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Maternal and Neonatal Outcomes of Pregnant Women With Coronavirus Disease 2019 (COVID-19) Pneumonia: A Case-Control Study

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(See the Editorial Commentary by Schwartz on pages 2042–4.)

Background. The ongoing pandemic of coronavirus disease 2019 (COVID-19) has caused serious concerns about its potential adverse effects on pregnancy. There are limited data on maternal and neonatal outcomes of pregnant women with COVID-19 pneumonia.

Methods. We conducted a case-control study to compare clinical characteristics and maternal and neonatal outcomes of pregnant women with and without COVID-19 pneumonia.

Results. During the period 24 January–29 February 2020, there were 16 pregnant women with confirmed COVID-19 pneumonia and 18 suspected cases who were admitted to labor in the third trimester. Two had vaginal delivery and the rest were cesarean delivery. Few patients presented respiratory symptoms (fever and cough) on admission, but most had typical chest computed tomographic images of COVID-19 pneumonia. Compared to the controls, patients with COVID-19 pneumonia had lower counts of white blood cells (WBCs), neutrophils, C-reactive protein (CRP), and alanine aminotransferase on admission. Increased levels of WBCs, neutrophils, eosinophils, and CRP were found in postpartum blood tests of pneumonia patients. Three (18.8%) of the mothers with confirmed COVID-19 pneumonia and 3 (16.7%) with suspected COVID-19 pneumonia had preterm delivery due to maternal complications, which were significantly higher than in the control group. None experienced respiratory failure during their hospital stay. COVID-19 infection was not found in the newborns, and none developed severe neonatal complications.

Conclusions. Severe maternal and neonatal complications were not observed in pregnant women with COVID-19 pneumonia who had vaginal or cesarean delivery. Mild respiratory symptoms of pregnant women with COVID-19 pneumonia highlight the need of effective screening on admission.

Keywords. COVID-19; pregnancy; maternal outcomes; vaginal delivery; neonates.

In December 2019, an outbreak of coronavirus disease 2019 (COVID-19)–associated pneumonia was reported in Wuhan, a mega-city in central China with a population of 11 million, and soon spread to other cities in China and overseas [1]. The causative pathogen was identified as a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. As of 15 April 2020, COVID-19 has caused nearly two million confirmed cases and more than 120 000 deaths globally, including 82 295 confirmed cases and 3342 deaths in China [2]. In response to this fast-spreading epidemic, the Chinese government has locked down the epicenter, Wuhan city, since 23 January 2020, and implemented a series of social distancing measures such as strict traffic restrictions, prohibition of social gatherings, and closure of residential communities [3]. The epidemiological data in China have showed that most cases had mild symptoms, with an overall case fatality rate of 2.3%. Although SARS-CoV-2 appears to be less virulent than 2 previous zoonotic coronaviruses, SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), it is far more efficient to transmit between close contacts [4]. In particular, this novel coronavirus has caused special concerns in pregnant women, because both SARS-CoV and MERS-CoV have been found to cause severe complications in pregnant women [5, 6]. Several reports on suspected vertical transmission of this virus have further increased such concerns [7]. Although recent laboratory studies and clinical reports have not found strong evidence to support a vertical transmission route, this possibility still cannot be completely ruled out [8–10].

Clinical and epidemiological features of COVID-19 infection have been widely reported [11–15]. However, clinical reports on maternal and neonatal outcomes of pregnant women with SARS-CoV-2 infection remain sparse. An earlier study

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by Chen et al reported 9 pregnant women with COVID-19 pneumonia who underwent cesarean delivery in a tertiary hospital of Wuhan [8]. These patients showed clinical symptoms similar to nonpregnant patients with COVID-19 pneumonia. The authors also claimed that there was no evidence of vertical transmission. To date, no previous studies have investigated the adverse effects of COVID-19 infection on pregnancy by comparing maternal and neonatal outcomes of pregnant women with COVID-19 pneumonia to those without pneumonia.

