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OBSTETRICS

Coronavirus disease 2019 in pregnant women: a report based on 116 cases

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BACKGROUND: The coronavirus disease 2019, caused by severe acute respiratory syndrome coronavirus 2, is a global public health emergency. Data on the effect of coronavirus disease 2019 in pregnancy are limited to small case series.

OBJECTIVE: To evaluate the clinical characteristics and outcomes in pregnancy and the vertical transmission potential of severe acute respiratory syndrome coronavirus 2 infection.

STUDY DESIGN: Clinical records were retrospectively reviewed for 116 pregnant women with coronavirus disease 2019 pneumonia from 25 hospitals in China between January 20, 2020, and March 24, 2020. Evidence of vertical transmission was assessed by testing for severe acute respiratory syndrome coronavirus 2 in amniotic fluid, cord blood, and neonatal pharyngeal swab samples.

RESULTS: The median gestational age on admission was 38^{+0} (interquartile range, 36^{+0}—39^{+1}) weeks. The most common symptoms were fever (50.9%, 59/116) and cough (28.4%, 33/116); 23.3% (27/116) patients presented without symptoms. Abnormal radiologic findings were found in 96.3% (104/108) of cases. Of the 116 cases, there were 8 cases (6.9%) of severe pneumonia but no maternal deaths. One of 8 patients who presented in the first trimester and early second trimester had a missed spontaneous abortion. Of 99 patients, 21 (21.2%) who delivered had preterm birth, including 6 with preterm premature rupture of membranes. The rate of spontaneous preterm birth before 37 weeks' gestation was 6.1% (6/99). One case of severe neonatal asphyxia resulted in neonatal death. Furthermore, 86 of the 100 neonates tested for severe acute respiratory syndrome coronavirus 2 had negative results; of these, paired amniotic fluid and cord blood samples from 10 neonates used to test for severe acute respiratory syndrome coronavirus 2 had negative results.

CONCLUSION: Severe acute respiratory syndrome coronavirus 2 infection during pregnancy is not associated with an increased risk of spontaneous abortion and spontaneous preterm birth. There is no evidence of vertical transmission of severe acute respiratory syndrome coronavirus 2 infection when the infection manifests during the third trimester of pregnancy.

Key words: ascending infection, coronavirus, coronavirus disease 2019, COVID-19, pandemic, pneumonia, pregnancy, pregnancy outcomes, pregnant women, preterm birth, PTB, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2, spontaneous abortion, spontaneous preterm birth, spontaneous PTB, vertical transmission

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global public health emergency. Since the first case of COVID-19 pneumonia was reported in Wuhan, Hubei Province, China, in December 2019, the infection has spread rapidly to the rest of China and beyond.[1–3] Coronaviruses are enveloped, nonsegmented, positive-sense RNA viruses belonging to the family Coronaviridae, order Nidovirales.[4] The epidemics caused by 2 β-coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), have caused more than 10,000 cumulative cases in the past 2 decades, with mortality rates of 10% for SARS-CoV and 37% for MERS-CoV.[5–9] Severe acute respiratory syndrome coronavirus 2 belongs to the same β-coronavirus subgroup, and it has genome similarity of about 80% and 50% with SARS-CoV and MERS-CoV, respectively.[10] The latest report from the World Health Organization (WHO) on March 3, 2020, estimated the global mortality rate of COVID-19 to be 3.4%,[11] although recent reports that have used appropriate adjustment for the case ascertainment rate and time lag between symptoms onset and death suggest the mortality rate to be lower at 1.4%.[12]

Pregnant women are especially susceptible to respiratory pathogens and severe pneumonia, because of the physiological changes in the immune and cardiopulmonary systems (eg, diaphragm elevation, increased oxygen consumption, and edema of the respiratory tract mucosa), which can render them intolerant to hypoxia. The 1918 influenza pandemic caused a mortality rate of 2.6% in the overall population, but 37% among pregnant women.[13] In 2009, pregnant women were reported to be at an increased risk for complications from the pandemic H1N1 2009 influenza virus infection, with a higher estimated rate of hospital admission than in the general population.[14] In 2003, it was reported that approximately 50% of pregnant women who received a diagnosis for SARS-CoV were admitted to the intensive care unit (ICU), around 33% of pregnant women with SARS-CoV required mechanical ventilation, and the mortality rate was as high as 25% for these women.[15]

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AJOG at a Glance

Why was this study conducted?

- To report maternal and neonatal outcome of coronavirus disease 2019 (COVID-19) in pregnancy of 116 patients.

Key findings

- There were 8 cases (6.9%, 8/116) of severe pneumonia but no maternal deaths.
- One of 8 patients (12.5%, 1/8) who presented in the first trimester and early second trimester had a missed spontaneous abortion.
- The rate of spontaneous preterm birth before 37 weeks' gestation was 6.1% (6/99).
- Eighty-six of 100 neonates tested for severe acute respiratory syndrome coronavirus (SARS-CoV-2), had negative results.

What does this add to what is known?

- SARS-CoV-2 infection during pregnancy is not associated with an increased risk of spontaneous abortion and spontaneous preterm birth.
- There is no evidence of vertical transmission of SARS-CoV-2 infection when the infection manifests during the third trimester of pregnancy.

To date, data on the effect of COVID-19 in pregnancy are limited to small case series.[16–20] This multicenter study aimed to evaluate the clinical characteristics and outcomes of 116 pregnant women with COVID-19 pneumonia and the vertical transmission potential of SARS-CoV-2 infection.

