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Case series of 20 pregnant women with 2019 novel coronavirus disease in Wuhan, China

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Abstract

Aim: To evaluate perinatal outcomes regarding clinical presentation in pregnancy and the vertical transmission potential of COVID-19.

Methods: Clinical records, laboratory findings, and chest computed tomography (CT) scans were retrospectively reviewed from 20 pregnant patients with laboratory-confirmed COVID-19 who were admitted to Renmin Hospital of Wuhan University and The Third Hospital of Wuhan, from Jan 20 to Mar 16, 2020, including three in the first-trimester, two in the second-trimester, and 15 in the third-trimester. Evidence of vertical transmission was assessed by testing for neonatal throat swab samples. The pathological changes of COVID-19 on the placenta is evaluated by hematoxylin-eosin staining.

Results: The most common symptoms of the pregnant women with SARS-CoV-2 infection were fever and cough, which is comparable to the nonpregnant adults with COVID-19 infection. Nobody was transferred to intensive care unit (ICU) for treatment and there were no maternal and neonatal deaths. However, there was one case with induced abortions on first-trimester (due to pregnant woman's concerns about COVID-19), one diagnosed with ectopic pregnancy, no intrauterine fetal deaths during the study period. Delivery occurred in 15 patients in the third trimester. Their incidence of preterm birth was 20%. Three of the four preterm births were spontaneous. The average length of stay was 20.77 days. No neonatal SARS-CoV-2 infection was detected. There were two placentas found with acute chorioamnionitis, one showed normal placenta morphology.

Conclusion: In this case series study, COVID-19 had no short-term adverse effect on pregnant women except premature birth. The vertical transmission of SARS-CoV-2 did not occur in our study.

Key words: COVID-19, perinatal outcomes, vertical transmission, Wuhan.

Introduction

In December 2019, the outbreak of novel coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred in Wuhan, Hubei Province, China. This virus is highly infectious and rapidly causes the global epidemic. The COVID-19 outbreak has been declared a global public health emergency by the World Health Organization (WHO).[1] SARS-CoV-2 is categorized as beta-coronaviruses, similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). The clinical characteristics, treatment, and outcomes of patients with COVID-19 have been comprehensively reported.[2,3] However, the reports on pregnant

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patients are limited. The changes in physiology and immunity that accompany pregnancy can predispose women to infectious illness acquisition and severity.[4] This virus has a similar pathogenic potential as SARS-CoV and MERS-CoV, which have been associated with more severe infections in pregnancy and worse perinatal outcomes,[5] SARS-CoV-2 seems to have the potential to cause severe pregnancy or perinatal outcomes.[6] It should be noted that the youngest patient with COVID-19 reported to date was a newborn several minutes after birth in London, UK,[7] which suggests the potential of perinatal transmission. In our study, we retrospectively analyzed the clinical characteristics and outcomes of 20 pregnant women with COVID-19, including some patients with early and middle pregnancy, as well as investigated the impact of the infection on the perinatal outcomes.

Methods

Study design and subjects

This study was approved by the institutional ethics board of Renmin Hospital of Wuhan University (WDRY2020-K015) and Wuhan Third Hospital (KY2020-004), and written informed consent was obtained from each individual patient who met the inclusion criteria (Laboratory-confirmed COVID-19) and agreed to participate in our study. We retrospectively reviewed the medical records of the recruited 20 pregnant women who were admitted to Renmin Hospital of Wuhan University and Wuhan Third Hospital between January 20th, 2020 and March 16th, 2020. All the pregnant women were diagnosed with COVID-19 referring to the "Diagnosis and Treatment Protocol for COVID-19 (Seventh Trial Edition) released by the National Health Commission of P. R. China".[8] Diagnostic criteria for COVID-19 were based on the detection of SARS-CoV-2 RNA in nasopharyngeal swab specimens by quantitative RT-PCR following the instruction of the Chinese Center for Disease Control and Prevention (CDC) recommended Kit.

