Clinical characteristics and outcomes of childbearing-age women with Coronavirus disease 2019 in Wuhan: a retrospective, single-center study

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Abstract

Background: Since December 2019, an outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly worldwide. Previous studies on pregnant patients were limited.

Objective: The objective of our study was to evaluate the clinical characteristics and outcomes of pregnant and non-pregnant women with COVID-19.

Methods: This study retrospectively collected epidemiological, clinical, laboratory, imaging, management, and outcome data of 43 childbearing-age women patients (including 17 pregnant and 26 non-pregnant patients) who presented with laboratory-confirmed of COVID-19 in Tongji Hospital, Wuhan, China, from Jan 19 to Mar 2, 2020. Clinical outcomes were followed up to Mar 28, 2020.

Results: Of 43 childbearing-age women in this study, none developed severe adverse illness and died. The median ages of pregnant and non-pregnant women were 33.0 and 33.5 years, respectively. Pregnant women had a markedly higher proportion of history exposure to hospitals within two weeks before onset (53% vs 19%, P=.02), and a lower proportion of other family members affected (24% vs 73%%, P=.004). Fever (47% vs 69%) and cough (53% vs 46%) were common onsets of symptoms for two groups. Abdominal pain (24%), vaginal bleeding (6%), reduced fetal movement (6%), and increased fetal movement (13%) were observed at onset in pregnant patients. Higher neutrophil and lower lymphocyte percent were observed in the pregnant group (79% vs 56%, P<.001; 15% vs 33%, P<.001, respectively). In both groups were observed elevated concentration of high sensitivity C-reactive protein, erythrocyte sedimentation rate, aminotransferase and lactate dehydrogenase. Concentrations of alkaline phosphatase and D-dimer in the pregnant group were significantly higher than those of the non-pregnant group (119.0 vs 48.0 U/L, P<.001; 2.1vs 0.3?g/mL, P<.001). Both pregnant (4/10; 40%) and non-pregnant (8/15; 53%) women were tested positive for influenza A virus. A majority of pregnant and non-pregnant groups received antiviral (76% vs 96%) and antibiotic (76% vs 88%) therapy. Additionally, both pregnant (2/11; 18%) and non-pregnant (2/19; 11%) recovered women re-detected positive for SARS-CoV-2 after discharge.

Conclusions: The epidemiology, clinical and laboratory features of pregnant women with COVID-19 were diverse and atypical, which increased the difficulty of diagnosis. Most pregnant women with COVID-19 were mild and moderate, and rarely developed severe pneumonia and severe adverse outcomes.

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Clinical characteristics and outcomes of childbearing-age women with Coronavirus disease 2019 in Wuhan: a retrospective, single-center study

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ABSTRACT

Background: Since December 2019, an outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly in Wuhan and worldwide. However, previous studies on pregnant patients were limited.

Objectives: The objective of our study was to evaluate the clinical characteristics and outcomes of pregnant and non-pregnant women with COVID-19.

Methods: This study retrospectively collected epidemiological, clinical, laboratory, imaging, management, and outcome data of 43 childbearing-age women patients (including 17 pregnant and 26 non-pregnant patients) who presented with laboratory confirmed of COVID-19 in Tongji Hospital, Wuhan, China, from January 19 to March 2, 2020. Clinical outcomes were followed up to March 28, 2020.

Results: Of 43 childbearing-age women in this study, none developed severe adverse illness and or died. The median ages of pregnant and non-pregnant women were 33.0 and 33.5 years, respectively. Pregnant women had a markedly higher proportion of history exposure to hospitals within two weeks before onset (53% vs 19%, *P*=.02), and a lower proportion of other family members affected (24% vs 73%%, *P*=.004). Fever (47% vs 69%) and cough (53% vs 46%) were common onset of symptoms for two groups. Abdominal pain (24%), vaginal bleeding (6%), reduced fetal movement (6%), and increased fetal movement (13%) were observed at onset in pregnant patients. Higher neutrophil and lower lymphocyte percent were observed in pregnant group (79% vs 56%, *P*<.001; 15% vs 33%, *P*<.001, respectively). In both groups, we observed elevated concentration of high sensitivity C-reactive protein, erythrocyte sedimentation rate, aminotransferase and lactate dehydrogenase. Concentrations of alkaline phosphatase and D-dimer in pregnant group were significantly higher than those of non-pregnant group (119.0 vs 48.0 U/L, *P*<.001; 2.1vs 0.3μg/mL, *P*<.001). Both pregnant (4/10; 40%) and non-pregnant (8/15; 53%) women were tested positive for influenza A virus. A majority of pregnant and non-pregnant groups received antiviral (76% vs 96%) and antibiotic (76% vs 88%) therapy. Additionally, both pregnant (2/11; 18%) and non-pregnant (2/19; 11%) recovered women re-detected positive for SARS-CoV-2 after discharge.

Conclusions: The epidemiology, clinical and laboratory features of pregnant women with COVID-19 were diverse and atypical, which increased the difficulty of diagnosis. Most pregnant women with COVID-19 were mild and moderate, and rarely developed severe pneumonia and severe adverse outcomes.

Keywords: COVID-19; SARS-CoV-2; childbearing-age; pregnancy, clinical characteristics; outcomes.

Introduction

In December 2019, a cluster of cases of pneumonia of unknown etiology was identified in Wuhan, China [1]. Further investigation revealed these cases were caused by a novel coronavirus, which was termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Pneumonia caused by SARS-CoV-2 was termed coronavirus disease 2019 (COVID-19) [2,3]. In the past two decades, two human coronaviruses, including severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), can cause severe lower respiratory tract infections [4,5]. SARS-CoV-2 is similar to SARS-CoV as both of them belong to the beta coronavirus genus, and SARS-CoV-2 share more than 79.6% sequence identity with SARS-CoV [6]. As of Apr 18, 2020, the cumulative number of confirmed cases of COVID-19 infection in China had exceeded 86,700, and the death toll more than 4,600. The cumulative total number of confirmed cases has globally exceeded 2,350,000, and continues to increase [7,8]. The World Health Organization has designated the COVID-19 pandemic a Public Health Emergency of International Concern.

Pregnant women have been hypothesized to be susceptible to respiratory pathogens and severe adverse outcomes of pneumonia, due to the normal physiological changes during pregnancy, including altered cell-mediated immunity and changes in pulmonary [9,10]. Previous studies reported that pregnant women infected with SARS-CoV or MERS-CoV were more susceptible to severe adverse outcomes including maternal morbidity and death. The case fatality rate (CFR) for pregnant women infected SARS-CoV reached 25-30%, much higher than that of general population [11,12]. Data for pregnant women infected with MERS-CoV is scarce. A case series of five pregnant women with MERS reported the CFR reached 40% [13]. Unfortunately, there is limited experience on the COVID-19 infection during pregnancy, and all current studies are single-center trials. Two studies with a small sample size reported none of pregnant women with COVID-19 died yet [14,15]. However, currently there is no vaccine or specific treatment for COVID-19 infection.

In this study, we described the clinical, laboratory, imaging findings and clinical outcomes of 43 childbearing-age women patients (including 17 pregnant and 26 non-pregnant women) in Wuhan infected with SARS-CoV-2. This will provide an insight into the prevention and treatment of pregnant women with COVID-19.

Materials and Methods

Recruitment

This study retrospectively recruited patients from January 19 to March 2, 2020, at Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, Hubei, China. According to the arrangements put in place by the Chinese Government, pregnant and non-pregnant women patients were admitted to the designated hospitals for managing the COVID-19 in Wuhan without selectivity. All patients were diagnosed with COVID-19 according to “Diagnosis and Treatment Protocol for COVID-19 (Sixth Trial Edition)” released by the National Health Commission of the People’s Republic of China” [16].

17 pregnant and 32 non-pregnant women’s throat swabs tested positive for SARS-CoV-2 ribonucleic acid (RNA) from January 19 to March 2, 2020, among them, 6 non-pregnant women with comorbidities were excluded (two had hypertension, one had diabetes, one had a history of kidney transplantation, one had lymphoma, and one had connective tissue disease). The remaining 17 pregnant women and 26 non-pregnant women did not have any underlying comorbidities due to a chronic disease (such as hypertension, diabetes, or heart disease). Two groups were matched with respect to age, gender, timing of contacting COVID-19, and the proportion of health care workers. Additionally, all patients recruited were Chinese residents and lived in Wuhan with no exposure to Huanan seafood market in Wuhan.

This study was reviewed and approved by the Ethics Committee of Tongji Hospital, Tongji Medical

College of Huazhong University of Science and Technology (TJ-IRB20200222). Informed consent for this retrospective study was waived. The anonymous data was collected and analyzed to facilitate better clinical decisions and treatment.

Data collection

We retrospectively collected epidemiological, clinical, laboratory, imaging, management, and outcome data for all the COVID-19 patients in the two groups. Clinical outcomes were followed up to Mar 28, 2020. Two researchers evaluated the participants and reviewed the data independently, disagreements resolved by consensus (LW and XG).

Throat swab specimens for all patients were tested for SARS-CoV-2 at Tongji Hospital. SARS-CoV-2 was confirmed following the World Health Organization (WHO) guidelines for quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR) [17]. Throat-swab specimens from the upper respiratory tract that were obtained from all patients on admission were maintained in viral-transport medium. Other pneumonia-related respiratory pathogens including influenza A virus, influenza B virus, respiratory-syncytial virus, adenovirus, parainfluenza viruses, legionella pneumophila, mycoplasma pneumoniae, and chlamydia pneumoniae were tested by enzyme-linked immunosorbent assay (ELISA). qRT-PCR and ELISA detection reagents were provided by Tongji Hospital. Additionally, except for one pregnant woman who did not consent, all the remaining patients took a chest computed tomography (CT).

Statistical analysis

Statistical analysis was performed with SPSS Version 23.0 (IBM, Armonk, NY, USA). Continuous variables were presented as median (interquartile range). Categorical variables were expressed as number and proportion (%). Mann Whitney U test was applied for the comparing two groups of continuous variables. χ^2 test, or Fisher's exact test were applied for discrete variables of two groups. A p-value with a two-tailed with test less than 0.05 was considered as statistically significant.

Results

Demographics and clinical characteristics of pregnant women and non-pregnant women.

17 pregnant and 26 non-pregnant women with COVID-19 were included in this study. Among the 17 pregnant women, one was in her first trimester, three were in their second trimester, and 13 were in their third trimester. None of them had a history exposure to Huanan seafood market. 18% of pregnant and 19% of non-pregnant women were health care workers. Pregnant women had a higher proportion of history exposure to hospitals within two weeks before onset (53% vs 19%, *P*=.02) and a lower proportion of other family members infected with COVID-19 (24% vs 73%, *P*=.004) than non-pregnant women. The median ages of pregnant and non-pregnant women were 33.0 and 33.5 years respectively. The median time from symptoms onset to hospital presentation in the pregnant and non-pregnant groups were 2.0 and 4.0 days. Two (12%) pregnant women and three (11%) non-pregnant women were diagnosed as severe type on admission. None of the patients developed critical illness (Table 1).

The symptoms at onset of pregnant COVID-19 women were similar to non-pregnant women. The most common symptoms at onset of pregnant and non-pregnant women were fever (47% vs 69%) and cough (53% vs 46%). Other pneumonia-related symptoms at onset including fatigue, expectoration, chest tightness, and shortness of breath were less common. Chills and rigors, headache and myalgia had not been observed in pregnant women prior to the infection. Both pregnant (6%) and non-pregnant (15%) groups had diarrhea at onset. Two (12%) asymptomatic pregnant women were diagnosed during hospitalization routine tests as a requirement before delivery. Two (8%) asymptomatic non-pregnant women were diagnosed by testing for SARS-CoV-2 of throat swabs because they had a history of contacting with infected person. Additionally, pregnancy-related symptoms were also observed in pregnant women, including abdominal pain (24%), vaginal bleeding (6%), reduced fetal movement (6%), and increased fetal movement (13%). Two pregnant women only had pregnancy-related symptoms until being diagnosed (Table 1).

Table 1: Epidemiological and clinical features of pregnant and non-pregnant women with coronavirus disease 2019.

Variables	Median (interquartile range) / No. (%)			
	Total (n=43)	Pregnancy (n=17)	Non-pregnancy (n=26)	*P* value
Median (IQR) age, years	33.0 (30.0-37.0)	33.0 (30.0-35.0)	33.5 (31.0-38.0)	0.28
Gestational age on admission				
First trimester	-	1 (6)	-	-
Second trimester	-	3 (18)	-	-
Third trimester	-	13 (76)	-	-
Health care workers	8 (19)	3 (18)	5 (19)	0.77
Hospital exposure within 2 weeks before onset	14 (33)	9 (53)	5 (19)	0.02
Other family members affected	23 (53)	4 (24)	19 (73)	0.004
Median (IQR) time from onset of symptom to first outpatient visit, days	3.5 (1.0-7.0)	2.0 (0.9-10.8)	4.0 (1.0-7.0)	0.75
Clinical classification				
Mild	3 (7)	2 (12)	1 (4)	0.54
Moderate	35 (81)	13 (76)	22 (85)	-
Severe	5 (12)	2 (12)	3 (12)	-
Critical	0 (0)	0 (0)	0 (0)	-
Symptoms at onset				
Fever	26 (60)	8 (47)	18 (69)	0.15
Chills and rigors	2 (5)	0 (0)	2 (8)	0.67
Headache	1 (2)	0 (0)	1 (4)	0.83
Dizziness	1 (2)	1 (6)	0 (0)	0.83
Fatigue	5 (12)	1 (6)	4 (15)	0.93
Cough	21 (49)	9 (53)	12 (46)	0.66
Expectoration	9 (21)	3 (18)	6 (23)	0.96
Chest tightness	5 (12)	2 (12)	3 (12)	0.64
Shortness of Breath	2 (5)	1 (6)	1 (4)	0.67
Myalgia	1 (2)	0 (0)	1 (4)	0.83
Diarrhea	5 (12)	1 (6)	4 (15)	0.64
Asymptomatic	4 (9)	2 (12)	2 (8)	0.93
Abdominal pain	-	4 (24)	-	-
Vaginal Bleeding	-	1 (6)	-	-
Reduced fetal movements	-	1 (6)	-	-
Increased fetal movement	-	2 (13)	-	-

