Clinical manifestations and perinatal outcomes of pregnant women with COVID-19: a systematic review and meta-analysis

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Abstract

This systematic review and meta-analysis aimed to evaluate the impact of COVID-19 on pregnant women. We searched for qualified studies in PubMed, Embase, and Web of Science. The clinical characteristics of pregnant women with COVID-19 and their infants were reported as means and proportions with 95% confidence interval (CI). Nine studies involving with 93 pregnant women with COVID-19 and 103 infants were included in the meta-analysis. Pregnant women with COVID-19 have relatively mild symptoms. However, abnormal proportions of laboratory parameters were similar or even increased, compared to general population. Around 30% of pregnant women with COVID-19 experienced preterm delivery, whereas the mean birth weight was 3214.7g. Fetal death, severe neonatal asphyxia, and detection of SARS-CoV-2 were observed in about 2%, whereas no neonatal death was found. In conclusion, the current review will serve as an ideal basis for future considerations in the treatment and management of COVID-19 in pregnant women.

Introduction

The recent outbreak of the coronavirus disease 2019 (COVID-19) pandemic has called for a prompt response from the scientific community. As of April 7, 2020, confirmed infections have amounted up to over 2,490,000 cases, with casualties reaching an alarming number of over 171,000 [1]. The fact that the disease is actively spreading in the United States implies that we must prepare for the worst; as a consequence, labs worldwide have pooled their efforts to identify possible therapeutic methods, estimate future progression trends of the pandemic, and sort out the most vulnerable from existing data in order to prepare patient-specific measures.

In this context, many research papers have shed light on the varying effect of COVID-19 depending on patient characteristics, including age and smoking [2-8]. Another important population that deserves meticulous consideration during the COVID-19 pandemic is the pregnant. Pregnancy is an extremely sensitive bodily status, and it is unsurprising that viral infections may affect pregnancy outcomes; previous literature has revealed that viral respiratory illnesses may lead to a higher risk of obstetric complications and adverse perinatal outcomes [9, 10], primarily due to changes in the immune response [11]. Furthermore, previous literature on the impact of the 2009 H1N1 influenza virus or the Zika virus suggest that infectious diseases may increase complications and even exhibit fatal effects on pregnant women [12, 13]. Such acknowledgement has led to vigorous investigation from many research groups on the status quo of pregnant COVID-19 patients [14-16]; yet the need to accumulate, organize and analyze such data is evident, given the urgency of the situation.

To that end, this study aims to systematically review previous literature on the impact of COVID-19 on pregnant women. Several important issues, such as perinatal outcome or vertical transmission, are additionally raised in the prognosis of COVID-19 in the pregnant population. Based on ample pre- existing evidence, the current paper attempts to unravel meaningful factors that may aid medical personnel in dealing with such issues and to discover symptoms or phenomena that are specific to the pregnant population.

Results

A total of 243 records were identified from searches of three databases, and 108 duplicates were excluded. After removing 82 studies during title and abstract screening, 53 were selected for full-text review. Thereafter, 44 articles were excluded for the following reasons: reviews and expert opinions (n=18); case series or case report with less than 5 cases (n=18); studies only including infants born to mothers without confirmed COVID-19 infection (n=4); and overlapping studies (n=4). Hence, nine studies on 93 pregnant women with COVID-19 and 103 neonates were ultimately included for meta- analysis. [17-25].

The main characteristics of the included studies are listed in Table 1. All studies were conducted in China. The mean age and gestational age at admission of the study population ranged from 29.3 to 32.1 years and from 32 to 39.2 weeks, respectively. Most pregnant women received Caesarean section. Diagnosis of COVID-19 was mostly confirmed according to either the World Health Organization interim guidance or Chinese National Health Commissions guideline [26, 27]. Regarding quality assessment, three studies [21, 22, 25] met all of the nine critical appraisal criteria defined by the Joanna Briggs Institute; however, six studies [17-20, 23, 24] didn't and the major concern was the consecutive and complete inclusion of participants.

The meta-analysis results of symptoms of pregnant patients with COVID-19 are shown in Table 2. Among the pregnant patients infected by severe acute respiratory coronavirus 2 (SARS-CoV-2), approximately 75% showed symptoms of fever (56.4%; 95% CI 34.5~77.3) and postpartum fever (24.9%; 95% CI 6.5~48.8), respectively. Other common symptoms such as cough, fatigue, and dyspnea were observed in about 30%, 20%, and 10% of pregnant women with COVID-19, respectively. The prevalence of other symptoms including sore throat, diarrhea, and chest pain was less than 10%. In terms of laboratory findings, approximately 75%, 50% and 25% of infected pregnant women had elevated CRP, lymphopenia, and leukocytosis, respectively.