Data collection

We reviewed comprehensively medical data for included 20 pregnant women with COVID-19. The main parameters evaluating characteristics of pregnant women with COVID-19 include gestational weeks, clinical symptoms, laboratory and pathogenic findings, imaging examinations, history of chronic underlying diseases, history of epidemiology, incubation period, length of stay, and ICU admission rates. We evaluated perinatal outcomes including: spontaneous abortion, intrauterine fetal demise, premature labor, neonatal asphyxia, and neonatal death. The incubation period was defined as the duration from the contact of the infectors to the onset of symptoms. In addition, the nasopharyngeal swab of each neonate was tested for SARS-CoV-2 by quantitative RT-PCR twice, which were separately carried out immediately after delivery and 3 days later. The following samples in three pregnant women who delivered after recovered from COVID-19 were tested for SARS-CoV-2 by quantitative RT-PCR: infant's nasopharyngeal swab, breast milk, vaginal secretions, cord blood, placenta, and amniotic fluid. We did not collect in all cases given an increase in the number of our medical staff who were infected.

Statistical analysis

Statistical analysis was performed with SPSS (version 19.0). Continuous variables were expressed as range or mean ± SD. Categorical variables were expressed as number (%).

Results

During our study period of over 9 months, a total of 20 pregnant women with laboratory-confirmed COVID-19 was recruited, that is, three in the first-trimester, two in the second-trimester and 15 in the third-trimester. Maternal age ranged from 24 to 40 years old. Six women had close contacts with patients diagnosed with COVID-19. The average incubation period was 10 days. None of the patients had chronic underlying diseases such as hypertension, diabetes or cardiovascular disease, except patient 18 who had a chronic nephritis. However, four patients has been diagnosed with obstetric complications including gestational diabetes mellitus, thrombocytopenia during pregnancy, or hypothyroidism during pregnancy (Table 1).

Thirteen of the 20 patients (65%) presented with fever within a range of 37.5–39.5°C. Two patients (#19 and #20) had a transient high fever (>39°C) prior to admission. Symptoms like cough (35%, 7/20) is common as well. Other symptoms such as muscle soreness, expectoration, fatigue, dyspnea, diarrhea, and congestion were rarely observed (Figure 1). As of April 20th, 2020, no patient was admitted to the ICU and none of them died to date.

TABLE 1 Demographics of pregnant women with COVID-19

Case	Healthcare personnel	Age (year)	Gravidity (G), Parity (P)	Gestational age on admission (wks)	Contact history of infector	Incubation period (d)	Complications	Length of stays (d)
1	—	24	G1P0	40^{+4}	—	Unknown	—	8
2	—	33	G1P0	39^{+5}	—	Unknown	—	12
3	—	33	G4P1	39+3	—	Unknown	GDM	6
4	—	27	G4P1	39+1	—	Unknown	GT	10
5	—	30	G1P0	33^{+4}	—	Unknown	—	10
6	—	29	G2P1	38+4	—	Unknown	—	12
7	—	34	G3P1	38^{+2}	—	Unknown	—	14
8	—	31	G2P1	38	Yes	10	—	21
9	—	27	G3P1	36^{+2}	—	Unknown	GDM	9
10	—	26	G1P0	35^{+5}	Yes	Unknown	—	24
11	—	26	G1P0	35	Yes	10	—	41
12	—	37	G1P0	33+1	—	Unknown	GH	12
13	—	33	G1P0	39+1	—	Unknown	—	4
14	—	28	G1P0	39	—	Unknown	—	12
15	—	26	G2P1	38^{+3}	—	Unknown	—	15
16	—	40	G2P1	8^{+5}	Yes	Unknown	—	35
17	—	32	G2P1	5+1	—	Unknown	—	32
18	—	29	G1P0	18+3	Yes	Unknown	CN	29
19	Yes	36	G2P1	16^{+1}	—	Unknown	—	35
20	—	28	G1P0	6^{+3}	Yes	Unknown	—	34
$\chi \pm s$		30.15 ± 4.13						18.75 ± 11.25

Abbreviations: CN, chronic nephritis; GDM, gestational diabetes; GH, gestational hypothyroidism; GT, gestational thrombocytopenia.