Laboratory and imaging characteristics of pregnant women and non-pregnant women

On admission, the median white blood cell count of patients in pregnant group with COVID-19 was significantly higher than non-pregnant group (7.8 vs 3.8×10^9/L, *P*<.001). Four (24%) pregnant women and zero (0%) non-pregnant women developed leukocytosis (white blood cell count >10.0 ×10^9/L). Neutrophil percentage and neutrophil count were higher in pregnant women (79% vs 56%, *P*<.001; 6.7 vs 2.3×10^9/L, *P*<.001, respectively) than non-pregnant women. Lymphopenia (lymphocyte count <1.0 ×10^9/L) occurred in seven (41%) of pregnant women and ten (38%) of non-pregnant women. There was no statistical difference in hemoglobin concentration and platelet count between the two groups. (Table 2)

In both pregnant and non-pregnant groups we observed elevated high sensitivity C-reactive protein (hs-CRP) (≥10 mg/L, 70% vs 33%) and erythrocyte sedimentation rate (ESR) (>20 mm/hr, 100% vs 53%). The mean concentrations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in the pregnant group were above the normal range, while non-pregnant group were normal. One patient in pregnant group had ALT of up to 882 U/L and AST of up to 783U/L. Concentration of lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) in pregnant group were observed higher than non-pregnant group (235.0 vs 193.0 U/L; 119.0 vs 48.0 U/L). Additionally, 92%

pregnant women were observed with an elevated D-dimer level, which was significantly higher than non-pregnant women (2.1 vs 0.3 μg/mL, *P*<.001) (Table 2).

Serological examination of pneumonia-associated pathogens was performed in pregnant and non-pregnant COVID-19 patients. Four (40%) of pregnant women and eight (53 %) of non-pregnant women tested positive for influenza A virus IgM. Other respiratory viruses had not been observed. One (10%) of legionella pneumophila and one (10%) of mycoplasma pneumoniae for pregnant women tested positive. Except for one pregnant women who refused to undergo chest CT scan, all patients accepted chest CT examination. 41(98%) patients displayed typical findings of pneumonia, in which 9(21%) patients had unilateral pneumonia and 32(76%) patients had bilateral pneumonia. (Table 2; Figure 1).

Table 2: Laboratory and imaging features of pregnant and non-pregnant women with coronavirus disease 2019.