The pregnancy and perinatal outcomes of pregnant patients who were infected by SARS-CoV-2 are presented in Table 3. Around 30% of pregnant women with COVID-19 experienced preterm delivery, whereas premature rupture of membranes and fetal distress were observed in about 11%. The mean birth weight was 3214.7g (95% CI 3133.5~3295.9). Mean Apgar scores at 1 minute and 5 minutes were 8.7 (95% CI 8.4~8.9) and 9.7 (95% CI 9.5~10.0), respectively. Fetal death, severe neonatal asphyxia, and detection of SARS-CoV-2 were observed in about 2%, whereas no neonatal death was found.

Table 4 displays the characteristics of four neonates who had positive SARS-CoV-2 test results after birth. Except one neonate (Case 4), all neonates were born full-term. One neonate (Case 1) experienced mild dyspnea without fever and cough, whereas two other neonates (Case 2 and Case 3) experienced fever and lethargy. The premature baby (Case 4), whose birth weight was 1580g, exhibited respiratory distress syndrome and suspected sepsis with abnormal laboratory manifestation. All the babies were fully recovered and discharged after confirmation of negative SARS-CoV-2 results.

Discussion

The first notable finding of this study is the difference in common COVID-19 symptoms between pregnant patients and non-pregnant patients. Well-known symptoms of COVID-19 include fever, cough, and dyspnea; in a previous study on non-pregnant COVID-19 patients, the proportion of those who show each symptom was shown to be 83%, 82%, and 31%, respectively [28]. In our study of pregnant women, the proportions decreased

to 57%, 31%, and 11%, indicating relatively mild symptoms. This result was in line with another previous study by Liu *et al.* that compared pregnant and non-pregnant COVID-19 patients, where more pregnant patients were classified as mild or common [20]. Milder symptoms in pregnant COVID-19 patients may be explained by the younger average age compared to the general COVID-19 patient population; additionally, as there was much fewer comorbidities, symptoms might have appeared to be less profound in the pregnant population.

Unlike common symptoms, various abnormalities of laboratory parameters showed a similar or even increased trend in pregnant women with COVID-19 compared to general patients. A previous meta- analysis using patients with COVID-19 reported that proportions of leukocytosis, lymphopenia, and elevated CRP levels were 17%, 43%, and 58%, respectively [29], while those in our study were 26%, 53%, and 72%. This gap between the pregnant and general patient population was probably attributable to changes in the immune response in pregnancy [11].

Of utmost importance is the effect of COVID-19 infection in pregnant women; in this regard, pregnancy outcomes were observed in the current study. In total, 29% of the study sample exhibited preterm delivery, a strikingly high number compared to the norm, which was reported to be between 5-18% [30]. In previous research on pregnant patients in past *coronaviridae* outbreaks, namely severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), the proportions of pregnant patients that experienced preterm delivery were 29% and 32%, respectively, which were approximately similar to the ratio in pregnant COVID-19 patients [31].

In addition, data on neonates born from COVID-19 patients showed varying tendencies compared to the non-infected. Average Apgar scores at 1 minute and 5 minutes were recorded to be an adequate 8.7 and 9.7, respectively, while average body weight was 3214.7g, which is considered normal. On the other hand, proportions of fetal distress and severe neonatal asphyxia were 11.2% and 2.1%, displaying dissimilarity to those of non-inflicted cases, which were 6.8% and 0.2~2% [32, 33]. While the rate of fetal death in China has been reported to be 0.43%, the present study population exhibited a rate of 1.7%, showing a significant gap as well [34]. Finally, there was no case of neonatal death in our study, which indicated that the presence of COVID-19 in the mother did not seem to result in a higher probability of neonatal death.

Vertical transmission is another crucial issue, primarily as newborns possess an underdeveloped protective system against external sources of potential harm. Yet controversy had existed regarding whether SARS-CoV-2 can be transmitted from the mother to the fetus within the uterus. Research on previous coronavirus outbreaks fail to provide definite evidence for or against vertical transmission in pregnant patients; on the other hand, in other respiratory viruses such as influenza or respiratory syncytial virus (RSV), cases of vertical transmission have been reported [35, 36]. In the present study, a total of four newborns were reported as SARS-CoV-2 positive, suggesting that vertical transmission of COVID-19 may not be negligible. In addition, several case reports have further strengthened this notion; according to Zeng et al [24], among 6 neonates born to the pregnant COVID-19 patients, virus- specific antibodies were detected in neonatal serum samples, although SARS-CoV-2 itself was undetected in the serum or throat swab via reverse transcriptase-polymerase chain reaction (RT-PCR) in the newborns. Among such antibodies, IgM was of particular interest, as it is not usually transferred to the fetus via the placenta due to its large macromolecular structure; interestingly enough, a newborn with elevated IgM numbers was discovered [37]. Combining the data on six neonates covered in the