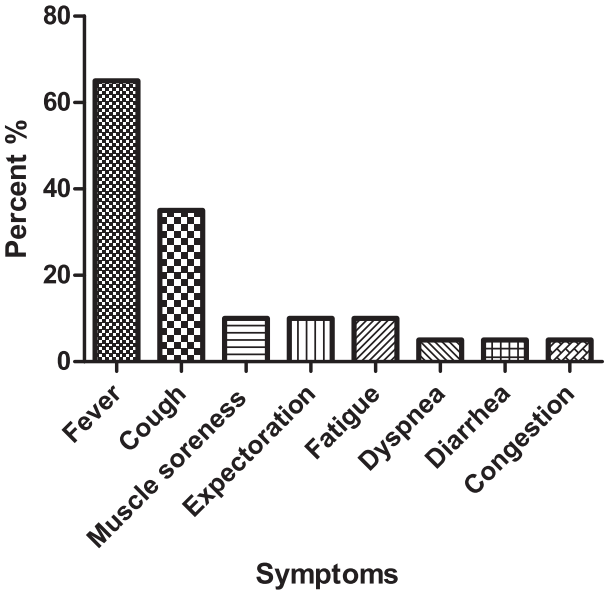

FIGURE 1 The percentage of symptoms in 20 patients. Thirteen of the twenty patients (65%) presented with fever. Symptoms like cough (35%) is common as well. Other symptoms such as muscle soreness (10%), expectoration (10%), fatigue (10%), dyspnea (5%), diarrhea (5%), and congestion (5%) were rarely observed.

For the laboratory test, lymphopenia (50%), elevated concentrations of C-reactive protein (CRP) (40%), and neutrophil granulocyte (50%) was observed in pregnant women. One patient (#20) showed transient elevated concentration of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) reaching 80 U/L and 115 U/L, respectively. The results of other tests were basically normal, including white cell count, myocardial enzymes, and coagulation function. All the 20 patients had been confirmed positive for SARS-CoV-2 by quantitative RT-PCR from the nasopharyngeal swab specimens. Seventeen pregnant patients showed typical ground-glass opacity on chest computed tomography (CT) scans (Figure 2), and the remain three pregnant woman refused to take the scan due to the concerns of teratogenic effects of radiation. Once laboratory-confirmed with COVID-19, all pregnant women were given oxygen support, empirical antibiotics (Cephalosporins, Azithromycin), antiviral therapy (Oseltamivir, Arbidol), and 18 patients received Chinese medicine (Lianhua Qingwen Capsule) treatment. For the refractory pneumonia, corticosteroid (methylprednisolone) was cautiously added (Table 2).

Seventeen patients in the third trimester had a live birth, including thirteen via cesarean section and four via vaginal delivery. Notably, four of 15 women who during the hospitalization delivered at less than 37 weeks of gestation, which made the premature birth rate reached 20%. Two women continued pregnancy after recovery from COVID-19 and gave birth at full-term pregnancy. All the pregnant women with premature delivery were in the stable condition. As of October 3, 2020, no adverse perinatal outcomes including spontaneous abortion and intrauterine fetal demise occurred. However, there was a case (#16) in the first trimester request induced abortion for the concerning about the adverse effects of COVID-19. Otherwise, one patient (#17) was diagnosed with ectopic pregnancy and was discharged after conservative treatment. Regrettably, one patient (#19) were found with multiple fetal malformation after recovered from COVID-19 for 1 month, and she chose to medically terminate the pregnancy due to severe fetal anomalies. All the patients recovered and were discharged. Their stay duration in hospital was 18.75 ± 11.25 days.

