during pregnancy.

Material and methods: We searched databases for all case reports and series from 12 February to 4 April 2020. Multiple terms and combinations were used including COVID-19, pregnancy, maternal mortality, maternal morbidity, complications, clinical manifestations, neonatal morbidity, intrauterine fetal death, neonatal mortality and SARS-CoV-2. Eligibility criteria included peer-reviewed publications written in English or Chinese and quantitative real-time polymerase chain reaction (PCR) or dual fluorescence PCR-confirmed SARS-CoV-2 infection. Unpublished reports, unspecified date and location of the study or suspicion of duplicate reporting, cases with suspected COVID-19 that were not confirmed by a laboratory test, and unreported maternal or perinatal outcomes were excluded. Data on clinical manifestations, maternal and perinatal outcomes including vertical transmission were extracted and analyzed.

Results: Eighteen articles reporting data from 108 pregnancies between 8 December 2019 and 1 April 2020 were included in the current study. Most reports described women presenting in the third trimester with fever (68%) and coughing (34%). Lymphocytopenia (59%) with elevated C-reactive protein (70%) was observed and 91% of the women were delivered by cesarean section. Three maternal intensive care unit admissions were noted but no maternal deaths. One neonatal death and one intrauterine death were also reported.

Conclusions: Although the majority of mothers were discharged without any major complications, severe maternal morbidity as a result of COVID-19 and perinatal deaths were reported. Vertical transmission of the COVID-19 could not be ruled out. Careful monitoring of pregnancies with COVID-19 and measures to prevent neonatal infection are warranted.

Abbreviations: BMI, body mass index; ICU, intensive care unit; qRT-PCR, quantitative real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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KEYWORDS

coronavirus, COVID-19, fever, maternal morbidity, maternal mortality, neonatal morbidity, neonatal mortality, pandemic, pregnancy, respiratory distress syndrome, SARS-CoV-2, virus

1 | INTRODUCTION

With over a million individuals infected, the global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been growing at an accelerating rate. The increasing mortality rate warrants identification and protection of the vulnerable populations in society. The knowledge gained from previous human coronavirus outbreaks, namely, the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), suggests that pregnant women and their fetuses are particularly susceptible to poor outcomes. Admission to intensive care is common and a case fatality rate of up to 35% has been documented.^{1,2}

The physiological changes occurring during pregnancy make the mother more vulnerable to severe infections.³ Anatomical changes such as an increase in the transverse diameter of the thoracic cage and an elevated level of the diaphragm, decrease maternal tolerance to hypoxia.⁴ Lung volume changes and vasodilation can lead to mucosal edema and increased secretions in the upper respiratory tract. In addition, alterations in cell-mediated immunity contribute to the increased susceptibility of pregnant women to be infected by intracellular organisms such as viruses.⁵ With regard to the fetus and the newborn, the immaturity of the innate and adaptive immune systems makes them highly susceptible to infections.⁶ Dysregulation of factors such as cytokines and the complement cascade can have deleterious consequences for brain development and function.⁷ To find out whether an infectious agent can infect the fetus or newborn by vertical transmission is therefore of particular interest.⁸ Pregnant women and their newborns should be evaluated for being potential risk groups in the current COVID-19 pandemic.

From the limited information gathered about the novel coronavirus and the drastically increasing burden of the disease,⁹ it is vital that scientific information concerning the disease is shared in a concise and practical manner. Data on the maternal and perinatal outcomes of pregnant women infected with the SARS-CoV-2 are limited to a handful of case reports and series. The sample sizes are small and the findings are diverse. Health policy changes in countries affected by the pandemic, continuously evolving clinical management guidelines and uncertainty about the reliability of the results make the findings of these reports difficult to interpret.

We aimed to conduct a systematic review of available published literature on pregnancies affected by COVID-19 and present a mixed narrative and quantitative synthesis of the clinical manifestations and maternal and perinatal outcomes.