present meta-analysis [24] and that of one neonate in the case report above [37], it was postulated that high levels of IgM in the mother was correlated with high IgM levels in the newborn. Specifically, three neonates exhibited abnormally high IgM levels (33.9 ± 15.6 AU/mL) and so did their mothers (200.1± 102.9 AU/mL). On the other hand, the other four neonates and their mothers showed low average (SD) IgM levels (AU/mL) of 1.7 (1.6) and 14.0 (14.2), respectively. Such data indicates that there might exist a relationship between neonatal and maternal IgM levels.

The present meta-analysis bears a few limitations that should be considered in the interpretation of results. To begin with, the limited number of studies and uniform geographical profile (Chinese) of the selected studies may hinder possibilities of generalization. In addition, in the selected studies, research was conducted on only late term pregnancy cases. As data on COVID-19 infection in different regions and patients accumulate, the results of the present study will be refined and polished to yield more general conclusions. Nevertheless, as a systematic review and meta-analysis on pregnant COVID-19 patients, the current review will serve as an ideal basis for future considerations in the treatment and management of COVID-19 in pregnant women.

Methods

Literature search strategy

Two researchers separately searched PubMed, Embase, and Web of Science for studies on clinical characteristics of pregnant women with COVID-19 and their neonates, published between 1 January 2020 and 3 April 2020. The following search terms were used ((Pregnan* OR gestation* OR maternal OR fetal OR perinatal OR obstetric* OR neonate* OR infant* OR newborn*)) AND (("coronavirus disease 2019" OR "coronavirus disease-19" OR "COVID-19" OR "2019-nCoV" OR "SARS-CoV-2" OR "novel coronavirus")). There was no restriction on language of publication. Duplicates and obviously irrelevant studies were excluded through initial screening of titles and abstracts, and the remaining articles were further reviewed according to inclusion and exclusion criteria. A flow diagram summarizing the study selection process is shown in Figure 1.

Inclusion and exclusion criteria

Eligible studies should describe the clinical characteristics of pregnant women with COVID-19 and their neonates. Exclusion criteria were: (1) reviews and expert opinions; (2) in vitro or animal studies; (3) studies on infants born to mothers without confirmed COVID-19 infection; or (4) case series or case report with less than 5 cases. In instances of overlapping data, only the most recent and comprehensive data were included in the meta-analysis.

Study selection, data extraction and quality assessment

Two investigators separately selected publications and extracted data, and discrepancies were resolved by consensus. The following information was extracted from each study: name of the first author, publication year, study setting, study design, patient age, gestational age at admission, percentage of Caesarean section, and diagnosis criteria of COVID-19. Also, prevalence of clinical symptoms and maternal and fetal outcomes were extracted, along with mean and standard deviation of birth weight and Apgar scores. The methodologic

quality of the selected studies was evaluated using the Joanna Briggs Institute critical appraisal checklist for case series by two researchers, independently [38].

Statistical analysis

The clinical characteristics of pregnant women with COVID-19 and their neonates were reported as means and proportions with 95% confidence interval (CI). Statistical heterogeneity was assessed using I2 statistics. To avoid bias from studies with a zero-event rate, proportions were transformed via the Freeman–Tukey Double ArcSine method. A random-effects model (DerSimonian-Laird method) was applied to consider the heterogeneity within and between studies and to give a more conservative estimate of statistical confidence. All statistical analyses were performed using R software (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria) with meta package. The review was written based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Declarations

Conflict of Interest

We declare no conflict of interests.

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Author Contributions

All the authors have made substantial contributions to the conception of the study. J.Y., W.K., K.E.L. and H.S.G. contributed to designing the study. J.Y., W.K. and K.E.L. contributed to acquisition and analysis of data. J.Y., W.K., J.M.H., N.L., H.Y.Y., and H.S.G. contributed to interpretation of data. J.Y., W.K., J.M.H., H.Y.Y. and N.L. contributed to drafting of the manuscript. K.E.L. and H.S.G. contributed to critical revision of the manuscript. All authors approved the final manuscript.

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Tables

Table 1. Characteristics of studies included in the meta-analysis.