Among the 17 neonates, 10 were males and seven were females. The nasopharyngeal swabs of all neonates were tested negative for SARS-CoV-2 twice by quantitative RT-PCR. Two of four premature neonates had a birth weight of <2500 g, and one of the premature neonates had a mild neonatal asphyxia. No neonatal deaths occurred. All neonates had a 1-min Apgar score of 7–9 and a 5-min Apgar score of 9–10. The neonates were all admitted to the neonatal department for intensive observation and fed with formulated infant milk (Table 2). Two neonates (#1 and #5) breastfeed after their mother recovered from COVID-19, the remaining neonates fed with formulated infant milk.

We collected several samples from three pregnant women who recovered from COVID-19, two of them (#18 and #20) continued pregnancy and delivered in full-term pregnancy, one case (#19) diagnosed as multiple malformations of the fetus 4 weeks after discharged. The breast milk, vaginal secretions, and intrauterine tissue samples, including cord blood, placenta, and amniotic fluid from three cases were all negative for SARS-CoV-2. Pathologic findings of placenta in case 20 show normal placenta structure with no significant calcification, avascular villi or inflammatory changes. However, the placentas from cases 18 and 19 were observed with maternal inflammatory response, acute chorioamnionitis. Furthermore, local

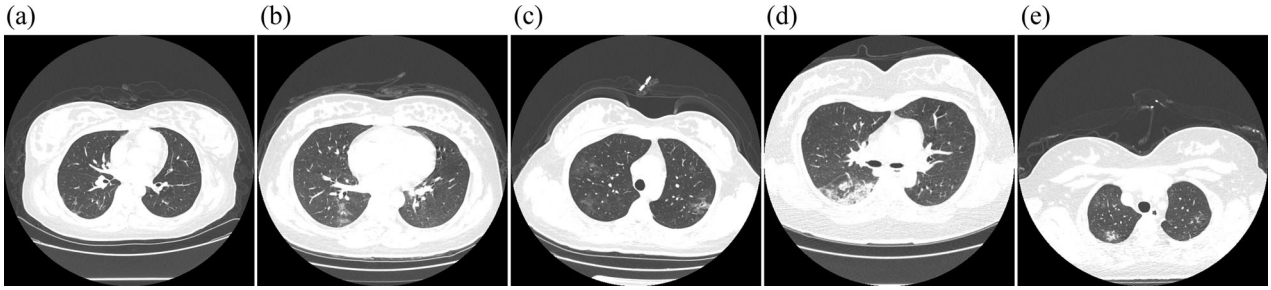

FIGURE 2 Chest computed tomography (CT) scans of five pregnant women with COVID-19. (a) On February 11, chest CT scan of patient 1 showed subpleural patchy ground glass opacity in the right lower lobe; (b) On February 14, chest CT scan of patient 2 showed patchy ground glass in the right lower lobe; (c) On February 15, chest CT scan of patient 4 showed bilateral multiple patchy ground glass opacity; (d) On February 5, chest CT scan of patient 11 showed patchy ground-glass opacity and consolidation shadow in the right lower lobe; (e) On February 9, chest CT scan of patient 8 showed bilateral multiple patchy ground glass opacity

placenta with infarction and calcification were found in case 18 (Figure 3).

Discussion

We reported a case series of 20 pregnant women with laboratory-confirmed COVID-19. As with non-pregnant adults with COVID-19, pregnant women showed a similar pattern of clinical features, laboratory, and imaging examinations as previously reported.[3,9,10] There were no adverse perinatal outcomes occurred in our study, and no cases of neonatal infection were detected.

In consistent with the general population as Zhong et al.[11] stated and pregnant women as Li et al. reported, fever and cough were the most common symptoms. Pregnant patients showed gastrointestinal symptoms as well. To be noted, 5% of the pregnant women were healthcare workers. Suwantarat et al.[12] also reported that healthcare personnel related infections with MERS and SARS reach among 1–27% and 11–57% of total cases, respectively. The occupational exposure of healthcare workers increases the risk of infection, especially at the beginning of outbreak owing to inappropriate and insufficient preventive measures. We noticed that several pregnant women refused CT examination because of adverse impact of radiation to fetus. A consensus has emerged that prenatal exposure to diaphragmatic radiations with doses lower than 50 mGy does not increase the adverse risk of fetus.[13] Actually, it is unlikely that a single-phase CT scan could reach this dose level of radiations.[14] It is safe for pregnant women with COVID-19 to perform CT examinations. Overall, if chest CT scan is necessary for a relevant diagnostic should not be contraindicated in case of pregnancy.

During pregnancy, the increase in maternal oxygen consumption and alteration in pulmonary function makes pregnant women are at greater susceptibility to become hypoxic.[15] Although the immune system changes of pregnant woman are not well understood, a shift from cell-mediated immunity toward humoral immunity is believed to occur.[16] As with other infectious diseases, the maternal changes in physiology and immunity that accompany pregnancy have been hypothesized to affect both susceptibility and severity of pneumonia.[17] During the 1957–1958 Asian flu epidemics, statistics suggested that the case fatality rate of pregnant women is twice as high as that infected non-pregnant women.[18] A case series study in Hong Kong reported that SARS during pregnancy is associated with high incidences of spontaneous miscarriage (57%), preterm delivery (80%), and intrauterine growth restriction (100%), as well as the fatality rate of pregnant women up to 25%.[5] Similarly, 10 (91%) presented with adverse outcomes, six (55%) neonates required admission to the intensive care unit, and three (27%) died in a review of 11 pregnant women infected with MERS-CoV.[19] In agreement with Chen et al,[9] unexpectedly, there is no evidence to suggest that COVID-19 could lead to the occurrence of adverse perinatal outcomes in pregnant women in our previous study.[20, 21] In this study, however, on patient admitted to ICU and no maternal deaths occurred. Although very limited sample size, with exception of preterm birth, no adverse perinatal outcomes were observed.

TABLE 2 Pregnant and neonatal outcomes of pregnant women with COVID-19

Case	Gestational age at diagnosis (wks)	Gestational age at delivery (wks)	Indications of delivery	Route of delivery	Neonatal sex	Apgar score	Neonatal weight (g)	Neonatal asphyxia	Neonatal death
1	post-partum Day 1	40^{+4}	Polyhydramnios	CS	Female	9–10	3300	No	No
2	post-partum Day 2	39^{+5}	Threatened labor	CS	Male	9–10	3200	No	No
3	38+3	39+3	Threatened labor	CS	Male	9–10	3000	No	No
4	39	39+2	Scarred uterus	CS	Female	9–10	3020	No	No
5	33^{+2}	38^{+6}	Breech, Threatened labor	CS	Male	9–10	3500	No	No
6	38+4	38+4	Threatened labor	CS	Male	7–9	2600	**Yes**	No
7	38+2	38^{+2}	Threatened labor	CS	Male	9–10	3100	No	No
8	Post-partum Day 2	38	Fetal distress?	CS	Male	9–10	3200	No	No
9	36^{+2}	36^{+2}	Threatened preterm labor	CS	Female	8–9	3100	No	No
10	35^{+5}	35^{+5}	Threatened preterm labor	CS	Female	8–9	2300	No	No
11	35	35	COVID-19	CS	Male	8–9	2500	No	No
12	33+1	34	PPROM	CS	Female	8–9	2170	No	No
13	39+1	39+1	In labor	VD	Male	9–10	3650	No	No
14	39	39	In labor	VD	Male	9–10	3200	No	No
15	38^{+3}	38^{+3}	Threatened labor	VD	Female	9–10	3150	No	No
16	8^{+2}	—	Induced abortion	—	—	—	—	—	—
17	4w+2	—	Ectopic pregnancy	—	—	—	—	—	—
18	17+1	37	Fetal distress	CS	Female	9—10	3000	No	No
19	15+6	26+2	Induction of labor	VD	Female	—	560	—	—
20	5+3	38+4	In labor	VD	Male	9–10	3420	No	No

Abbreviations: COVID-19, novel coronavirus disease 2019; CS, cesarean section; PPRO, premature rupture of preterm membranes, VD, vaginal delivery.

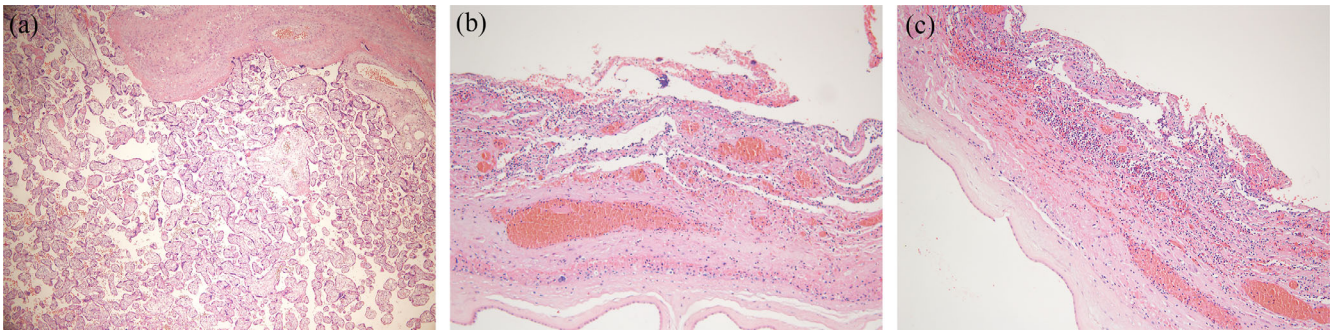

FIGURE 3 Microscopy of the placental pathologic findings. (a) Normal vessels of stem villi and terminal villi in case 20; (b and c) Acute chorioamnionitis in cases 18 and 19.

Notably, four of 20 women diagnosed in the third trimester delivered at <37 gestational weeks and the premature birth rate reached 20%, including three spontaneous premature birth and one iatrogenic premature birth. The causes of spontaneous premature birth was threatened premature labor and premature rupture of membranes. The iatrogenic premature births were ascribed to aggravation of COVID-19. COVID-19 is not an indication for delivery; however, delivery timing should be individualized based on gestational age and maternal-fetal status.[22] As recommended by professor Qi,[23] timely termination of pregnancy over 32–34 weeks of gestation may be beneficial for subsequent treatment and safety of pregnant women. In this study, all of three women (100%) after premature delivery recovered and were discharged. Zhu et al. reported the high premature birth rate (60%) in women with COVID-19 as well.[24] Similar to SARS and MERS, COVID-19 contributes to high-premature birth rate in pregnant women.[5,25] It is obvious that breastfeeding makes many benefits for newborns whereas except the women who infected with SARS-CoV-2.[26] But for a mother recovered from COVID-19 has the potential to transmit protective maternal antibodies to neonates through breastmilk,[27] which is also favors the emotional bond between mother and child.

Previous studies demonstrated that cesarean section might reduce the risk of perinatal transmission for some viruses, such as HIV and HBV.[28,29] Newborns may swallow amniotic fluid and vaginal secretions while passing through the mother's birth canal. As Dong et al. have proved the possible vertical transmission SARS-CoV-2 from an infected mother to her neonate.[30] It has been suspected that whether vaginal delivery increases the risk of intrapartum transmission for COVID-19.[9] In our study, 15 women in the third trimester delivered successfully. