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Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study



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Summary

Background In December, 2019, coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China. The number of affected pregnant women is increasing, but scarce information is available about the clinical features of COVID-19 in pregnancy. This study aimed to clarify the clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19.

Methods In this retrospective, single-centre study, we included all pregnant women with COVID-19 who were admitted to Tongji Hospital in Wuhan, China. Clinical features, treatments, and maternal and fetal outcomes were assessed.

Findings Seven patients, admitted to Tongji Hospital from Jan 1, to Feb 8, 2020, were included in our study. The mean age of the patients was 32 years (range 29–34 years) and the mean gestational age was 39 weeks plus 1 day (range 37 weeks to 41 weeks plus 2 days). Clinical manifestations were fever (six [86%] patients), cough (one [14%] patient), shortness of breath (one [14%] patient), and diarrhoea (one [14%] patient). All the patients had caesarean section within 3 days of clinical presentation with an average gestational age of 39 weeks plus 2 days. The final date of follow-up was Feb 12, 2020. The outcomes of the pregnant women and neonates were good. Three neonates were tested for SARS-CoV-2 and one neonate was infected with SARS-CoV-2 36 h after birth.

Interpretation The maternal, fetal, and neonatal outcomes of patients who were infected in late pregnancy appeared very good, and these outcomes were achieved with intensive, active management that might be the best practice in the absence of more robust data. The clinical characteristics of these patients with COVID-19 during pregnancy were similar to those of non-pregnant adults with COVID-19 that have been reported in the literature.

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Introduction

In December, 2019, a series of pneumonia cases of unknown cause emerged in Wuhan (Hubei, China), with clinical presentations resembling viral pneumonia.^{1–3} Deep sequencing analysis from lower respiratory tract samples indicated a novel coronavirus that was later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).⁴ Thus far, more than 49 000 confirmed cases, including health-care workers, have been identified in Wuhan, and many cases have been confirmed in other provinces in China, and in Italy, Iran, South Korea, Spain, and other countries worldwide.^{5–9} The number of pregnant women with COVID-19 is also increasing; there were already more than 30 pregnant patients with COVID-19 in China by Feb 8, 2020.

At present, information regarding the epidemiology and clinical features of pneumonia in pregnancy caused by COVID-19 is scarce.¹⁰ Furthermore, there is no previous treatment experience with COVID-19 in pregnancy. Up to now, seven liveborn infants have been delivered by pregnant women with COVID-19 at Tongji Hospital

(Wuhan, China). We aim to describe epidemiological, clinical, laboratory, and radiological characteristics, treatment, and maternal and fetal outcomes of full-term pregnant women confirmed to have SARS-CoV-2 infection.

Methods

Study design and participants

For this retrospective, single-centre study, we recruited patients from Jan 1 to Feb 8, 2020, at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China). According to the arrangements put in place by the Chinese Government, pregnant women were admitted centrally to the hospital from all of Wuhan without selectivity. All pregnant women in Tongji Hospital who were diagnosed with COVID-19 according to the WHO interim guidance were enrolled in this study.⁴ Among them, three patients were directly admitted to Tongji hospital for fever and four patients were transferred from other hospitals across Wuhan. This study was approved by the ethics committee of Tongji Hospital, and written informed consent was

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Research in context

Evidence before this study

We searched PubMed and Google Scholar on Feb 8, 2020, for articles describing the features of patients in pregnancy infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; previously known as 2019 novel coronavirus [2019-nCoV]), using the search terms “novel coronavirus” or “2019 novel coronavirus” or “2019-nCoV” and “pregnancy” or “maternal infection” or “neonatal outcomes”. We also searched the China National Knowledge Infrastructure database and Wanfang Data using the same terms in Chinese. We found several epidemiological, clinical, laboratory, management, and outcomes studies regarding the epidemiology and clinical features of pneumonia caused by SARS-CoV-2. We identified no reports on management of pregnant women with COVID-19 and scarce evidence of mother-to-child vertical transmission.

Added value of this study

We assessed the incubation period, clinical manifestations, laboratory findings, chest CT scans, maternal and fetal

management, therapeutic schedule, and maternal and fetal outcomes of full-term pregnant women confirmed to have COVID-19 pneumonia caused by SARS-CoV-2 infection. With intensive, active management, the outcomes of the pregnant women and neonates were good. Although one neonate was found to be infected with SARS-CoV-2 36 h postpartum, up to the follow-up day, no pneumonia and other clinical symptoms and signs were found in all seven neonates. To the best of our knowledge, we provide the first evidence that clinical features of COVID-19 in full-term pregnant women were similar to those of non-pregnant adult patients with COVID-19 and outcomes were good following intensive active management of the disease.

Implications of all the available evidence

The outcomes observed in late pregnancy appear very good in light of all the evidence and we suggest that intensive, active management might be best practice in the absence of more robust data.

obtained from the patients for the publication of individual data from before enrolment when data were collected retrospectively.

Procedures

We obtained epidemiological, demographic, clinical, laboratory, management (multidisciplinary assessment, delivery methods, and treatments), and maternal and fetal (complications and follow-up visits) outcomes data from patients' medical records. The incubation period was defined as the interval between the potential earliest date of contact of the transmission source (wildlife or person with suspected or confirmed case) and the potential earliest date of symptom onset (ie, cough, fever, fatigue, or myalgia). If data were missing from the records or clarification was needed, data were obtained by direct communication with attending doctors and other healthcare providers. All data were checked by two physicians (WL and NY).

Laboratory confirmation of SARS-CoV-2 infection was done at Tongji Hospital. Throat swab specimens from the upper respiratory tract that were obtained from all patients at admission were maintained in viral transport medium. SARS-CoV-2 infection was confirmed by real-time RT-PCR using the same protocol as described previously.³ Real-time RT-PCR detection reagents were provided by Tongji Hospital. Other respiratory viruses, including influenza A virus, influenza B virus, respiratory syncytial virus, parainfluenza virus, and adenovirus were also tested for by real-time RT-PCR. Sputum or endotracheal aspirates were obtained at admission for the identification of possible causative bacteria or fungi. Additionally, all patients were given chest CT examinations. All the patients delivered infants

by caesarean section, and then the neonates were transferred to the neonatology department.

Outcomes

We describe epidemiological data, demographics, signs and symptoms on admission, comorbidities, laboratory results, coinfection with other respiratory pathogens, chest radiography and CT findings, treatment received for COVID-19, and clinical maternal, fetal, and neonatal outcomes.

Statistical analysis

Statistical analysis was done using SPSS, version 20.0. Continuous variables are directly expressed as ranges. Categorical variables are expressed as number (%).

Role of the funding source

The sponsor of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and takes final responsibility for the decision to submit for publication.

Results

Between Jan 1 and Feb 8, 2020, seven pregnant patients with COVID-19 were included in this study (table 1). None of them had a history of exposure to Huanan Seafood Wholesale Market, and none of them were medical staff. Three of the seven patients were primiparous and four were multiparous, with a mean age of 32 years (range 29–34 years) and mean gestational age of 39 weeks plus 1 day (range 37 weeks to 41 weeks plus 2 days) at admission. Two (29%) patients had chronic diseases (hypothyroidism and polycystic ovary

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age, years	34	30	31	33	29	34	34
Gravida (parity)	2 (0)	2 (0)	2 (1)	5 (1)	1 (0)	2 (1)	2 (1)
Gestational age at admission, weeks + days	39 + 6	38 + 5	41 + 2	37	40 + 4	38 + 2	38 + 4
Exposure to Huanan seafood market	No	No	No	No	No	No	No
Contact history of epidemic area	Yes	Yes	Yes	Yes	Yes	Yes	Yes
History of chronic basic diseases	Hypothyroidism	Polycystic ovary syndrome	No	No	No	No	No
Pregnancy complications	No	No	No	Uterine scarring	No	Uterine scarring	Uterine scarring
Clinical manifestations of obstetrics	Abdominal pain (labour)	No	Abdominal pain (premonitory labour)	Increased fetal movement	Abdominal pain (premonitory labour)	Abdominal pain (premonitory labour)	No
Pneumonia-related manifestations							
Fever (days)	Yes (3)	Yes (4)	Yes (14)	No	Yes (3)	Yes (4)	Yes (8)
Cough	No	No	No	Yes	No	No	No
Shortness of breath	No	Yes	No	No	No	No	No
Diarrhoea	No	No	Yes	No	No	No	No
Incubation period, days	5	7	4	2	9	5	3

Table 1: Maternal characteristics of seven patients with COVID-19

syndrome) and three (43%) patients had uterine scarring. The average incubation period was 5 days (range 2–9 days). On admission, six (86%) patients had fever, one (14%) patient had cough, one (14%) patient had shortness of breath, and one (14%) patient had diarrhoea (table 1).