Study ID	Number of pregnant women	Number of neonates	Maternal agea (years)	Gestational age at admission (weeks)	C-section (%)	COVID-19 diagnosis	Setting	Enroll period
Chen H, et al. [18]	9	9	29.8 ± 4.8	37.4 ± 1.2	9 (100.0)	Guidance for COVID- 19 by NHC of China (4th edition)	Zhongnan Hospital of Wuhan University	From Jan 20 to Jan 31, 2020
Chen R, et al. [19]	17	17	29.4 ± 2.9	82.3% were ≥37 weeks	17 (100.0)	Guidance for COVID- 19 by NHC of China (6th edition)	Renmin hospital of Wuhan University	From Jan 30 to Feb 23, 2020
Liu D, et al. [20]	15	11	32 ± 5	32 ± 8	10 (90.9)	Guidance for COVID- 19 by NHC of China (5th edition)	Union Hospital of Tongji medical college	From Jan 20 to Feb 10, 2020
Liu H, et al. [21]	16	-	30 (22-42)	range: 22w to 40w5d	NA	Laboratory-confirmed SARS-CoV-2 positive with clinical criteria	Maternal and child health hospital of hubei province	From Jan 27 to Feb 14, 2020
Liu Y, et al. [22]	13	10	29.7 ± 4.0	34.0 ± 4.0	10 (100.0)	Laboratory-confirmed SARS-CoV-2 positive	Hospitals in Zhejiang, Fujian, Shanxi, Beijing, Guangdong, Jiangxi, Heilongjiang and Anhui and other cities of Hubei.	From Dec 8 2019 to Feb 25 2020

Yu N, et al. [23]	7	7	32.1 ± 2.1	39.2 ± 1.5	7 (100.0)	WHO interim guidance	Tongji Hospital	From Jan 1 to Feb 8, 2020
Zeng H, et al. [24]	-	6	-	-	6 (100.0)	Laboratory-confirmed SARS-CoV-2 positive with clinical symptoms and CT scan	Zhongnan Hospital of Wuhan University	From Feb 16 to Mar 6, 2020
Zeng L, et al. [25]	-	33	-	-	NA	Guidance for COVID- 19 by NHC of China (5th edition)	Wuhan Children's Hospital	From Jan 30 to Feb 15, 2020
Zhang L, et al. [26]	16	10	29.3 ± 2.9	38.7 ± 1.4	16 (100.0)	Guidance for COVID- 19 by NHC of China (5th edition)	East Campus of Wuhan University People's Hospital	From Jan 30 to Feb 17, 2020

COVID-19: Coronavirus disease 2019; NA: not available; NHC: National Health Commission; SARS-CoV-2: SARS-coronavirus 2; WHO: World Health Organization.

aData are represented as mean mean ± SD or median (range)

Table 2. Meta-analysis of maternal symptoms (n=7)

	Number of studies	Event N	Total N	Prevalence (%)	95% CI	I2 (%)
Fever	7	55	112	56.4	34.5~77.3	79.3
Postpartum fever	4	17	75	24.9	6.5~48.8	75.3
Cough	7	36	112	31.4	21.9~41.6	11.6
Sore throat	3	4	39	9.4	1.2~21.9	0
Dyspnea	7	13	112	10.7	4.9~17.9	0
Diarrhea	5	4	66	4.5	0.1~12.3	0
Myalgia	2	6	26	22.5	7.4~41.5	0
Chest pain	2	2	26	5.5	0.0~21.4	15.6
Fatigue	5	14	72	18.5	9.7~29.0	0
Leukocytosis	4	16	49	26.4	7.4~50.5	62.1
Lymphopenia	5	35	66	53.2	37.6~68.6	31.4
Elevated CRP	5	43	65	72.0	49.4~90.4	67.3

N: number; CRP: C-reactive protein.

Table 3. Meta-analysis of pregnancy and perinatal outcome (n=8)

	Number of studies	Event N	Total N	Prevalence (%) or mean	95% CI	I2 (%)
PROM	4	9	71	11.7	4.5~21.1	0
Fetal distress	4	6	45	11.2	1.9~24.6	14.0
Preterm delivery (<37 week)	4	17	68	29.4	9.6~53.6	70.7
Birthweight	4	NA	49	3214.7	3133.5~3295.9	0
Apgar score at 1 minute	3	NA	36	8.7	8.4~8.9	0
Apgar score at 5 minutes	2	NA	26	9.7	9.5~10.0	0
Fetal death	5	2	56	1.7	0.0~8.8	0
Neonatal death	4	0	70	0.0	0.0~2.5	0
Severe neonatal asphyxia	5	3	86	2.1	0.0~7.5	0
SARS-CoV-2 positive	6	4	68	2.2	0.0~9.3	0

N: number; PROM: premature rupture of membranes; SARS-CoV-2: SARS-coronavirus 2; NA: not available.