MATERIALS AND METHODS

Study Design and Patients

We retrospectively reviewed medical records of pregnant women who were admitted to the Hubei Provincial Maternal and Child Health Center, a tertiary hospital in Wuhan with 1900 hospital beds, during 24 January–29 February 2020. We followed the clinical diagnosis criteria for COVID-19 pneumonia in the New Coronavirus Pneumonia Prevention and Control Program (fifth edition) by the National Health Commission of China [16]. Throat swabs were collected from all of these patients and sent to the laboratory of the Wuhan Center for Disease Control and Prevention for tests of SARS-CoV-2 using the standard kit (BioGerm, Shanghai, China). Diagnosis criteria of COVID-19 infection include (1) typical chest computed tomographic (CT) imaging of patchy shadowing and ground glass opacity; and (2) positive reverse-transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2. However, previous studies have argued that false-negative cases might be common for COVID-19 infection cases due to low virus titers, sampling at late stage of illness, and inappropriate swabbing sites [8]. Given overloaded healthcare systems and limited test capacities during our study period, we may have missed some COVID-19 cases if solely relying on laboratory tests. Therefore, in this study we also included the suspected patients with typical chest CT imaging but negative by RT-PCR tests. Eleven pregnant women who tested positive for SARS-CoV-2 were classified as the "laboratory-confirmed case group," and 18 with typical chest CT imaging but who tested negative by RT-PCR as the "suspected case group."

The control group of pregnant women without pneumonia during hospital stay was randomly selected from the medical records by an investigator (M. P.) who was not involved in statistical analysis. Only those aged 25–35 years were selected, to match the age range of cases. We selected 121 women who were admitted during the same period ("control 2020 group"). Considering the potential adverse effects of mental stress caused by city lockdown and severe epidemics, we also included a second control group of 121 women admitted during 24 January–11 February 2019 ("control 2019" group). Blood test results were also retrieved from medical records. The 2 case groups underwent blood tests every 3 days, but the 2 control groups only underwent blood tests once, on admission.

Data Analysis

Clinical characteristics, laboratory test results, and maternal and neonatal outcomes were collected from medical records and reviewed independently by 2 investigators (Y. Lv. and Y. O.). Fisher exact tests and Mann-Whitney *U* tests were used to compare the group differences for categorical and continuous variables, respectively. Friedman tests were used to test for the difference of blood test results across time within the same subjects. All data analysis was conducted using R version 3.6.2 software.

Ethical Considerations

Ethical approval for this study was obtained from the ethics committee of the Hubei Provincial Maternal and Child Health Center.

RESULTS

Clinical Characteristics and Maternal Outcomes

The demographic characteristics of the 2 case groups and 2 control groups are shown in Table 1. The age of confirmed cases ranged from 26 to 37 years, and all were in the third trimester of pregnancy. Two confirmed cases (12.5%) and 1 suspected case had chronic conditions of hypertension, polycystic ovary syndrome, and hepatitis B. Their gestational weeks on admission ranged from 33 weeks plus 6 days to 40 weeks plus 4 days. Approximately 70% of 2 case groups had other maternal

Table 1. Demographic Characteristics of the Case and Control Groups

	Confirmed Cases (n = 16)	Suspected Cases (n = 18)		Control Group 2020 (n = 121)		Control Group 2019 (n = 121)	
Characteristic	No. (%)	No. (%)	*P* Value[a]	No. (%)	*P* Value[a]	No. (%)	*P* Value[a]
Age, y, mean ± SD	30.9 ± 3.2	29.8 ± 2.3	.624	30.1 ± 3.3	.509	29.3 ± 2.6	.090
Cesarean delivery	14 (87.5)	16 (88.9)	1.000	57 (47.1)	.003	44 (36.4)	< .001
Preterm delivery	3 (18.8)	3 (16.7)	1.000	7 (5.8)	.094	6 (5.0)	.071
Chronic illness	2 (12.5)	1 (5.6)	.591	5 (4.1)	.190	0 (0.0)	.013
Complications in pregnancy	11 (68.8)	13 (72.2)	1.000	38 (31.4)	.005	32 (33.3)	.011

Data are presented as no. (%) unless otherwise indicated.

Abbreviation: SD, standard deviation.

[a]Fisher exact tests and Mann-Whitney *U* tests. Laboratory-confirmed cases are the reference group.

complications, which was significantly higher than the controls (31%–33%). All of these complications developed before the diagnosis of pneumonia.