Clinical outcomes were followed up to Feb 12, 2020. Data from laboratory tests showed that all patients had a normal leucocyte count and five (71%) had neutrophil levels above the normal range (appendix 2 pp 1–2). Lymphocytes were below the normal range in five (71%) patients, platelets were below the normal range in two (29%) patients, and D-dimer was above the normal range in all patients. Two (29%) patients had differing degrees of liver function abnormality, as well as increased alanine aminotransferase or aspartate aminotransferase, or both. Regarding infection-related biomarkers, procalcitonin (measured in six patients) and erythrocyte sedimentation rate (measured in five patients) were above the normal ranges in four (57%) patients and all patients had abnormally high concentrations of C-reactive protein. Interleukin-6 was tested in four patients, all of whom had levels above the normal range. Two patients had H1N1 and one had *Legionella pneumophila* co-infections. According to chest CT, six (86%) patients had bilateral pneumonia and the remaining one (14%) had unilateral pneumonia (appendix 2 pp 1–2; figure).

All patients received oxygen therapy, via nasal catheter, in isolation. All patients received antiviral treatment, including oseltamivir (75 mg every 12 h, orally), ganciclovir (0.25 g every 12 h, intravenously), and interferon (40 µg daily, atomisation inhalation) and arbidol tablets (200 mg three times daily, orally; appendix 2 p 2). Traditional

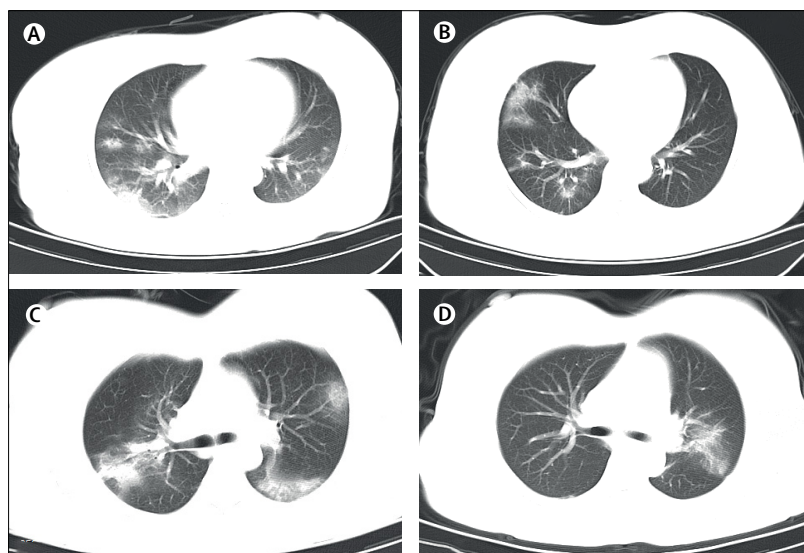


Figure: Chest CT of four patients

Patient 1 (A), patient 3 (B), patient 4 (C), and patient 6 (D). The brightness of both lungs is diffusely decreased, showing a large area of multiple ground-glass opacities or patchy shadow with an uneven density.

Chinese medicines, such as Jinyebaidu granules and Lianhuaqingwen capsules, were also given. All patients were given antibiotic treatment: two (29%) patients were treated with a single antibiotic and five (71%) patients were given combination therapy. The antibiotics used were cephalosporins, quinolones, and macrolides. Five (71%) patients were also treated with methylprednisolone after caesarean section (appendix 2 p 2).

All the patients had caesarean section after consultation with a multidisciplinary team. The time of delivery was

See Online for appendix 2

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Pregnancy outcome	Discharged	Discharged	Discharged	Discharged	Discharged	Discharged	Discharged
Neonatal outcome	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Birthweight, g	3250	3350	3200	3000	3500	3300	3250
Apgar score (1 min)	8–9	8–9	8–9	8–9	8–9	8–9	8–9
Apgar score (5 min)	9–10	9–10	9–10	9–10	9–10	9–10	9–10
Admission to neonatology department	Yes	No	Yes	No	No	No	Yes
Nucleic acid test of SARS-CoV-2	Positive (36 h)	Not tested	Negative	Not tested	Not tested	Not tested	Negative
Days of follow-up	40	28	28	28	28	28	28
Neonatal complications	No	No	No	No	No	No	No

None of the women were admitted to intensive care. Normal=no respiratory symptoms or fever or neonatal complications, such as neonatal respiratory distress syndrome, feeding abnormalities, or abnormal growth or development. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Table 2: Maternal and neonatal outcomes of seven patients with COVID-19

from 37 weeks to 41 weeks plus 5 days, with a mean of 39 weeks plus 2 days (appendix 2 p 3). Regarding anaesthesia, six patients had combined spinal and epidural anaesthesia and one received general anaesthesia. Intraoperative oxygen saturation was maintained at a minimum of 98%, mean intraoperative infusion volume was 1036 mL (range 500–1500 mL), mean intraoperative bleeding volume was 193 mL (50–300 mL), and mean oxytocin use was 26 units (20–30 units).

The outcomes of the pregnant women were good. There were no intensive care unit admissions for mothers throughout the study period, including before and after delivery. At the end of follow-up (March 12, 2020), all patients had been discharged from the hospital per the following discharge criteria: body temperature returned to normal for more than 3 days; respiratory symptoms improved significantly; pulmonary imaging showed a significant improvement in acute exudative lesions; and nucleic acid test of respiratory specimens such as results of sputum and nasopharyngeal swabs were negative twice in a row (sampling interval ≥ 24 h). The neonatal birthweights and Apgar scores were normal. Four infants were taken home and were not tested for SARS-CoV-2; no fever, pathological jaundice, or other symptoms were reported during the follow-up call at 28 days after birth. Another three infants remained for observation in the neonatology department and were tested for SARS-CoV-2. Nucleic acid test for the throat swab of one neonate (child of patient 1) was positive at 36 h after birth; nucleic acid tests for the other two were negative. Subsequently, this infected neonate was transferred to Wuhan Children's Hospital, a designated hospital for children infected with COVID-19. After admission, the neonate had no fever and cough, with mild shortness of breath symptoms. Chest x-ray revealed mild pulmonary infection. The shortness of breath relieved quickly under neonatal care and monitoring. The neonate was discharged after 2 weeks following two consecutive negative nucleic acid test results. At 28 days after birth, the remaining three neonates were healthy and had no respiratory symptoms or fever (table 2).

Discussion

This is a descriptive study on the clinical characteristics and obstetric and neonatal outcomes of pregnant women infected with COVID-19. At present, few cases of infected pregnant women have been reported. This study is one of the first to report the maternal, fetal, and neonatal outcomes of pregnant women with COVID-19 who are in their third trimesters. We have presented seven cases of COVID-19 in late pregnancy with good outcomes for both mother and infant.

Human coronaviruses are among the most common pathogens that cause respiratory infection. SARS-CoV-2 has enveloped virions that measure about 50–200 nm in diameter with a single positive-sense RNA genome.¹¹ COVID-19 is transmitted through respiratory droplets, physical contact, and aerosols, and there is evidence of human-to-human transmission.^{12–13} None of our pregnant patients had a history of exposure to Huanan Seafood Wholesale Market, but all of them lived in the epidemic area. In terms of clinical manifestations, the common symptoms of these pregnant women at the onset of COVID-19 were fever and cough, and the less common symptoms were diarrhoea and shortness of breath. Laboratory tests showed that absolute lymphocyte counts were reduced, C-reactive protein, erythrocyte sedimentation rate, and D-dimer were increased, and leucocytes were normal in most of the seven pregnant patients. In our study, these patients showed a pattern of clinical characteristics similar to those reported in non-pregnant adults with COVID-19.