Table 4. Summary of the neonates who had positive SARS-CoV-2 test results after birth.

	Case 1 [23]	Case 2 [26]	Case 3 [26]	Case 4 [26]
Gestational age at delivery	40w	40w	40w+4d	31w+2d
Birthweight (g)	3250	3250	3360	1580
Apgar score at 1 minute	8~9	NA	NA	3
Apgar score at 5 minute	9~10	NA	NA	4
Age at remission of SARS-CoV-2 positive	36h	Day 2 and 4	Day 2 and 4	Day 2 and 4
Symptoms	Mild dyspnea without fever and cough	Fever and lethargy without abnormal laboratory findings	Fever, lethargy, and vomiting with leukocytosis, lymphocytopenia, and an elevated creatinine kinase- MF fraction	Respiratory distress syndrome and suspected sepsis, with an *Enterobacter* agglomerates- positive blood culture, leukocytosis, thrombocytopenia, and coagulopathy
Age at remission of SARS-CoV-2 after treatment	Before day 14	Day 6	Day 6	Day 7

SARS-CoV-2: SARS-coronavirus 2

Figures

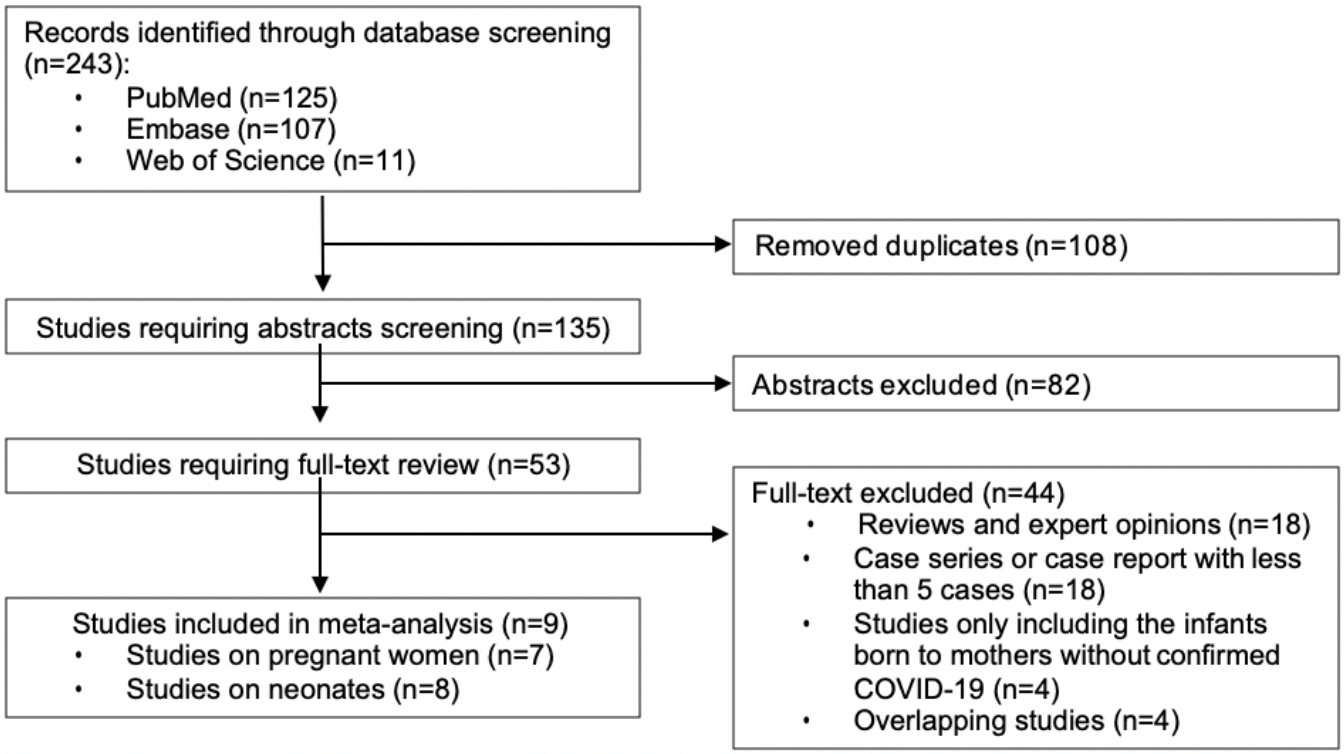

Figure 1

Flow diagram of study selection.