Variables	Median (interquartile range) / No. (%)			
	Total (n=43)	Pregnancy (n=17)	Non-pregnancy (n=26)	*P* value
Routine blood test				
Median (IQR) white blood cell count, ×10^9/L	5.2 (3.8-7.6)	7.8 (6.6-10.2)	3.8 (3.6-5.1)	<0.001
<4.0 ×10^9/L	12 (28)	0 (0)	12 (46)	0.003
>10.0 ×10^9/L	4 (9)	4 (24)	0 (0)	0.04
Median (IQR) neutrophil percent, %	64.4 (55.9-79.4)	80.5 (72.2-85.2)	58.0 (49.4-63.0)	<0.001
>75 %	12 (28)	12 (71)	0 (0)	<0.001
Median (IQR) neutrophil count, ×10^9/L	3.3 (2.1-5.5)	6.7 (5.3-8.2)	2.3 (1.9-2.9)	<0.001
<1.5 ×10^9/L	1 (2)	0 (0)	1 (3)	0.83
Median (IQR) lymphocyte percent, %	24.9(14.4-35.9)	13.0 (11.6-20.1)	32.7 (26.4-39.7)	<0.001
<20 %	14 (33)	13 (77)	1 (4)	<0.001
Median (IQR) lymphocyte count, ×10^9/L	1.4 (1.0-1.8)	1.1 (0.9-1.6)	1.4 (1.0-2.0)	0.21
<1.0 ×10^9/L	17 (40)	7 (42)	10 (38)	0.86
Median (IQR) hemoglobin, g/L	122.5 (113.8-128.5)	117.0 (111.0-132.0)	123.0 (117.0-127.0)	0.86
<115 g/L	12 (28)	6 (35)	6 (23)	0.38
Median (IQR) platelet count, ×10^9/L	209.0 (160.0-242.0)	198.0 (138.0-227.3)	210.0 (171.0-250.3)	0.24
<150 ×10^9/L	10 (23)	6 (35)	4 (15)	0.25
Other laboratory features				
Median (IQR) high sensitivity C-reactive protein, mg/L	6.7 (0.7-25.3)	16.7 (7.1-47.6)	1.6 (0.4-13.0)	0.07
≥10mg/L, n/N (%)	14/31 (45)	7 /10 (70)	7/21 (33)	0.12
Median (IQR) procalcitonin, ng/mL	0.04 (0.03-0.05)	0.05 (0.03-0.17)	0.04 (0.03-0.05)	0.16
≥ 0.05ng/mL, n/N (%)	0/23 (0)	0/9 (0)	0/14 (0)	-
Median (IQR) erythrocyte sedimentation rate, mm/h	26.0 (12.0-41.0)	36.5 (26.3-82.0)	24.0 (7.0-38.0)	0.08
>20mm/h, n/N (%)	13/20 (65)	5/5 (100)	8/15 (53)	0.11
Median (IQR) alanine aminotransferase, U/L	16.5 (9.0-26.0)	13.0 (9.0-28.0)	23.0 (9.0-26.5)	0.72
≥ 45 U/L, n/N (%)	6/42 (14)	3/17 (18)	3/25 (12)	0.95
Median (IQR) aspartate aminotransferase, U/L	17.0 (13.0-28.3)	20.0 (14.0-42.5)	15.0 (10.5-25.0)	0.047
≥ 35 U/L, n/N (%)	9/42 (21)	5/17 (29)	4/25 (16)	0.51
Median (IQR) lactate dehydrogenase, U/L	204.0 (172.0-286.0)	235.0 (182.0-309.0)	193.0 (161.0-277.0)	0.13
≥250 U/L, n/N (%)	13/38 (34)	6/15 (40)	7/23 (30)	0.73
Median (IQR) alkaline phosphatase, U/L	57.5 (46.5-111.3)	119.0 (77.0-142.0)	48.0 (42.0-57.0)	<0.001
≥100 U/L, n/N (%)	11/38 (29)	10/15 (67)	1/23 (4)	<0.001
Median (IQR) creatinine, μmol/L	52.5 (46.0-61.0)	50.0 (43.2-59.5)	53.0 (48.0-62.5)	0.21
≥106 μmol/L, n/N (%)	0/38 (0)	0/14 (0)	0/24 (0)	-
Median (IQR) creatine kinase, U/L	51.5 (35.8-70.8)	81.0 (29.0-147.5)	48.5 (37.3-61.0)	0.34
≥140 U/L, n/N (%)	1/20 (5)	1/6 (17)	0/14 (0)	0.30
Median (IQR) D-dimer, μg/mL	0.7 (0.3-2.0)	2.1 (1.7-3.1)	0.3 (0.2-0.7)	<0.001
≥0.5 μg/mL n/N (%)	19/34 (56)	11/12 (92)	8/22 (36)	0.003
Pneumonia-associated pathogens				
Respiratory-Syncytial Virus	0/24 (0)	0/10 (0)	0/14 (0)	-
Adenovirus	0/24 (0)	0/10 (0)	0/14 (0)	-
Influenza A virus	12/25 (48)	4/10 (40)	8/15 (53)	0.69

Influenza B virus	0/25 (0)	0/10 (0)	0/15 (0)	-
Parainfluenza Viruses	0/24 (0)	0/10 (0)	0/14 (0)	-
Legionella pneumophila	1/24 (4)	1/10 (10)	0/14 (0)	0.42
Mycoplasma pneumoniae	2/22 (9)	1/10 (10)	1/12 (8)	>0.99
Chlamydia pneumoniae	0/23 (0)	0/10 (0)	0/13 (0)	-
Chest computed tomographic findings				
Normal	1/42 (2)	0/16 (0)	1/26 (4)	0.67
Unilateral pneumonia	9/42 (21)	3/16 (19)	6/26 (23)	-
Bilateral pneumonia	32/42 (76)	13/16 (81)	19/26 (73)	-