Fourteen patients had cesarean delivery, because confirmed or suspected COVID-19 pneumonia has become an indication for cesarean delivery in our hospital since 24 January 2020. Two patients had vaginal delivery because neither presented any respiratory symptoms when admitted for full-term labor. One of them had fever 2 days after childbirth and another had CT images of patchy shadowing in the right lung on the same day of labor. Twenty-two patients (12 confirmed and 10 suspected cases) underwent emergency cesarean delivery because of active labor at the time of admission, and 8 had scheduled cesarean delivery (3 confirmed and 5 suspected cases).

In addition to pneumonia, 11 of 16 confirmed cases had gestational complications on admission, including gestational diabetes mellitus (n = 3), premature rupture of membranes (n = 1), gestational hypertension (n = 3), hypothyroidism (n = 2), preeclampsia (n = 1), and sinus tachycardia (n = 1). Only 1 of them had >1 complication (gestational diabetes mellitus and hypertension). Among 3 confirmed cases with preterm delivery, 2 were caused by premature rupture of membranes, and 1 by placental bleeding. Two suspected cases had preterm delivery due to gestational hypertension/preeclampsia, and 1 suspected case due to placenta previa.

None of the confirmed COVID-19 patients reported an exposure history. Four were admitted with fever for investigation, and 8 developed fever after childbirth (Table 2). None presented other respiratory symptoms on admission nor during hospital stay. Two of the patients with suspected COVID-19 pneumonia reported cough, sore throat, dyspnea, diarrhea, and vomiting.

Table 2. Clinical Characteristics of Pregnant Women With Confirmed or Suspected Coronavirus Disease 2019 (COVID-19) Pneumonia

Characteristic	Confirmed Cases	Suspected Cases
Length of stay, d, median (IQR)	9.5 (5.8–11)	6.0 (5.0–9.3)
Symptoms		
Fever on admission	4 (25.0)	1 (5.6)
Fever after childbirth	8 (50.0)	6 (33.3)
Cough	0 (0.0)	1 (5.6)
Sore throat	0 (0.0)	1 (5.6)
Dyspnea	0 (0.0)	1 (5.6)
CT imaging		
Pneumonia in 1 lung	8 (50.0)	10 (55.6)
Pneumonia in 2 lungs	7 (43.8)	7 (38.9)
Treatment		
Steroid	0 (0.0)	0 (0.0)
Antibiotics	16 (100.0)	18 (100.0)
Antivirals	4 (25.0)	0 (0.0)
High-throughput oxygen	0 (0.0)	0 (0.0)
ECMO	0 (0.0)	0 (0.0)
Outcome		
Discharge	8 (50.0)	18 (100.0)
Transfer	8 (50.0)	0 (0.0)

Abbreviations: CT, computed tomography; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range.

Laboratory Investigations and Treatment

All patients underwent chest CT scans. Seven of the confirmed cases had typical imaging of pneumonia in both lungs and 8 in a single lung. Seventeen of the 18 suspected cases had either both lungs or a single lung affected. Compared to the controls, the 2 case groups had slightly lower counts of white blood cells (WBCs), neutrophils, C-reactive protein (CRP), and alanine aminotransferase (ALT) on admission, although none reached statistical significance and most were marginally beyond the normal range (Table 3). Lymphocytes, eosinophils, and aspartate aminotransferase were comparable between the cases and controls. An increase of WBCs, neutrophils, and CRP were observed in the first postpartum blood test of confirmed cases, followed by a decrease in the second postpartum test (Figure 1). This transient change was not found in suspected cases. Lymphocytes remained at the lower end of normal range in the 2 case groups.

All COVID-19 pneumonia patients received antibiotics, and 4 patients received antivirals during hospital stay. All of them have been discharged or transferred to the designated hospitals for COVID-19 patients, and the length of stay in our hospital ranged from 3 to 26 days, with a median of 6.5 days. None were admitted into the intensive care unit because of COVID-19 pneumonia or severe maternal complications.