Key message

Pregnant women with COVID-19 often presented with fever and coughing. Lymphocytopenia and elevated C-reactive protein were common. Although the majority of mothers were discharged without any major complications, severe maternal morbidity as a result of COVID-19 could not be ruled out.

2 | MATERIAL AND METHODS

We conducted a comprehensive literature search using MEDLINE, Embase and Google Scholar. The search covered the period from 8 December 2019 through 4 April 2020. We used combinations of the following search terms: COVID-19, pregnancy, maternal mortality, maternal morbidity, complications, clinical manifestations, neonatal morbidity, intrauterine fetal death, neonatal mortality and SARS-CoV-2. Titles and abstracts were reviewed by both the authors to evaluate their relevance to our study. We identified several case reports and case series. Full-text articles were retrieved for further consideration for inclusion. Eligibility criteria included laboratory-confirmed COVID-19 infection using quantitative real-time polymerase chain reaction (qRT-PCR) or dual fluorescence polymerase chain reaction (PCR), patient pregnant on admission, reports written in English or Chinese, and availability of clinical characteristics including maternal and perinatal outcomes. Published guidelines on systematic reviews recommend a quality assessment of the included literature, but since only a handful of case reports and series were available, the authors decided to include as many studies that fitted the eligibility criteria as possible. Two studies where the full-text was written in Chinese were translated with the help of a Chinese translator who worked in the medical profession. Exclusion criteria were as follows: unpublished reports, unspecified date and location of the study or suspicion of duplicate reporting, cases with suspected COVID-19 that were not confirmed by a laboratory test, and unreported maternal or perinatal outcomes. Efforts were made to ensure that there was no overlap in the results and that no case was counted twice. This assessment was based on several criteria as described by Thornton:¹⁰ participant admission date, gestational age at birth, date of publication of the report, author names, name and location of the hospital/university, maternal and perinatal outcome data, etc.

Variables extracted and analyzed included maternal age, clinical signs and symptoms on admission, gestational age at admission and

TABLE 1 Maternal characteristics from 108 pregnancies with confirmed SARS-CoV-2 infection

	Case reports	Case series				Total, n/N (%)
	Chen et al, ¹³ Liu et al, ¹⁴ Li et al, ¹⁵ Fan et al, ¹⁶ Zhu et al, ¹⁷ Wang et al, ¹⁸ Chen et al, ¹⁹ Zambrano et al, ²⁰ Wang et al, ²¹ Gidlöf et al, ²² Yu et al, ²³ Breslin et al, ²⁴ Iqbal et al, ²⁵ Lee et al ²⁶ (N = 58)	Liu et al ²⁷ (N = 16)	Zhang et al ²⁸ (N = 16)	Liu et al ²⁹ (N = 15)	Chen et al ³⁰ (N = 3)	
Maternal characteristics						
Age (y) (mean ± SD)	31 ± 4	30	29 ± 3	32 ± 5	30 ± 6	
Gestational age in days (mean ± SD)	253 ± 25	N/A	271 ± 10	224 ± 8	260 ± 14	
Delivery characteristics						
Total number of deliveries	50	6	16	11	3	86/108 (80%)
Patients not delivered at time of reporting of studies	8	10	0	4	0	22/108 (20%)
Delivery by cesarean section	44	6	16	10	3	79/86 (92%)
Vaginal delivery	6	0	0	1	0	7/86 (8%)
Presenting signs and symptoms						
Fever on admission	42	7	N/A	13	1	63/92 (68%)
Cough	19	6	3	9	0	37/108 (34%)
Malaise	7	3	0	4	0	14/108 (13%)
Dyspnea	5	3	3	1	1	13/108 (12%)
Myalgia	8	0	0	3	0	11/108 (10%)
Sore throat	7	0	0	1	0	8/108 (7%)
Diarrhea	3	0	3	1	0	7/108 (6%)
Laboratory characteristics						
Lymphocytopenia (<1 × 10 ⁹ /L)	18 ^a	9	N/A	12	1	40/68 (59%)
Elevated C-reactive protein concentration (mg/L)	19 ^b	13	N/A	10	3	45/64 (70%)
Confirmed SARS-CoV-2	58	16	16	15	3	108/108 (100%)
Other parameters						
Maternal mortality	0	0	0	0	0	0/108 (0%)
Maternal ICU admission	3	0	0	0	0	3/108 (3%)
Neonatal mortality	1 ^c	0 ^d	0	0 ^f	0	1/87 (1%)
Intrauterine fetal death	1 ^c	0 ^d	0	0 ^f	0	1/87 (1%)
Vertical transmission	1 ^c	N/A	0 ^e	0 ^f	0	1/75 (1%)