Materials and Methods

Study design and participants

This study was reviewed and approved by the Medical Ethics Committee of Zhongnan Hospital of Wuhan University (reference 2020004) and Renmin Hospital of Wuhan University (reference WDRY2020-K015, WDRY2020-K016). For the collection of clinical data, verbal consent from pregnant women was obtained, and written informed consent was waived considering the urgent need to collect data. Written informed consent was obtained from pregnant women who agreed to the testing of biological samples and neonatal pharyngeal swab samples. Data were analyzed and interpreted by the authors. All the authors reviewed the manuscript and vouched for the accuracy and completeness of the data and for the adherence of the study to the protocol. The funding agencies did not participate in the study design, data collection, data analysis, or writing of the report.

Data collection

This was an expanded series from 4 previous small case series.[16,18–20] We obtained the medical records and compiled clinical and outcome data for consecutive pregnant women with COVID-19 pneumonia from 25 hospitals (Supplemental Material) within and outside of Hubei Province between January 20, 2020, and March 24, 2020. COVID-19 was diagnosed on the basis of the New Coronavirus Pneumonia Prevention and Control Program published by the National Health Commission of China.[21–24] A laboratory-confirmed case of COVID-19 was defined as a positive result by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) assay of maternal pharyngeal swab specimens. At the peak of the COVID-19 outbreak within Hubei Province, China, cases with relevant symptoms, marked epidemiologic history, and typical chest computed tomography (CT) findings were clinically diagnosed as COVID-19 pneumonia, whereas the viral nucleic acid test was reported to have a false-negative rate of 30%.[22]

Complete epidemiologic history, clinical symptoms or signs, laboratory and radiologic findings, treatment measures, and outcome data were extracted from electronic medical records by a team of experienced clinicians and curated with customized data collection form. All laboratory testing and radiologic assessments, including chest CT, were performed according to the clinical care needs of the patient. Laboratory assessments consisted of complete blood cell count, liver and renal function, electrolytes, C-reactive protein, and coagulation testing. We determined the presence of a radiologic abnormality based on the documentation or description in medical charts. The date of onset of disease was defined as the day when the symptoms were noticed. The intervals from onset of disease to hospital admission and delivery were recorded. Data on pregnancy and neonatal outcome, including gestational age at delivery, mode of delivery, indication for cesarean delivery, complications, neonatal birthweight, Apgar scores, and neonatal intensive care unit (NICU) admission, were collected. The date of data cutoff for outcomes was March 24, 2020. The degree of severity of COVID-19 pneumonia (severe vs nonsevere) was defined by the Infectious Diseases Society of America/American Thoracic Society guidelines for community-acquired pneumonia.[25]

Two study investigators (J.Y. and J.J.) independently reviewed the data collection forms to verify data accuracy. Major disagreement between them was resolved by consultation with a third investigator (H.Y.).

Sample collection

Amniotic fluid samples from patients with COVID-19 pneumonia were obtained through direct needle syringe aspiration at the time of cesarean delivery. Cord blood and neonatal pharyngeal swab samples were collected immediately after delivery in the operating or delivery room. Evidence of vertical transmission was evaluated by testing for the presence of SARS-CoV-2 in these clinical samples. In addition, vaginal secretion samples were collected from the lower third of the vagina on admission, and breast milk samples were

collected at first lactation in Zhongnan Hospital of Wuhan University and Renmin Hospital of Wuhan University. All samples were processed at the State Key Laboratory of Virology, Institute of Medical Virology, School of Basic Medical Sciences, Wuhan University, and Laboratory Medicine Center of Renmin Hospital of Wuhan University for further testing. Sample collection, processing, and laboratory testing complied with WHO guidance.[26] All samples, as described above, were tested for SARS-CoV-2 using qRT-PCR with the Chinese Center for Disease Control and Prevention—recommended kit.

Study outcomes

The primary endpoint was admission to ICU, use of mechanical ventilation, or death. Secondary endpoints were the rates of spontaneous abortion, preterm delivery, cesarean delivery, and neonatal COVID-19.

Statistical analysis

Continuous variables were expressed as means (standard deviations [SDs]) or medians (interquartile ranges [IQRs]) or simple ranges, as appropriate. Categorical variables were summarized as numbers and percentages. The results were presented in the total study population and according to the methods of diagnosis for COVID-19 pneumonia. The statistical software SPSS for Windows version 23 (SPSS, IL) was used for data analyses.

Results

Clinical characteristics

The characteristics and outcomes of the study population of 116 cases, including 65 cases of laboratory-confirmed and 51 cases of clinically diagnosed COVID-19 pneumonia, are presented in Table 1. The mean age was 30.8 (range 24—41) years, and median gestational age on admission was 38^{+0} (IQR 36^{+0}—39^{+1}) weeks. In 59.5% (69/116) of cases, women reported a history of relevant environmental exposure, and 32.8% (38/116) had contact with infected persons. The most common symptoms at presentation were fever in 50.9% (59/116), cough in 28.4% (33/116), and fatigue in 12.9% (15/116) of cases. In 23.3% (27/116) of cases, there were no signs or symptoms of the disease, 77.8% (21/27) of which were clinically diagnosed with COVID-19 pneumonia. All these 21 cases underwent investigations because of marked epidemiologic history.