Because COVID-19 is an emerging infectious disease, the optimal treatment for affected individuals has not yet been established. In our study, most patients were treated with ribavirin, corticosteroids, and antibiotics. Although remdesivir and other antiviral drugs have been used in the clinical treatment of patients with COVID-19, no data of their safety and efficacy as COVID-19 treatments have been published. No safety concerns have been identified related to the use of traditional Chinese medicine in our study. Five of our patients were treated with steroids (methylprednisolone 1–2 mg/kg per day); however, animal

studies have shown that the use of large doses of corticosteroids during pregnancy might lead to fetal malformation, and some studies have shown that the easy passage of corticosteroids through the placenta might increase the incidence of low birthweight in infants.¹⁴ Therefore, steroids were only used after caesarean section in this study. Thus far, no complications related to the steroids have been recorded in the mothers and infants, but their safety still needs more data to draw conclusions. Because of alterations in hormone levels and decreased lung volumes caused by increases in uterus size during pregnancy, patients might have a more rapid clinical deterioration. Additionally, the influence of the virus itself and these antivirals and Chinese medicines on fetal development is unknown. Therefore, for full-term pregnant women, after consultation with a multidisciplinary team, delivering as soon as possible might be a better choice for the sake of safety considerations. Timely use of antibiotics to prevent secondary bacterial infections and strengthen immune support treatment can reduce complications and mortality, so antibiotics were used routinely after operation.¹⁵ COVID-19 pneumonia in pregnancy is a complicated clinical scenario, and a multidisciplinary team of medical personnel is needed to care for and treat these patients comprehensively. Relevant specialty areas include obstetrics, infectious diseases, internal medicine, paediatrics, anaesthesia, psychology, and infection control. No medical staff had SARS-CoV-2 infections during the whole treatment period.

The sequence similarity between SARS and SARS-CoV-2 is as high as 79%;¹⁶ the mortality rate of SARS infection is 10%,¹⁷ and the mortality rate of SARS in pregnant women was 25%.¹⁸ Studies have reported that the mortality rate of patients with COVID-19 is about 1.4%.¹⁹ In our study, the maternal, fetal, and neonatal outcomes of pregnant women with COVID-19 pneumonia are better than those with SARS infection. This might be associated with our small number of cases and short delivery time (ie, as soon as possible after diagnosis). Previous studies have shown no evidence of perinatal SARS infection in infants born to mothers who had SARS infection during pregnancy.^{18,20} One neonate in our study was infected with COVID-19 36 h after birth. However, the viral nucleic acid tests of the placenta and cord blood in this patient were negative for SARS-CoV-2, so intrauterine vertical transmission might not have occurred; thus, further study is needed.

However, this study has several limitations. First, only seven pregnant women with COVID-19 were included in the analyses. More infected pregnant women and comparative studies (eg, cohorts, case-control) should be analysed to get a more comprehensive understanding of COVID-19 in pregnancy. Second, all enrolled patients were in the third trimester, so the effect of the virus infection on the fetus in the first or second trimester is unknown. Third, due to the short time of the outbreak, the long-term outcomes of the neonates and whether

mother-to-child transmission exists require further study. However, the data in this study permit an early assessment of the clinical characteristics and maternal and fetal outcomes of COVID-19 in late pregnancy in women in Wuhan, China.

In conclusion, the clinical characteristics of these patients with COVID-19 during late pregnancy are similar to those reported by non-pregnant adults with COVID-19. The maternal, fetal, and neonatal outcomes of those pregnant women infected in late pregnancy appear very good, and these outcomes are achieved with intensive, active management, which might be the best practice in absence of more robust data. Long-term outcomes and potential mother-to-child vertical transmission needs further study.

Contributors

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. NY, WL, QK, and ZX were responsible for study concept and design. SW, XL, YL, JX, HL, DD, SC, WZ, and LF were responsible for the acquisition, analysis, or interpretation of data. NY, WL and JW were responsible for drafting the manuscript. NY and JW were responsible for statistical analysis.

Declaration of interests

We declare no competing interests.

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