N/A, data not available.

^aData unavailable in 24 cases.^bData unavailable in 28 cases.^cData unavailable from 8 women still pregnant at the end of the study. One twin delivery (Gidlöf et al²²).^dData unavailable from 10 women still pregnant at the end of the study.^eData unavailable in 6 neonates.^fData unavailable from 4 women still pregnant at the end of the study.

laboratory testing. Maternal and perinatal outcome data were also recorded. Any maternal to fetal transmission of the virus was also noted.

Case reports and case series are uncontrolled study designs known for increased risk of bias. To evaluate the methodological quality, we chose the framework for appraisal, synthesis and application of evidence suggested by Murad et al¹¹ based on the domains

of selection, ascertainment, causality and reporting. Both authors read all papers and assessed the methodological quality. There was considerable heterogeneity between the studies and factors such as publication bias and selective reporting of the results could not be accounted for. This systematic review did not have a "stand alone" study protocol. We followed the PRISMA guidelines¹² when reporting outcomes for the current study.

2.1 | Statistical analyses

Statistical analysis was done with SPSS, version 25.0 (IBM Corp.). Continuous variables were expressed as mean with standard deviation. Categorical variables were expressed as number of cases and percentages (%).

3 | RESULTS

Eighteen studies were screened for the eligibility criteria and included in the current systematic review. The results from 14 case reports are summarized together to facilitate interpretation.¹³⁻²⁶ These were published from 7 March 2020 through 1 April 2020. Data related to the clinical manifestations of COVID-19 at admission including laboratory testing and maternal and perinatal characteristics are presented in Table 1.

The remaining case series²⁷⁻³⁰ were published in 1-8 March 2020 and data were described collectively in cohorts. We therefore report these data in separate columns (Table 1). It is pertinent to mention that Zhang et al²⁸ tested for SARS-CoV-2 using the New Coronavirus (2019) Nucleic Acid Detection Kit (Dual Fluorescence PCR) provided by Jiangsu Shuo Shi Biotechnology Co., Ltd. The diagnostic criteria of COVID-19 were based on the New Coronavirus Infected Pneumonia Diagnosis and Treatment Plan (Trial Fifth Edition) issued by the National Health and Health Commission of China.

A total of 108 pregnant women with COVID-19 were identified. The majority of the studies originated from China, but cases from Sweden, USA, Korea and Honduras were also included. One of the cases was a premature twin delivery;¹⁷ however, since the maternal qRT-PCR was negative, this case was excluded from the study. Gidlöf et al²² reported another twin delivery and as the mother had a positive qRT-PCR, the neonates counted for two separate cases in the perinatal data.

We made an overall judgement of the quality of the reports included in the analysis based on the questions deemed most critical. In the domain "selection" there was wide variation, ranging from case reports involving only one case to small case series, but authors generally aimed to report all cases known and the overall quality was assessed to be medium. For "ascertainment", exposure and outcome should be adequately ascertained, which was deemed high by both authors. As for the "causality", the case reports could not rule out alternative causes that might explain the observations, no challenge/re-challenge was possible and follow up was short, which rendered a judgement of low-quality. Finally, the cases described were of varied but mostly sufficient detail, rendering a medium quality in the domain "reporting".

3.1 | Maternal characteristics and mode of delivery

Mean maternal age ranged from 29 to 32 years of age and women reported mostly in their third trimester. Twenty-two pregnant women

(20%) presented in earlier gestational weeks and were discharged, undelivered, without any major complications. The outcomes of these pregnancies are not known. Mean gestational age varied in the cited literature, and birth before 37 completed weeks of gestation was not uncommon (20 of 48 reported cases, ~42%). Pregnant women presented with a number of comorbidities or complications in their pregnancies such as preeclampsia, gestational diabetes, hypothyroidism, placenta previa, previous uterine surgeries etc. Cesarean section accounted for 92% of all deliveries; successful vaginal delivery was reported in 7 of 85 cases (8%). From analysis of the available data, fetal distress was commonly reported to as the indication for cesarean section. We were unable to determine whether "fetal distress" referred to abnormal cardiotocograph findings or other factors such as meconium stained amniotic fluid, abnormal fetal scalp lactate or blood flow changes.

Of the clinical signs and symptoms, pregnant women with COVID-19 commonly presented with a fever at admission (68%). A persistent, dry cough (34%) along with malaise (13%) and dyspnea (12%) were less commonly described. Diarrhea was identified in only seven cases (6%).

Lymphocytopenia was reported in 40 of 68 cases (59%) where the information was recorded. Similarly, an elevated C-reactive protein concentration (>10 mg/L) was recorded in 45 of 64 cases (70%). From the papers that included information about the treatment provided to the pregnant women, it was found that oxygen (25 of 28 available cases) and antiviral therapy (20 of 22 available cases) were given to the majority of patients. Treatment with antibiotics was also generously prescribed (all cases), possibly to prevent superimposed bacterial infection or as prophylaxis before cesarean section. However, we identified only four cases where corticosteroids were administered (4 of 28 available cases). From the reasoning provided in the published papers, corticosteroid administration was given to relieve inflammation due to maternal pneumonia rather than for fetal lung maturation.

3.2 | Maternal and perinatal outcomes

Regarding the perinatal outcomes, most authors^{13,15,18-25,28,29} did not report any adverse events. In contrast, Zhu et al¹⁷ report one neonatal death (see below) and a total of six admissions to the neonatal intensive care unit (ICU). The first symptom in the newborns was shortness of breath, observed in six neonates. Other initial symptoms were fever, thrombocytopenia accompanied by abnormal liver function, tachycardia, vomiting and pneumothorax. In the Zhu et al¹⁷ cohort, six of 10 were neonates born prematurely and eight of 10 were delivered by cesarean section, two factors that may have contributed to the morbidity. Fan et al¹⁶ presented two cases of SARS-CoV-2-positive pregnancies. One term baby developed low-grade fever and abdominal distension with lymphocytopenia on day 3 and the day after, a chest radiograph revealed diffuse haziness. The baby was discharged 9 days after delivery. The second baby was delivered by cesarean section at

36⁺⁵ weeks gestational age; and went on to develop mild neonatal pneumonia with lymphocytopenia, which was treated with antibiotics. The neonate recovered within 2 days.

There was one case of intrauterine fetal death and one case of neonatal death (Table 1). Liu et al¹⁴ reported one pregnancy where multiple organ dysfunction syndrome (MODS) with acute respiratory distress syndrome (ARDS) led to an emergency cesarean section. The neonate was stillborn and the mother required intubation with ventilator support and extracorporeal membrane oxygenation (ECMO). The outcome of this patient is not known.