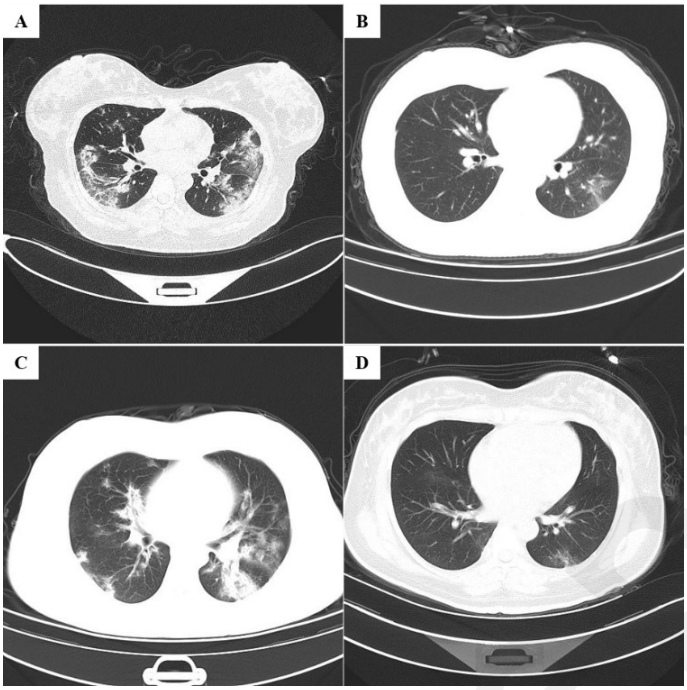

Figure 1: Chest CT scans of four COVID-19 patients.
A and B are chest CT showing axial view lung window of two pregnant women with COVID-19. A: Chest CT from a 34-year-old woman who was 38 weeks and 4 days pregnant, showing multiple bilateral ground-glass opacities. B: Chest CT from a 30-year-old woman who was 39 weeks and 1 day pregnant, showing left-sided ground-glass opacity. C and D are chest CT showing axial view lung window of two non-pregnant women with COVID-19. C: Chest CT from a 30-year-old woman showing multiple bilateral ground-glass opacities. D: Chest CT from a 33-year-old woman showing left-sided ground-glass opacity.

Management and clinical outcomes of pregnant women and non-pregnant women

A majority of pregnant and non-pregnant COVID-19 patients received antiviral (76% vs 96%) and antibiotic (76% vs 88%) therapy. Four (24%) of pregnant and five (19%) of non-pregnant women received glucocorticoid therapy, and one (6%) of pregnant and three (124%) of non-pregnant women received immunoglobulins therapy. Compared with pregnant group the proportion of patients received antitussive therapy in non-pregnant group significantly increased (69% vs 35%, *P*=.03). Additionally, oxygen support was administered in 35% of pregnant and 54% of non-pregnant women with COVID-19. None of patients underwent mechanical ventilation, continuous renal replacement therapy, and extracorporeal membrane oxygenation (Table 3).

None of the patients was lost in the follow-up during the study. None of the patients in the two groups were admitted to the intensive care unit (ICU), and none developed acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), renal failure, heart failure, secondary bacterial pneumonia and sepsis. And none of the patients died so far (Table 3).

Two pregnant women were classified as severe illness on admission, neither progressed to critical

illness. And no miscarriage was observed in pregnant women. Ten of 11 pregnant women underwent cesarean sections (two had preterm birth) (Appendix).

The median length of hospitalization for pregnant and non-pregnant groups was 17.0 and 22.0 days. And the median interval from onset to diagnose for SARS-CoV-2 were 4.0 and 10.0 days. The median duration of viral shedding after COVID-19 onset was 24.0 and 26.0 days. All patients who recovered from COVID-19 were placed in an isolation center for quarantine a period of two weeks. 11 pregnant and 19 non-pregnant women re-detected SARS-CoV-2 after discharge. Two (18%) of pregnant and two (11%) of non-pregnant women tested positive for SARS-CoV-2, and all were readmitted at hospitals for COVID-19 treatment (Table 3).

Table 3: Clinical treatment and outcomes of pregnant and non-pregnant women with coronavirus disease 2019.

Variables	No. (%)			
	Total (n=43)	Pregnancy (n=17)	Non-pregnancy (n=26)	*P* value
Management				
Antiviral therapy	38 (88)	13 (76)	25 (96)	0.14
Antibiotic therapy	36 (84)	13 (76)	23 (88)	0.54
Glucocorticoid therapy	9 (21)	4 (24)	5 (19)	0.96
Immunoglobulin	4 (9)	1 (6)	3 (12)	0.93
Cough-suppressant therapy	24 (56)	6 (35)	18 (70)	0.03
Oxygen support (nasal cannula)	20 (47)	6 (35)	14 (54)	0.23
Mechanical ventilation	0 (0)	0 (0)	0 (0)	-
Non-invasive	0 (0)	0 (0)	0 (0)	-
Invasive	0 (0)	0 (0)	0 (0)	-
Continuous renal replacement therapy	0 (0)	0 (0)	0 (0)	-
Extracorporeal membrane oxygenation	0 (0)	0 (0)	0 (0)	-
Clinical outcomes				
Intensive care unit admission	0 (0)	0 (0)	0 (0)	-
Acute respiratory distress syndrome	0 (0)	0 (0)	0 (0)	-
Disseminated intravascular coagulation	0 (0)	0 (0)	0 (0)	-
Renal failure	0 (0)	0 (0)	0 (0)	-
Heart failure	0 (0)	0 (0)	0 (0)	-
Secondary bacterial pneumonia	0 (0)	0 (0)	0 (0)	-
Sepsis	0 (0)	0 (0)	0 (0)	-
Death	0 (0)	0 (0)	0 (0)	-
Median (IQR) time of hospitalization, days	22.0 (14.0-28.0)	17.0 (11.0-28.0)	22.0 (15.5-26.5)	0.53
Median (IQR) time from onset to diagnosis, days	9.5 (6.3-17.0)	4.0 (2.0-17.0)	10.0 (7.5-17.0)	0.09
Median (IQR) time of viral shedding after onset of symptom, days	25.0 (19.0-29.0)	24.0 (14.0-26.0)	26.0 (20.0-29.0)	0.21
Re-detectable positive for discharged patients	2/30 (7)	2/11 (18)	2/19 (11)	0.61

IQR, Interquartile range.

Discussion

Principle Results

This study retrospectively analyzed the epidemiological, clinical, laboratory, imaging characteristics and clinical outcomes of 43 women of childbearing age infected with COVID-19, including 17 pregnant women and 26 non-pregnant women. As of March 28, 2020, none of the patients involved in this study developed severe pneumonia or died. Based on our findings, currently there is no

evidence indicating that pregnant women are more susceptible to the occurrence and severe adverse outcomes of COVID-19 than the general population.

A woman's body is highly in an immunosuppressive state after pregnancy, and the anatomy, physiology and biochemistry will always change. For example, the immunity of T lymphocyte changes, the oxygen consumption increases and the diaphragm elevates, which increases the risk of respiratory infection of pregnant women [9,10]. Studies during the outbreak of influenza virus and SARS-CoV have demonstrated that pregnant women are more susceptible to severe illness. In the outbreak of "Spanish flu" in 1918, 675,000 people died, with an overall mortality rate of 1-2%, while 27% of pregnant women died, and the mortality rate of pregnant patients reached 50% or higher when complicated with secondary bacterial pneumonia [18,19]. In the outbreak of SARS in 2003, among 12 pregnant women diagnosed with SARS, six (50%) needed to be admitted to ICU, six (50%) underwent mechanical ventilation, the mortality rate was 25% [11]. Another study reported that six of ten (60%) pregnant women with SARS were admitted to ICU, four (40%) underwent mechanical ventilation, three (30%) progressed renal failure, and two (20%) progressed secondary sepsis, two (20%) progressed secondary DIC, and the mortality rate reached 30% [12]. During the COVID-19 outbreak in 2019, one study reported that none of the nine pregnant patients progressed to critically illness or dead [14]. Of the 16 cases of pregnant women with COVID-19, one was classified as severe but did not develop severe adverse outcomes in the later stage [20]. This is consistent with our findings that none of pregnant women with COVID-19 developed severe adverse outcomes. Although critical pneumonia and death have not been reported in pregnant women, we should still be alert to the possibility of pregnant women developing severe adverse outcomes considering the high similarity of genomic sequence between SARS-CoV and SARS-CoV-2 [6].

Comparison with Prior Work

In this study, none of the pregnant women had a history of exposure to Huanan Seafood Market, 53% had a routine prenatal care within two weeks before onset, 24% had a family cluster of COVID-19. Therefore, during the epidemic, it was recommended that pregnant women to delay their routine prenatal care for safety, unless it was necessary, or to take the form of online clinic in order to reduce the risks of nosocomial infection. Similar to previous studies, common symptoms at the onset of COVID-19 were fever and cough, and less common symptoms were expectoration, chest tightness and diarrhea [14,15,21,22]. Notably, the onset of symptoms for several pregnant women were atypical, given that they had no fever or cough before diagnosis but only symptoms related to pregnancy were observed, including abnormal pain, vaginal bleeding, increased or reduced fetal movement, which indicated that attention should be paid to the occurrence of atypical symptoms in pregnant women. Laboratory findings were significantly different in hematological parameters between the two groups. Leukocytosis featured prominently in pregnant patients [14,15], while leukopenia featured prominently in non-pregnant patients [21,22]. Lymphopenia is likely to occur in both groups. Elevated concentration of hs-CRP, D-dimer and liver enzymes (including ALT, AST, LDH and ALP) in pregnant COVID-19 patients were observed, none of them developed liver failure or coagulation disorders. Recently, a study of 274 cases of patients with COVID-19 found that deceased patients generally had markedly higher level of CRP and LDH than recovered patients [22]. Therefore, the possibility that pregnant women with COVID-19 develop severe adverse outcomes cannot be eliminated. Additionally, a certain proportion of co-infection of SARS-CoV-2 and influenza A virus were showed in two groups. Given the similar clinical manifestations caused by two viruses and a relatively low positive rate for SARS-CoV-2 RNA test, it is recommended that a comprehensive assessment including epidemiological exposure, symptoms, laboratory, and imaging tests is necessary to the diagnosis of COVID-19.

Currently, vaccine or specific treatment for COVID-19 infection is absent. Majority of patients received antiviral (such as arbidol and oseltamivir) and empirical antibiotics treatment, while few patients received glucocorticoid and immunoglobulin therapy. Arbidol is an antiviral agent with a unique mechanism of action targeting the S protein/ angiotensin-converting enzyme 2 (ACE2)

interaction and inhibiting membrane fusion of the viral envelope [23]. In vitro data suggested its activity against SARS [24]. And a nonrandomized study of 67 patients with COVID-19 reported that, compared with arbidol-untreated patients, arbidol-treated patients with a treatment for a median time of 9 days, showing a lower mortality rates (0% vs 16%) and higher discharge rates (33% vs 19%) [25]. However, limited data are available on the safety of medications used during pregnancy. Oseltamivir is a neuraminidase inhibitor approved for the treatment of influenza, but it has no documented in vitro activity against SARS-CoV-2. Antibiotics were used routinely after operation to prevent secondary bacterial infections. Routinely systemic corticosteroids for treatment of COVID-19 is not recommended [3]. A large proportion of non-pregnant women used antitussive drugs in this study, which was related to higher proportion of cough (77%) during disease progression (Appendix). Supportive therapy and oxygen therapy are important management for COVID-19 [3].
No significant difference in the length of hospitalization of COVID-19 patients was observed in two groups. Notably, both pregnant and non-pregnant recovered patients tested positive for SARS-CoV-2 RNA during isolation. Fortunately, none of them suffered symptoms again or developed severe pneumonia. A case series including four patients with COVID-19 who had three repeated qRT-PCR after discharge or discontinuation of quarantine, four (100%) re-detected positive (RP) for SARS-CoV-2 RNA. All of them did not contact suspected or confirmed COVID-19 patients, and no family member was infected [26]. Thus, at least a proportion of recovered patients may still be virus carriers, and quarantine is still indispensable even after the patient with COVID-19 is discharged.

Limitations

Our study has some notable limitations. Firstly, this study is limited by its small sample size. More cases infected with COVID-19 should be enrolled for analysis. Secondly, only one pregnant woman were in her first trimester and three in their second trimester were included in this study respectively. The effect of COVID-19 on maternal and fetus in early pregnancy still needs to be clarified. Thirdly, this is a retrospective study, the uncertainty of the exact dates and related information on exposure (recall bias) might have an inevitable impact on assessment. Fourth, this study only included pregnant women and non-pregnant women, another group of healthy pregnant women should be included to assess pregnant outcomes of maternal and fetus, and intrauterine vertical transmission potential of COVID-19.

Conclusion

In the study, the clinical outcomes of pregnant women with COVID-19 appeared good, and none of the patients developed severe adverse outcomes. Additionally, the epidemiology of pregnant women with COVID-19 was complicated, and nosocomial infection cannot be underestimated. Fever and cough were the most common onset of symptoms in pregnant women. Notably, pregnancy-related symptoms (i.e., abdominal pain, vaginal bleeding, increased or decreased fetal movement) might be specific onset of symptoms for pregnant women with COVID-19. Quarantine is still needed after hospital discharge as a small proportion of recovered patients may still be virus carriers. In conclusion, early detection and active management effectively helps in the risk of developing severe pneumonia and death in pregnant women with COVID-19.

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Author contributions: SW and LF made substantial contributions to the study concept and design.

LW and XG were in charge of the manuscript draft. SC, WZ and JW were responsible for obtaining written consent from patients, obtaining ethical approval, collecting data, and confirming the data accuracy. XL, HZ and LM Sharifu did the analysis and interpretation. LC was the paediatrician in charge of treatment of the newborn babies. All authors critically revised the manuscript for important intellectual content and gave final approval for the version to be published.

Abbreviations

ACE2: angiotensin-converting enzyme 2
ALP: alkaline phosphatase
ALT: alanine aminotransferase
ARDS: acute respiratory distress syndrome
AST: aspartate aminotransferase
CFR: case fatality rate
COVID-19: coronavirus disease 2019
CT: computed tomography
DIC: disseminated intravascular coagulation
ELISA: enzyme-linked immunosorbent assay
ESR: erythrocyte sedimentation rate
hs-CRP: high sensitivity C-reactive protein
ICU: intensive care unit
IQR: interquartile range
LDH: lactate dehydrogenase
MERS-CoV: Middle East respiratory syndrome coronavirus
qRT-PCR: quantitative real-time reverse transcription polymerase chain reaction
RNA: ribonucleic acid
RP: re-detectable positive
SARS-CoV: severe acute respiratory syndrome coronavirus
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
WHO: The World Health Organization

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Supplementary Files

Figures

Untitled.