Of note, there were 9 patients (7.8%, 9/116) with gestational diabetes and 5 (4.3%, 5/116) with hypertensive disorders, including 4 (3.4%, 4/116) with preeclampsia, and these pregnancy complications were unrelated to COVID-19 pneumonia. There were 8 patients (6.9%, 8/116) with severe pneumonia, all required ICU admission, 1 of whom (0.9%, 1/116) required plasmapheresis, 6 (5.2%, 6/116) received noninvasive ventilation, 2 (1.7%, 2/116) received invasive mechanical ventilation, and 1 (0.9%, 1/116) received extracorporeal membrane oxygenation. Clinical details of severe pneumonia cases are presented in the Supplemental Table. A total of 76 (65.5%, 76/116) cases had been discharged. There were no cases of maternal death.

On admission, lymphocytopenia was present in 44.0% (51/116) of the patients and leukopenia was present in 24.1% (28/116) of patients, according to pregnancy-specific reference ranges.[27] Elevated levels of C-reactive protein were found in 44% of the patients. Patients with severe disease had more prominent laboratory abnormalities (including lymphocytopenia and leukopenia) than those with nonsevere disease. In cases that underwent chest CT scans at the time of admission, 96.3% (104/108) revealed abnormal results. Of note, all cases of clinically diagnosed COVID-19 pneumonia exhibited abnormal chest CT findings (Table 2).

Pregnancy outcomes

Of the 116 pregnant women with COVID-19 pneumonia, 8 cases presented before 24 weeks' gestation. One case (12.5%, 1/8) was complicated with a missed spontaneous abortion at 5^{+2} weeks at presentation with fever and fatigue. In the remaining 7 ongoing cases, 4 had reached 20 weeks, and morphology scan revealed normal anatomy and fetal growth. Ten cases presented between 24 and 33^{+6} weeks, of which 7 cases are ongoing, 1 delivered at term, and 2 cases (20%, 2/10) had iatrogenic preterm delivery. One had a cesarean delivery at 28^{+1} weeks on the same day of admission for severe pneumonia; 1 had a cesarean delivery at 31^{+6} weeks on the same day of admission for twin pregnancy. Of the 22 cases presented between 34 and 36^{+6} weeks, 19 delivered preterm, 2 delivered at term, and 1 case remained undelivered. There were 27.3% (6/22) women who had preterm premature rupture of membranes (PPROM), 2 cases (33.3%, 2/6) resulted in vaginal delivery; 4 cases (66.7%, 4/6) required cesarean delivery, with 3 cases indicated for symptomatic COVID-19 pneumonia and 1 because of history of previous cesarean delivery. There are 16 ongoing pregnancies, with 1 patient with gestational diabetes mellitus and the other 15 patients with no fetal or maternal complications reported as of March 24, 2020.

A total of 99 pregnant women, including 1 with twin pregnancy, delivered their babies during hospitalization, of whom 85.9% (85/99) underwent cesarean delivery and 14.1% (14/99) had a vaginal delivery (Table 3). Cesarean delivery was indicated for COVID-19 pneumonia in 38.8% (33/85), previous cesarean delivery in 18.8% (16/85), fetal distress in 10.6% (9/85), and failure to progress in 5.9% (5/85) (Table 3). The rates of preterm delivery before 34 weeks and 37 weeks were 2.0% (2/99) and 21.2% (21/99), respectively (Table 3). Among the 21 preterm deliveries, 28.6% (6/21) had PPROM, 2 of which resulted in vaginal deliveries. There were no cases with spontaneous onset of labor. The rate of spontaneous preterm birth before 37 weeks was therefore 6.1% (6/99). No cases of spontaneous preterm delivery before 34 weeks were reported.

There were no cases of fetal deaths. Among 100 neonates, there was 1 case of severe neonatal asphyxia. There were 47.0% (47/100) neonates transferred to the NICU for further treatment (Table 3). There was 1 case of neonatal death. The mother of this neonate experienced severe pneumonia and

TABLE 1
Demographics, baseline characteristics, and clinical outcomes of coronavirus disease 2019 infection in pregnant women

Clinical characteristics	All patients (n=116)	Laboratory confirmed (n=65)	Clinically diagnosed (n=51)
Age, y			
Mean±SD	30.8±3.8	30.3±3.7	31.3±4.0
Range	24.0–41.0	24.0–40.0	24.0–41.0
Gestational age on admission, wk			
Median (IQR)	38.0 (36.0, 39.1)	36.7 (33.8, 38.4)	39.0 (38.0, 39.4)
Range	$5–41^{+2}$	$5–41^{+2}$	30–41
$<13^{+6}$, n (%)	4 (3.4)	4 (6.2)	0
$14–27^{+6}$, n (%)	6 (5.2)	6 (9.2)	0
$28–36^{+6}$, n (%)	30 (25.9)	24 (36.9)	6 (11.8)
≥37, n (%)	76 (65.5)	31 (47.7)	45 (88.2)
Parity			
Nulliparous, n (%)	64 (55.2)	37 (56.9)	27 (52.9)
Multiparous, n (%)	52 (44.8)	28 (43.1)	24 (47.1)
Epidemiologic history	107 (92.3)	65 (100)	42 (82.3)
Relevant environmental exposure, n (%)	69 (59.5)	39 (60.0)	30 (58.8)
Contact with infected person, n (%)	38 (32.8)	26 (40.0)	12 (23.5)
Symptoms			
Fever[a], n (%)	59 (50.9)	45(69.2)	14 (27.5)
Cough, n (%)	33 (28.4)	28 (43.1)	5 (9.8)
Fatigue, n (%)	15 (12.9)	13 (20.0)	2 (3.9)
Shortness of breath, n (%)	9 (7.8)	8 (12.3)	1 (2.0)
Sore throat, n (%)	10 (8.6)	10 (15.4)	0
Myalgia, n (%)	6 (5.2)	5 (7.7)	1 (2.0)
Dyspnea, n (%)	3 (2.6)	3 (4.6)	0
Diarrhea, n (%)	1 (0.9)	1 (1.5)	0
No symptoms, n (%)	27 (23.3)	6 (9.2)	21 (41.2)
Pregnancy complications			
Gestational diabetes mellitus	9 (7.8)	3 (4.6)	6 (11.8)
Hypertensive disorders	5 (4.3)	2 (3.1)	3 (5.9)
Preeclampsia	4 (3.4)	1 (1.5)	3 (5.9)
Disease severity			
Severe	8 (6.9)	6 (9.2)	2 (3.9)
Nonsevere	108 (93.1)	59 (90.8)	49 (96.1)
Treatment			
Antibiotic therapy	109 (94.0)	58 (89.2)	51 (100)
Antiviral therapy	63 (54.3)	48 (73.8)	15 (29.4)
Use of corticosteroid	37 (31.9)	26 (40.0)	11 (21.6)
ICU admission	8 (6.9)	6 (9.2)	2 (3.9)
Noninvasive ventilation	6 (5.2)	6 (9.2)	0

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(continued)

TABLE 1
Demographics, baseline characteristics, and clinical outcomes of coronavirus disease 2019 infection in pregnant women *(continued)*

Clinical characteristics	All patients (n=116)	Laboratory confirmed (n=65)	Clinically diagnosed (n=51)
Invasive mechanical ventilation	2 (1.7)	2 (3.1)	0
ECMO	1 (0.9)	1 (1.5)	0
Plasmapheresis	1 (0.9)	0	1 (2.0)
Clinical outcomes			
Remained in hospital	40 (34.5)	24 (36.9)	16 (31.4)
Discharged	76 (65.5)	41 (63.1)	35 (68.6)
Died	0	0	0

ECMO, extracorporeal membrane oxygenation; *ICU*, intensive care unit; *IQR*, interquartile range; *SD*, standard deviation.

[a] Including postpartum fever cases. Data are expressed as n (%). Outcomes were followed up until March 24, 2020.

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septic shock after admission and required ICU admission for invasive ventilation. The neonate (male) was delivered at 35^{+2} weeks' gestation by cesarean delivery, and severe neonatal asphyxia was reported. He had 1-minute, 5-minute, and 10-minute Apgar scores of 1, 1, and 1, respectively. He was treated with invasive ventilation and died within 2 hours of birth. As of March 24, 2020, 76.0% (76/100) neonates had been discharged, and 23.0% (23/100) neonates remained in the hospital (Table 3).

There were 86.0% (86/100) of neonates who underwent testing for SARS-CoV-2 viral nucleic acid on pharyngeal swab samples and the results were negative. Of these 86 neonates, paired amniotic fluid and cord blood samples from 10 neonates tested for SARS-CoV-2 had negative results.[16,20] In addition, 6 patients consented and had their vaginal secretion samples tested; the test results were negative.[20] Twelve patients had their breast milk samples tested, and the test results were negative.[16,20]

Comments

Principal findings

We report clinical data from 116 pregnant women with COVID-19 pneumonia. This descriptive study found that (1) the clinical characteristics of these patients with COVID-19 pneumonia during pregnancy were similar to those of nonpregnant adults with COVID-19 pneumonia, as previously reported[28,29]; (2) 23.3% (27/116) of pregnant patients did not present with symptoms, but most of these patients were diagnosed as having COVID-19 pneumonia based on clinical criteria during the peak of the outbreak in Hubei Province, China; (3) 6.9% (8/116) of pregnant patients experienced severe pneumonia that required ICU admission and none died as of March 24, 2020; (4) the rate of spontaneous abortion was 12.5% (1/8); (5) the rate of preterm birth before 37 weeks was 21.2% (21/99), one-third of which had PPROM that resulted in 6.1% (6/99) spontaneous preterm birth rate; and (6) 86.0% (86/100) neonates who were tested for SARS-CoV-2 viral nucleic acid on pharyngeal samples had negative results; 10 of these 86 neonates had paired amniotic fluid and cord blood samples that also had negative results for SARS-CoV-2.

Clinical implications

To date, summarized data from 5 small series, with a total of 56 pregnant women[16–20] diagnosed as having COVID-19 during the second and third trimester, indicated that the most common symptoms at presentation were fever and cough; two-third of the patients had lymphopenia and increased C-reactive protein, and 83% of cases had chest CT scan revealing multiple patches of ground-glass opacity in the lungs. The rate of preterm delivery before 37 weeks was 44%, and 94% of cases had cesarean delivery. Our data were an expanded series that included 33 published cases.[16,18–20] We had reported clinical, laboratory, and radiologic characteristics that are similar to published pregnant and nonpregnant cases of COVID-19 pneumonia.[28,29] Notably, our series included cases of COVID-19 diagnosed by clinical criteria. Most of these cases presented at term, and all women exhibited abnormal chest CT findings. During the peak of the COVID-19 outbreak, it was considered acceptable to not wait for repeated qRT-PCR testing to establish diagnosis. There were fewer cases of severe pneumonia in those who were diagnosed clinically compared with laboratory-confirmed cases; cesarean delivery rate and neonatal outcome were similar between the 2 groups.