Regarding maternal morbidity, Breslin et al²⁴ reported two cases of maternal ICU admission. The first case was a 38-year-old woman with a body mass index (BMI) of 38 kg/m², presenting at 37 weeks of gestation for induction. Poorly controlled type 2 diabetes mellitus and intrahepatic cholestasis complicated her pregnancy. Cesarean section was indicated when labor did not progress and the mother developed a fever prior to the operation. Intraoperatively, uterine atony led to massive hemorrhage (1.5 L) and the mother was intubated. Bronchospasm and wheezing ensued and a chest X-ray performed during the operation revealed hazy opacities in the lungs. A qRT-PCR test was positive for SARS-CoV-2. The clinical condition of the patient improved after the cesarean section, and she spent 8 hours in the ICU. The patient was discharged after 4 days without any major complications. The second patient was a 33-year-old patient with a BMI of 47 kg/m² who presented at 37 weeks of gestation for induction due to worsening chronic hypertension. Her past medical history included asthma and type 2 diabetes mellitus. Failed induction led to the delivery by cesarean section the next day. Twenty-five hours after delivery, the patient developed respiratory distress, high fever with reduced oxygen saturation and tachycardia. A qRT-PCR was positive and the patient was admitted to ICU due to severe hypertension. Five days postoperatively, the patient was still hospitalized, requiring supplementary oxygen and suffering from an acute kidney injury. In light of these findings, severe maternal morbidity cannot be ruled out with COVID-19 infection during pregnancy.

The neonatal death reported in the literature involved a male newborn¹⁷ born at 34⁺⁵ weeks gestational age with an Apgar score of 8 at 5 minutes. The neonate developed refractory shock and gastric bleeding with multiple organ failure and disseminated intravascular coagulation (DIC). A throat swab obtained 9 days after delivery was negative for SARS-CoV-2 nucleic acid testing, and Zhu et al¹⁷ mentioned poor immune function of the neonate and massive viremia as possible factors which could have contributed to the neonatal death.

The available literature has found no clear evidence for vertical transmission of COVID-19 from the mother to the fetus. However, on 26 March 2020, JAMA published two reports^{31,32} on three newborns with elevated SARS-CoV-2 IgM antibodies, although repeated nasopharyngeal samples from the infants were negative. In the editorial, Kimberlin & Stagno³³ point out that IgM assays can be prone to false-positive and false-negative results, along with cross-reactivity and testing challenges.

Wang et al¹⁸ reported one case with parallel findings of positive qRT-PCR in both the mother and the neonate. The mother was

admitted with fever at 40 weeks of gestation and computerized tomography (CT) scan of chest showed ground-glass opacities in the lungs. She underwent emergency cesarean section and the baby was born with normal Apgar scores. The mother wore an N95 mask during the surgery, and the baby had no contact with the mother after birth and was transferred to the neonatology department 10 minutes after birth for observation. The neonate had lymphocytopenia, deranged liver function and elevated creatine kinase, although it was clinically stable and appeared well. The mother's pharyngeal swab was positive for SARS-CoV-2 and, as a result, a pharyngeal swab was collected from the baby 36 hours after birth. This turned out to be positive. Swabs from umbilical cord blood and placenta were negative, but a possible mother-to-child transmission of SARS-CoV-2 cannot be excluded. Both mother and child recovered and were discharged.

4 | DISCUSSION

The first cases of COVID-19 pneumonia were reported in December 2019 from Wuhan, Hubei Province in China. Since then, the infection has rapidly spread all over the world.^{34,35} As obstetricians began to identify cases of COVID-19 in pregnancy, some reports have appeared in the literature. This review summarizes the findings from 108 pregnancies confirmed to have COVID-19. We found that COVID-19 during pregnancy may be associated with severe maternal morbidity and the possibility of maternal-fetal transmission could not be ruled out completely.

The SARS-CoV-1 outbreak during 2002-2003 was associated with a high maternal mortality rate (case fatality rate of 25%), spontaneous miscarriages during the first trimester and intrauterine growth restriction in the second and third trimesters.¹ Similarly, Alfaraj et al² reported a case series of 11 patients with MERS-CoV infection where the case fatality rate was 35% for pregnant women and 27% for infants. Nevertheless, a recent editorial on COVID-19 in pregnancy³⁶ argues that management guidelines should be based on data from the current epidemic rather than drawing on the limited experience from previous outbreaks, as their epidemiology, clinical course and response to treatment may differ. Indeed, our review of 108 pregnant women with confirmed SARS-CoV-2 infection showed three cases of maternal intensive care admission (3%) and no confirmed fatalities. The two maternal ICU admissions reported by Breslin et al²⁴ involved mothers with high BMI (>35) and complicated medical history which leads one to question whether COVID-19 increases the risk of severe morbidity in high-risk pregnancies. Future studies are needed to address this subject. One neonatal death and one intrauterine fetal death were also reported.

With regard to the mode of delivery, cesarean section was performed in the majority of cases and several authors^{13,27,28} cited fetal distress as the reason behind the decision. However, the seven cases of spontaneous vaginal delivery were not associated with poorer outcomes. In line with Huang et al,³⁴ the most common presenting

sign was fever and a non-productive cough. Tiredness, shortness of breath and diarrhea were reported only occasionally. In all, 21% of the pregnancies presented at earlier gestations, and they were all discharged without any serious complications; however, due to lack of data on the perinatal outcomes, we cannot draw any conclusions about any maternal and neonatal consequences of the infection when it is acquired early during the pregnancy.

In our review, we found that one of 75 newborns tested was positive for SARS-CoV-2 infection. This baby did well clinically but had transient lymphocytopenia and deranged liver function tests.¹⁸ Among the 10 cases (all babies SARS-CoV-2-negative) reported by Zhu et al,¹⁷ two developed disseminated intravascular coagulation and recovered, and one had multiple organ failure and died. Fan et al¹⁶ reported two neonates with mild lymphocytopenia and radiological findings of pneumonia, although both appeared clinically well and eventually made a full recovery. From these findings, we cannot exclude that the fetus and newborn baby might show a response, often sub-clinical, to the mother's infection and, thus, vertical maternal-fetal transmission cannot be ruled out. This view has been seconded by a recently published study³⁷ where three infants born by cesarean section tested positive for SARS-CoV-2, 2 days after birth. However, in their analysis of 38 infected pregnancies, Schwartz et al³⁸ did not find any evidence for intrauterine transmission. Nevertheless, lymphocytopenia and thrombocytopenia have been repeatedly reported, as well as radiological findings in seemingly healthy babies born to SARS-CoV-2-infected women. Therefore, we encourage clinicians to monitor the newborns of mothers with COVID-19 closely.

The main limitation of our review is related to the fact that the primary studies currently available in the literature were not of sufficiently high quality regarding their methodology. Several studies had missing outcome data and selective reporting bias could not be ruled out. Our study has some strengths. Only pregnant women with laboratory-verified SARS-CoV-2 infection were included in our review. Thus, the clinical manifestations and maternal-neonatal outcomes are representative of the disease. By including all cases available in the published literature, we were able to achieve a relatively large sample size. However, the majority of the individual reports describe only a small number of cases, and it is difficult for the clinicians to draw any definitive conclusions about the clinical manifestations and outcomes of the SARS-CoV-2 infection in the pregnant women and their neonates. With the disease burden accelerating every day, we hope that our synthesis can help physicians to better understand the nature of the disease at a glance and to make informed decisions when treating pregnant women with COVID-19 infection.

5 | CONCLUSION

Current evidence suggests the possibility of severe maternal morbidity requiring ICU admission and perinatal death with COVID-19 infection in pregnancy. Maternal-fetal transmission of the SARS-CoV-2 virus was not detected in the majority of the reported cases, although one neonate had a positive qRT-PCR 36 hours after birth

despite being isolated from the mother. Careful monitoring of pregnancies with COVID-19 and measures to prevent neonatal infection are warranted.

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CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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