Neonatal Outcomes

Sixteen patients with confirmed COVID-19 pneumonia gave birth to 17 babies (15 singletons and 2 twins). Two singletons were born prematurely due to premature rupture of membranes and placental abruption. Of the premature births, 23.5% and 21.1% were from the mothers with confirmed or suspected COVID-19 pneumonia, respectively—significantly higher than those from the controls (5.8% and 5.0% in the 2020 and 2019 controls, respectively) (Table 4). Low birth weight also occurred more often in infants of the 2 case groups (17.6% and 10.5% among confirmed and suspected cases, respectively) than in the 2 control groups (2.5% in each). Newborns from the cases and controls showed no significant differences in key neonatal indicators including gestational age at birth, Apgar score at 5 minutes, and intrauterine fetal distress. Of 3 newborns with intrauterine fetal distress, 2 were from the COVID-19–confirmed mothers, 1 of whom also had sinus tachycardia. One case of fetal distress was from the mother who had suspected COVID-19 pneumonia but no other comorbidity. No events of severe neonatal asphyxia and deaths occurred in these newborns.

Table 3. Comparison of Blood Test Results on Admission Between the Case and Control Groups

		Confirmed Cases	Suspected Cases		Control Group 2020		Control Group 2019	
Blood Test	Reference Range	Mean (SD)	Mean (SD)	*P* Value[a]	Mean (SD)	*P* Value[a]	Mean (SD)	*P* Value[a]
WBC count, $\times 10^9$/L	3.5–9.5	8.6 ± 1.8	11.6 ± 4.5	.026	10.3 ± 3.1	.021	9.6 ± 2.4	.179
Lymphocytes, $\times 10^9$/L	1.1–3.2	1.5 ± 0.4	1.3 ± 0.5	.512	1.5 ± 0.5	.622	1.5 ± 0.4	.404
Lymphopenia (< 1 × 10^9/L), No. (%)	…	2 (12.5%)	5 (27.8%)	.405	15 (12.6%)	1.000	14 (11.6%)	1.000
Neutrophils, $\times 10^9$/L	1.8–6.3	6.6 ± 1.8	9.3 ± 5.0	.098	8.4 ± 2.7	.007	7.4 ± 2.2	.161
CRP, mg/L	0–4.0	4.8 ± 4.8	11.1 ± 12.9	.043	23.0 ± 41.5	.194	8.5 ± 15.7	.574
Elevated CRP (> 4.0 mg/L), No. (%)	…	5 (31.3%)	11 (61.1%)	.101	68 (58.1%)	.060	57 (47.1%)	.290
Eosinophils, $\times 10^9$/L	0.02–0.52	0.04 ± 0.05	0.02 ± 0.03	.109	0.08 ± 0.2	.008	0.07 ± 0.05	.002
ALT, U/L	0–40	11.6 ± 5.0	20.6 ± 40.4	.679	11.2 ± 8.9	.236	11.6 ± 13.9	.181
AST, U/L	0–35	16.3 ± 5.2	27.8 ± 45.5	.569	18.3 ± 6.2	.129	17.2 ± 9.7	.728

Data were missing in 2 patients for WBC count, 2 for lymphocytes, 3 for neutrophils, 4 for CRP, 4 for eosinophils, 2 for ALT, and 2 for AST.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C- reactive protein; SD, standard deviation; WBC, white blood cell.

[a]Fisher exact tests and Mann-Whitney *U* tests; the laboratory-confirmed cases were the reference group.

To reduce contact transmission, all COVID-19 patients were immediately moved to isolation wards after delivery or cesarean delivery, and their newborns were cared for by other family members. Three newborns (including 2 twins) who were delivered by cesarean section underwent throat swabs at 4 and 14 days after birth. All of them tested negative for SARS-CoV-2.