Normal pregnancy has been proposed to be a state of physiological activation of the innate limb of the immune response. Pregnant women with acute infection were reported to display a more activated phenotype.[30] In our study, 8 of 116 (6.9%) pregnant women experienced severe COVID-19 pneumonia, which is similar to the rate of severe disease that has been reported across China.[28,29] This finding can be attributed to our proactive and aggressive management of diagnosed pregnant cases to minimize

TABLE 2
Laboratory and radiologic findings of pregnant women with coronavirus disease 2019 on admission

Laboratory and radiologic findings	All patients (n=116)	Laboratory confirmed (n=65)	Clinically diagnosed (n=51)
Leucocytes (*10^9/L; reference range[a])			
Median (IQR)	7.9 (5.9, 10.6)	7.5 (5.2, 9.8)	8.9 (6.7, 11.0)
Decreased, n (%)	28 (24.1)	20 (30.8)	8 (15.7)
Normal, n (%)	85 (73.3)	42 (64.6)	43 (84.3)
Increased, n (%)	3 (2.6)	3 (4.6)	0
Lymphocytes (*10^9/L; reference range, 1.1−3.2)			
Median (IQR)	1.2 (0.9, 1.6)	1.0 (0.8, 1.6)	1.3 (1.1, 1.6)
Decreased, n (%)	51 (44.0)	38 (58.5)	13 (25.5)
Normal, n (%)	64 (55.1)	26 (40.0)	38 (74.5)
Increased, n (%)	1 (0.9)	1 (1.5)	0
C-reactive protein concentration (mg/L; reference range, 0−10)			
Median (IQR)	9.3 (3.3, 28.0)	16.6 (5.3, 37.9)	5.9 (2.6, 21.6)
Increased, n (%)	51 (44.0)	32 (49.2)	19 (37.3)
Normal, n (%)	53 (45.7)	24 (36.9)	29 (56.9)
CT chest findings (n=108)			
Patchy shadowing or ground-glass opacity, n (%)	104 (96.3)	53 (93.0)	51 (100%)
Negative finding, n (%)	4 (3.7)	4 (7.0)	0

CT, computed tomography; *IQR*, interquartile range.

[a] Reference range in pregnancy: first trimester, 5.7−13.6 *10^9/L; second trimester, 5.6−14.8 *10^9/L; and third trimester, 5.9−16.9 *10^9/L (from *Williams Obstetrics 25th Edition*[27]). Data are expressed as n (%). Increased means over the upper limit of the reference range and decreased means below the lower limit of the reference range.

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the risk of disease progression. There was a lack of clarity at the beginning of the COVID-19 outbreak, and we could only base our practice on past experience with SARS-CoV. As we encountered more COVID-19 cases, we adapted our management, and care was provided by a multidisciplinary team including obstetricians, intensivists, obstetrical anesthetists, virologists, microbiologists, neonatologists, and infectious-disease specialists.

It has been reported that viral pneumonia in pregnant women is associated with an increased risk of preterm birth, fetal growth restriction (FGR), and perinatal mortality.[31] Based on the nationwide population-based data, it has been indicated that pregnant women with viral pneumonia other than COVID-19 (n=1462) have an increased risk of preterm birth, FGR, and having a newborn with low birthweight and Apgar score <7 at 5 minutes compared with those without pneumonia (n=7310).[32] A case series of 12 pregnant women with SARS-CoV in Hong Kong, China, reported 3 maternal deaths; 4 of 7 patients (57%) who presented in the first trimester had spontaneous abortion, 4 of 5 patients (80%) who presented after 24 weeks had preterm birth, and 2 mothers recovered without delivery but their ongoing pregnancies were complicated by FGR.[9] Our study found reassuring data suggesting that the risk of spontaneous abortion is not increased in pregnant women with SARS-CoV-2 infection from the background risk of the general population.[33] Our data also suggests that although the risk of any preterm birth before 37 weeks' gestation is increased, COVID-19 is not associated with an increased risk of spontaneous preterm birth before 37 weeks. For the 15 cases of iatrogenic preterm birth, cesarean delivery was indicated for pneumonia (n=5), twin pregnancy (n=1), transverse lie with placenta previa (n=1), previous cesarean delivery (n=3), fetal distress (n=3), preeclampsia (n=1), and poor obstetrical history (n=1).

Research implications

One main focus of this study was to investigate the possibility of vertical transmission of SARS-CoV-2 infection. We chose to evaluate amniotic fluid, cord blood, and neonatal pharyngeal swab samples at birth to ascertain the possibility of vertical transmission. Our results indicated that SARS-CoV-2 was negative in all of the above biological samples, suggesting that no intrauterine fetal infection occurred because of SARS-CoV-2 infection during the third trimester of pregnancy when the time interval from clinical manifestation to delivery was up to 38 days. Our findings are in agreement with what was observed with SARS-CoV. However, 2 recent research letters reported on 3 neonates born to women with confirmed COVID-19 who tested positive for immunoglobulin G and immunoglobulin M antibodies despite having a negative viral nucleic acid result,[34,35] raising the possibility of vertical transmission, but more data are needed. In addition, this study explored whether vaginal delivery increases the risk of mother-to-child transmission during delivery by evaluating the vaginal secretions of COVID-19 cases at presentation and these samples had negative results. In this expanded series, our results further showed negative results for breast milk samples from 12 mothers with COVID-19 that were tested for SARS-CoV-2.[16]

Strengths and limitations

This is the biggest pregnant series to date. Unlike the other case series, our data were collected using a standardized methodology by a team of experienced

TABLE 3
Pregnancy and neonatal outcomes of coronavirus disease 2019

Outcome	All deliveries (n=99)	Laboratory confirmed (n=50)	Clinically diagnosed (n=49)
Mode of delivery			
Cesarean delivery, n (%)	85 (85.9)	44 (88.0)	41 (83.7)
Vaginal delivery, n (%)	14 (14.1)	6 (12.0)	8 (16.3)
Indication of cesarean delivery[a]			
COVID-19 pneumonia, n (%)	33 (38.8)	19 (43.2)	14 (34.1)
Previous cesarean delivery, n (%)	16 (18.8)	8 (18.2)	8 (19.5)
Fetal distress, n (%)	9 (10.6)	7 (15.9)	2 (4.9)
Failure to progress, n (%)	5 (5.9)	3 (6.8)	2 (4.9)
Preeclampsia, n (%)	4 (4.7)	1 (2.3)	3 (7.3)
Abnormal fetal growth, n (%)	2 (2.4)	0	2 (4.9)
Placenta previa, n (%)	3 (3.5)	0	3 (7.3)
Others, n (%)	13 (15.3)	6 (13.6)	7 (17.1)
Onset of symptoms to delivery, d			
Median (IQR)	2.5 (1.0, 6.7)	4.0 (1.0, 7.0)	4.0 (0.5, 8.5)
Range	0–38.0	0–38.0	0–22.0
Gestational age at delivery			
Median (IQR)	38.4 (37.3, 39.4)	38.0 (36.6, 39.2)	39.0 (38.1, 39.4)
Range	28.1–41.3	28.1–41.3	31.9–41.0
<34 wk, n (%)	2 (2.0)	1 (2.0)	1 (2.0)
34–36^{+6} wk, n (%)	19 (19.2)	15 (30.0)	4 (8.2)
≥37 wk, n (%)	78 (78.8)	34 (68.0)	44 (89.8)
Preterm delivery before 34 wk, n (%)	2 (2.0)	1 (2.0)	1 (2.0)
Spontaneous labor-PPROM	0	0	0
Preterm delivery before 37 wk, n (%)	21 (21.2)	16 (32.0)	5 (10.2)
Spontaneous labor-PPROM	6 (6.1)	3 (6.1)	3 (6.1)
Clinical outcome of neonates (n=100)[b]			
Neonatal birthweight (g)	3108±526	3087±504	3130±553
Apgar 1-min, median (IQR)	9 (8, 9)	9 (8, 9)	9 (9, 9)
Apgar 5-min, median (IQR)	10 (9, 10)	10 (9, 10)	10 (10, 10)
Severe neonatal asphyxia, n (%)	1 (1.0)	1 (2.0)	0
Transferred to NICU, n (%)	47 (47.0)	17 (34.0)	30 (60.0)
Remained in hospital, n (%)	23 (23.0)	13 (26.0)	10 (20.0)
Discharged, n (%)	76 (76.0)	36 (72.0)	40 (80.0)
Neonatal death, n (%)	1 (1.0)	1 (2.0)	0

COVID-19, coronavirus disease 2019; *IQR*, interquartile range; *PPROM*, preterm premature rupture of membranes; *NICU*, neonatal intensive care unit.

[a] n (cesarean delivery)=85; [b] including 1 pair of twins. Data are expressed as n (%). Outcomes were followed up until March 24, 2020.

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clinicians, curated with customized data collection form, and verified independently by 2 investigators. There are some notable limitations. First, there were only 8 cases of COVID-19 pneumonia during the first and early second trimester of pregnancy. There are 7 cases with ongoing pregnancy, and we do not have complete data on the risk of

congenital anomalies and FGR. Furthermore, 4 cases have reached 20 weeks and a morphology scan has revealed normal anatomy and fetal growth. Because the COVID-19 pandemic has reached a critical stage, we believe it is important to report our pregnant cases in relation to the risk of spontaneous abortion, preterm birth, and vertical transmission, without waiting for complete outcome data to be available. This would delay this publication by several months. Second, we included cases that were diagnosed on the basis of clinical criteria in this series. According to the WHO, these cases would have been classified as probable cases of COVID-19 pneumonia. Given that all clinically diagnosed cases had patchy shadowing or ground-glass opacity on chest CT scan and marked epidemiologic exposure, we believed it was important to include these cases in the total cohort and present the clinical characteristics and outcome data separately from the laboratory-confirmed cases. Third, 34.5% (40/116) of the patients remained in the hospital and some outcomes were unknown at the time of data cutoff. Fourth, we missed patients who were asymptomatic or had nonsevere disease and who received treatment at home; hence our study cohort may represent the more severe end of COVID-19. Fifth, we cannot comment on the risk of vertical transmission when the clinical manifestation to delivery interval is beyond 38 days. Sixth, only a small number of cases had vaginal secretion sample collection at presentation and breast milk samples evaluated for SARS-CoV-2. This study has the limitation to conclude that vaginal delivery and breastfeeding do not increase the risk of mother-to-child transmission of SARS-CoV-2. Intrapartum vaginal secretion samples followed by placental tissue, amniotic fluid, and amnion-chorion interface swap samples should be tested for SARS-CoV-2 to explore whether there is a risk of ascending infection during labor.

Conclusion

The clinical characteristics of pregnant women with COVID-19 pneumonia are similar to those of nonpregnant adults with COVID-19 pneumonia. Currently, there is no evidence that pregnant women with COVID-19 are more prone to experience severe pneumonia than nonpregnant patients. Reassuringly, the risks of spontaneous abortion and spontaneous preterm birth are not increased. There is no evidence of vertical transmission of SARS-CoV-2 when the infection manifests during the third trimester of pregnancy. Ongoing collection of clinical data and research is currently underway with the aim to answer some of the questions in relation to the risk of congenital infection, intrapartum management, and mode of delivery. ■

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SUPPLEMENTAL TABLE

Clinical characteristics, pregnancy outcomes, and treatment for severe cases

Case	1	2	3	4	5	6	7	8
Clinical characteristics								
Date of admission	2020/2/1	2020/1/28	2020/1/31	2020/2/17	2020/1/28	2020/1/26	2020/2/5	2020/2/2
Age	32	35	34	33	28	30	35	32
Occupation	/	Nurse	/	Bank staff	Company employee	/	/	/
Gravidity	5	2	4	3	2	1	6	3
Parity	2	1	1	1	1	0	2	1
Gestational age on admission (wk)	35^{+2}	34^{+2}	37^{+6}	36^{+2}	39^{+0}	39^{+1}	38^{+2}	28^{+1}
Residence	Zhongshan, Guangdong	Wuhan, Hubei	Zaoyang, Hubei	Wuhan, Hubei	Wuhan, Hubei	Wuhan, Hubei	Badong, Hubei	Huangshi, Hubei
Epidemiologic history	+	+	+	+	+	+	+	+
Description of epidemiology	Relevant environmental exposure (Xiaogan, Hubei)	Contacts with infected person	Contacts with person who came back from Wuhan	Relevant environmental exposure (Wuhan, Hubei)	Relevant environmental exposure (Wuhan, Hubei)	Relevant environmental exposure (Wuhan, Hubei)	Contacts with person who came back from Wuhan	Relevant environmental exposure (Wuhan, Hubei)
Other family members affected	-	-	+	-	-	-	+	-
Onset to delivery (d)	4	Onset after delivery	0	10	Onset after delivery	Onset after delivery	5	7
Complications	-	PPROM	Anemia; tachycardia	PPROM; elevated aminotransferase	Anemia; hypothyroidism	Preeclampsia	HBsAg (+); hypoproteinemia	Anemia
Onset of symptoms								
Fever/postpartum fever	+	-	+	+	+	+	+	+
Cough	+	+	-	-	-	-	+	+
Fatigue	-	-	+	-	-	-	+	-
Shortness of breath	-	+	-	-	-	-	-	-
Sore throat	+	-	-	-	-	-	-	+
Dyspnea	-	-	+	-	-	-	-	-
Heart rate (bpm)	128	79	118	100	78	100	113	102
Respiratory rate (bpm)	23	30	20	20	20	20	28	25
Mean arterial pressure (mm Hg)	83	97	96	86	127	101	58	87

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(continued)

SUPPLEMENTAL TABLE

Clinical characteristics, pregnancy outcomes, and treatment for severe cases *(continued)*

Case	1	2	3	4	5	6	7	8
Laboratory characteristics								
White blood cell count (10^9/L)	6.80	7.10	10.65	11.67	14.95	11.50	4.00	13.16
Low or normal leukocyte count ($<$5.9–16.9 *10^9/L)	+	+	+	+	+	+	+	+
Lymphocyte count (10^9/L)	0.884	0.69	1.42	1.5	0.54	1.02	0.3	1.09
Lymphopenia ($<$1.1 *10^9/L)	+	+	-	-	+	+	+	+
Neutrophil count (10^9/L)	/	6.01	8.87	9.83	4.78	7.41	/	10.64
Platelet count (10^9/L)	160	184	269	282	202	274	146	271
CRP (mg/L)	60.8	73.63	102.8	41.2	152.4	52.74	94	41.98
Elevated CRP ($>$10 mg/L)	+	+	+	+	+	+	+	+
Prothrombin time (s)	/	11.6	10.3	18.5	9.8	10.9	/	11.7
Activated partial thromboplastin time (s)	/	30.7	33.4	40	31.7	24.5	/	32.5
D-dimer (mg/L)	/	3.93	1.28	/	1.31	1.94	6.54	0.68
Elevated aminotransferase ($<$45U/L, AST$<$35U/L)	+	+	+	+	-	-	+	-
ALT (U/L)	142	51	72	181	17.6	6.9	90	17
AST (U/L)	235	22	50	213	28.2	12.6	59	28
Creatine kinase (U/L)	/	24	32.94	638	40.18	54.62	/	23
Creatine kinase-MB (U/L)	/	9	1.59	137	19.66	13.86	/	11
Lactate dehydrogenase (U/L)	/	452	322.7	638	196.3	195.5	/	276
Total bilirubin (mmol/L)	/	7.8	19.78	123.1	6.1	1.8	19.2	14.8
Blood urea nitrogen (mmol/L)	2.3	3.4	1.52	5.5	4.21	3.35	4.44	1.24
Creatinine (μmol/L)	85	46.8	56.62	152.6	54.6	49.1	61.98	38
Procalcitonin (ng/mL)	7.29	0.89	0.89	1.56	0.222	0.122	0.05	0.31
Blood gas analysis								
pH	7.41	7.27	7.41	/	/	/	/	7.42
Lactate (mmol/L)	4	3.4	/	/	/	/	/	1.8
PaO_2 (mm Hg)	60.5	117	66	/	/	/	/	86

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(continued)

SUPPLEMENTAL TABLE

Clinical characteristics, pregnancy outcomes, and treatment for severe cases *(continued)*

Case	1	2	3	4	5	6	7	8
$PaCO_2$ (mm Hg)	17.7	73	36.7	/	/	/	/	24
Confirmatory test (SARS-CoV-2 by qRT-PCR)	+	+	+	-	+	/	+	+
CT evidence of pneumonia								
Bilateral distribution of patchy shadows or ground-glass opacity		+	+	+	+	+	+	+
Local patchy shadows or ground-glass opacity	+							
Mode of delivery	CS	Vaginal delivery	CS	Vaginal delivery	CS	CS	Vaginal delivery	CS
Indication for CS	Previous CS Pneumonia Septic shock	/	Previous CS Pneumonia	/	Previous CS Pneumonia	Preeclampsia Pneumonia	/	Pneumonia
Treatment								
Oxygen support (nasal cannula)	+	+	+	+	+	+	+	+
Antibiotic therapy	Piperacillin and sulbactam sodium, imipenem	Moxifloxacin, cephalosporin, imipenem, linezolid, meropenem, polymyxin B, sulfanilamide	Moxifloxacin, cefoperazone/ sulbactam	Moxifloxacin, meropenem	Cefaxone/ tazobactam	Cefoperazone/ sulbactam	Azithromycin, levofloxacin, vancomycin	Cefamandole, ornidazole, cefmenoxime
Antiviral therapy	Oseltamivir	Ganciclovir, arbidol, interferon	Lopinavir, peramivir, arbidol, interferon	Arbidol	Oseltamivir, interferon	Interferon	Aciclovir, oseltamivir, ribavirin, Interferon	Arbidol
Use of corticosteroid	-	Methylprednisolone, prednisone	Methylprednisolone	Methylprednisolone	-	-	-	Methylprednisolone
Admitted to an ICU (d)	+	30	+	14	6	3	16	15
Noninvasive ventilation (d)	Withdrew ventilation 36 d after CS	8	6	-	6	-	3	3
Invasive mechanical ventilation (d)		11	-	-	-	-	-	-
ECMO (d)	Withdrew ECMO 26 d after CS	-	-	-	-	-	-	-
Plasmapheresis	-	-	-	+	-	-	-	-

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(continued)

SUPPLEMENTAL TABLE

Clinical characteristics, pregnancy outcomes, and treatment for severe cases *(continued)*

Case	1	2	3	4	5	6	7	8
Duration of hospitalization (d)	Remain in hospital	Remain in hospital	29	16	14	4	16	15
Pregnancy outcome								
Gestational age at delivery (wk)	35^{+2}	34^{+2}	37^{+6}	36^{+2}	39^{+1}	39^{+1}	38^{+3}	28^{+1}
Birthweight (g)	2700	2350	3500	2670	3750	3800	3200	1530
Preterm delivery	+	+	-	+	-	-	-	+
Low birthweight	-	+	-	-	-	-	-	+
Apgar score (1-min, 5-min)	1, 1	9, 10	9, 10	8, 9	10, 10	10, 10	9, 10	8, 9
Neonatal asphyxia	+	-	-	-	-	-	-	-
Transferred to NICU	+	-	-	+	-	-	-	+
Noninvasive ventilation	-	-	-	-	-	-	-	-
Invasive mechanical ventilation	+	-	-	-	-	-	-	+
Neonatal death	+	-	-	-	-	-	-	-
Neonatal outcomes	Died	Discharged	Discharged	Discharged	Discharged	Discharged	Discharged	Remained in hospital
Fetal death or stillbirth	-	-	-	-	-	-	-	-

Outcomes were followed up until March 22, 2020.

ALT, alanine transaminase; *AST*, aspartate aminotransferase; *COVID-19*, coronavirus disease 2019; *CRP*, C-reactive protein; *CT*, computed tomography; *ECMO*, extracorporeal membrane oxygenation; *ICU*, intensive care unit; *NICU*, neonatal intensive care unit; *PPROM*, preterm premature rupture of membranes; *qRT-PCR*, quantitative reverse transcriptase polymerase chain reaction; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2.

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Supplemental Material

List of hospitals from which clinical records were retrospectively reviewed for 116 pregnant women with coronavirus disease 2019 pneumonia

Zhongnan Hospital of Wuhan University

Renmin Hospital of Wuhan University

The Central Hospital of Wuhan

Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

The Central Hospital of Suizhou

Yichang Central People's Hospital

Beijing YouAn Hospital

Hanchuan People's Hospital of Hubei Province

Jiangnan Branch of the Yichang Central People's Hospital

Egang Hospital

Jianli County People's Hospital

Zaoyang First People's Hospital

Xinglin Branch of the First Affiliated Hospital of Xiamen University

Maternal and Child Hospital of Hubei Province

The First People's Hospital of Xiaochang County

Maternal and Child Health and Family Planning Service Center of Dawu County

Anlu Pu'ai Hospital

Affiliated Taihe Hospital of Hubei University of Medicine

Badong County People's Hospital in Hubei Province

Xiangyang Central Hospital

Jingmen No. 1 People's Hospital

Jingzhou Maternal and Child Health Hospital

The First People's Hospital of Xianning

Huangshi Maternity and Children's Health Hospital

Yangxin People's Hospital in Hubei Province

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