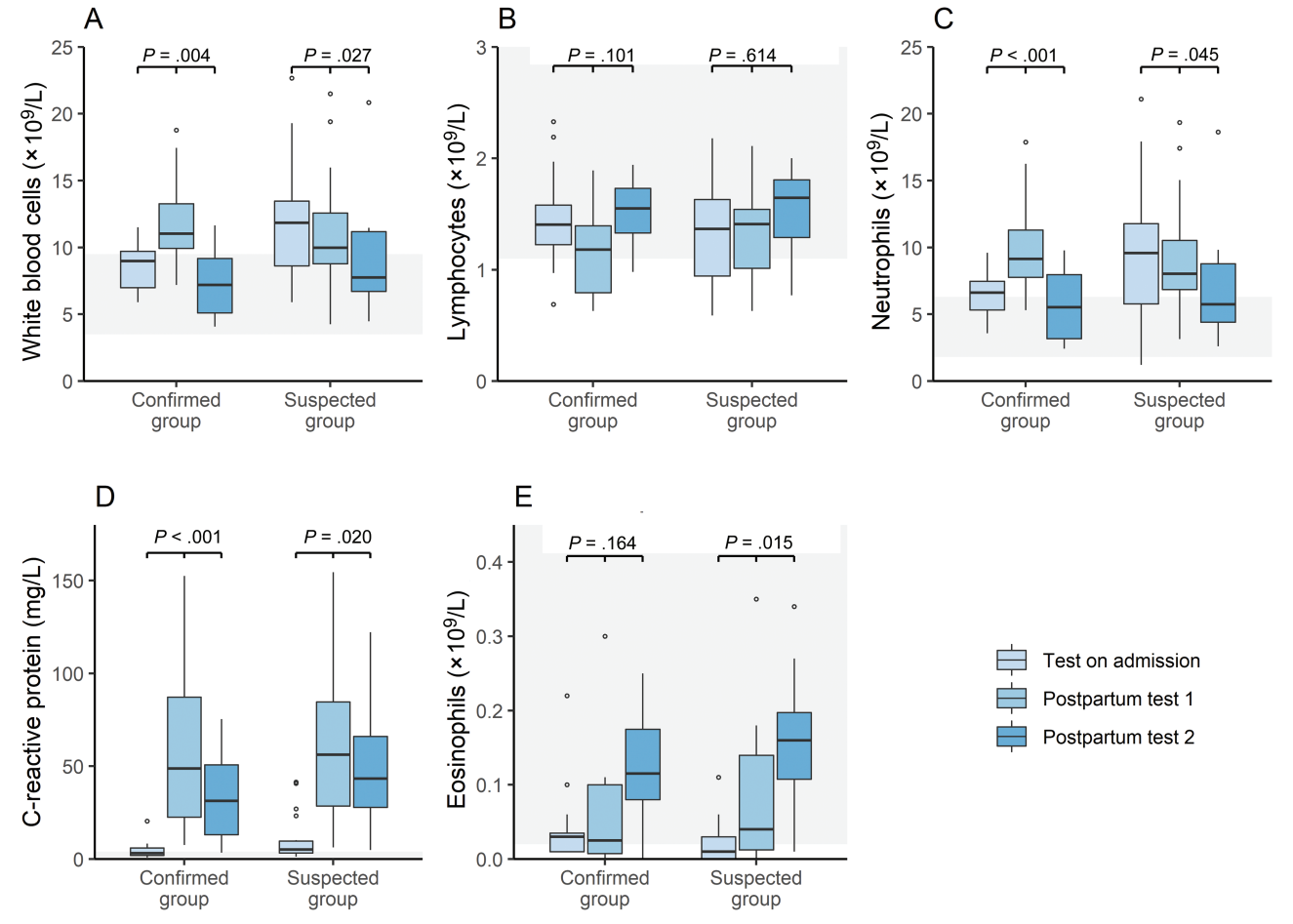

Figure 1. *A–E*, Box plots of blood test results of the confirmed and suspected case groups. Reference ranges of blood tests results are highlighted in gray. *P* values were calculated from Friedman tests for difference of blood test results across 3 tests.

Table 4. Clinical Characteristics of Newborns From the Case and Control Groups

Characteristic	Confirmed Cases (n = 17)	Suspected Cases (n = 19)	*P* Value[a]	Control Group 2020 (n = 121)	*P* Value[a]	Control Group 2019 (n = 121)	*P* Value[a]
Gestational age at birth, mean, wk ± d	38 ± 0.2	38 ± 2.9	.612	39 ± 0.7	.102	38 ± 6.9	.139
Singleton, no. (%)	15 (88.2)	17 (89.5)	1.000	121 (100.0)	.014	121 (100.0)	.014
Birth weight, g, mean ± SD	3066.7 ± 560.2	3198.7 ± 522.6	.657	3317.1 ± 455.3	.118	3307.9 ± 419.3	.115
Low birth weight, no. (%)[b]	3 (17.6)	2 (10.5)	.650	3 (2.5)	.025	3 (2.5)	.025
Premature birth, no. (%)[c]	4 (23.5)	4 (21.1)	1.000	7 (5.8)	.031	6 (5.0)	.021
Apgar score at 1 min after birth, mean ± SD	9.6 ± 0.5	9.6 ± 0.5	.970	9.8 ± 0.4	.012	9.9 ± 0.3	<.001
Apgar score at 5 min after birth, mean ± SD	10.0 ± 0.0	10.0 ± 0.0	1.000	10.0 ± 0.0	1.000	10.0 ± 0.0	1.000
Intrauterine fetal distress, No. (%)	2 (11.7)	1 (5.3)	.593	6 (5.0)	.256	6 (5.0)	.256

Abbreviation: SD, standard deviation.

[a]Fisher exact tests and Mann-Whitney *U* tests; the laboratory-confirmed cases are the reference group.

[b]Neonates who were born weighing < 2500 g.

[c]Neonates who were born before the start of the 37th week of pregnancy.

DISCUSSION

To our best knowledge, this is the first case-control study to comprehensively compare maternal and neonatal outcomes of pregnant women with COVID-19 pneumonia to those with non–COVID-19 pneumonia and without pneumonia. We found that SARS-CoV-2 infection caused generally mild respiratory symptoms in pregnant women. Clinical signs and symptoms mainly included fever and pneumonia, but other respiratory symptoms were less common. Our results echo the findings of a previous study in pregnant women with SARS in Hong Kong, which reported that fever was the dominant presenting symptom [17]. However, it is of note that most patients did not have any symptoms on admission. For the purpose of screening for suspected cases, we asked all prelaboring pregnant women to take low-dose chest CT scans with their abdominal region covered, and found that 2.1% fulfilled the criteria of COVID-19 pneumonia (patchy shadowing and ground glass opacity in single or both lungs). This highlights the need of enhancing screening for COVID-19 pneumonia on admission, as well as strengthening infection control measures in obstetric wards during the epidemics.

Compared to other patients with COVID-19 pneumonia, pregnant women generally had no or mild respiratory symptoms. None of our patients developed severe respiratory complications to require critical care. Laboratory investigations on admission found lower counts of WBCs, neutrophils, CRP, and ALT in pregnant women, compared to the nonpneumonia controls. These findings are consistent with those reported in other hospitalized COVID-19 patients who often had lymphopenia and decreased WBC count [11]. Slightly increased WBCs, neutrophils, eosinophils, and CRP were found in postpartum blood tests. We also notice that confirmed and suspected cases shared similar dynamic profiles, suggesting that laboratory test results might not be very useful in making differential diagnosis.

An earlier clinical descriptive study by Chen et al reported the clinical features of 9 pregnant women with laboratory-confirmed COVID-19 infection cases, all of whom underwent cesarean delivery in 1 tertiary hospital in Wuhan [8]. In our study, in addition to 14 cesarean delivery patients, we also reported 2 pregnant women who had a full-term vaginal delivery and were confirmed with COVID-19 pneumonia on the day of delivery. We observed a higher incidence rate of premature delivery in confirmed cases (18.8%), but none was due to severe maternal respiratory failure. This rate was higher than in suspected patients (16.7%) and in the 2 control groups (~5%) of our study, but lower than the rate of 44% in confirmed COVID-19 pneumonia patients reported by Chen et al [8]. All these events of preterm delivery were triggered by gestational complications such as premature rupture of membranes and placental bleeding, which might not be directly related to COVID-19 pneumonia. We did not observe any deaths or events of severe

complications associated with COVID-19 pneumonia that required critical care in the pregnant women and newborns. Hence, the adverse effects of COVID-19 pneumonia on pregnancy appear to be less severe than those of SARS-CoV and MERS-CoV. Three pregnant women died during the 2003 SARS outbreak in Hong Kong, and preterm delivery was as high as 80% [18]. Although no maternal deaths were recorded in the MERS-CoV outbreak, more than half of their newborns required critical care, and nearly 30% eventually died [19]. Zhu et al reported 10 newborns born to mothers with COVID-19 pneumonia in Wuhan; 1 newborn died from multiple organ failure and disseminated intravascular coagulation (DIC), and another had DIC but recovered. However, none of these 10 newborns tested positive for SARS-CoV-2 [20]. A previous study also reported that SARS-CoV infection could increase the risk of preterm delivery in the second trimester and spontaneous abortion in the first trimester [17]. Because all of the patients in our study and others were in the third trimester, the potential adverse effect of SARS-CoV-2 infection in the first and second trimesters remains to be investigated.

In response to this unprecedented COVID-19 outbreak in Wuhan, confirmed and suspected COVID-19 infection has been included as an indication for cesarean delivery in our hospital, because there was only 1 negative pressure operation room suitable for airborne precautions. Two patients had vaginal delivery in positive pressure labor rooms before they were diagnosed with COVID-19 pneumonia. No transmission events occurred in the doctors and midwives, who were wearing a full set of personal protective equipment (N95 respirators, protective gown, coveralls, gloves, and goggles) during the delivery procedure. Healthcare workers need to stay vigilant against COVID-19 infection when there is an epidemic in the neighborhood or when pregnant women have a travel history to an epidemic area within 14 days. As suggested by Favre et al, vaginal delivery could be considered for the benefit of patients, when there is a labor room properly equipped for airborne precautions [21]. All healthcare workers in close contact should strictly adhere to contact and airborne precautions in addition to standard precautions.

Similar to 2 previous reports of pregnant women with confirmed COVID-19 infection [8, 22], we did not find any evidence to support the vertical transmission of SARS-CoV-2 from mother to fetus via placenta or during cesarean delivery. However, 1 newborn in Wuhan, who was born to a mother with COVID-19 pneumonia under emergent cesarean delivery, tested positive for SARS-CoV-2 at 36 hours after birth [23]. None of these studies has detected the virus in breast milk, cord blood, or placenta. Therefore, there is limited evidence of vertical transmission via placenta or during cesarean delivery. Our study also adds some evidence to suggest that the risk of vertical transmission during vaginal delivery might also be trivial. There were 2 patients with vaginal delivery: 1 of them had symptom onset 2 days after delivery, and another had delivery during the course of illness. Neither of their newborns had respiratory systems after birth. Unfortunately, neither of them gave us consent to collect the respiratory specimens of their neonates. Given the small sample size of our study, the possibility of vertical transmission during vaginal delivery still cannot be ruled out.

There are a few caveats in our study. First, this is a retrospective case-control study from a single center, which could be subject to recall bias and selection bias. Second, we collected the data of 16 pregnant women with laboratory-confirmed COVID-19 pneumonia and 18 suspected cases with typical CT imaging. Although this is the largest number of pregnant women with COVID-19 pneumonia in the literature thus far, the sample size is still relatively small. Nevertheless, given the ongoing global pandemic caused by SARS-CoV-2, we believe our study could be one of the important clinical studies to guide clinical diagnosis and treatment to this vulnerable group.

CONCLUSIONS

In this study, we did not find any evidence to suggest that COVID-19 pneumonia causes severe maternal and neonatal complications among pregnant women who had vaginal or cesarean delivery. Few patients presented respiratory symptoms on admission. The profile of laboratory investigations was not different from pregnant women without pneumonia, except that a transient increase of WBCs, neutrophils, and CRP was found in postpartum blood tests. Given the time delay in PCR tests, chest CT scans in the third trimester might be an effective way of screening for COVID-19 pneumonia in pregnant women, particularly in areas with ongoing epidemics.

Notes

Author contributions. L. Yang and M. P. originated and designed the study. Y. L., K. L., L. Yue, Q. L., and Y. O. contributed to data collection and cleaning. L. H. conducted data analysis. N. L., L. H., G. S., L. C., and L. Yang interpreted the findings and drafted the manuscript. All authors approved the final version of this manuscript.

Data sharing. All data and materials used in this work are available based on reasonable request to the corresponding author.

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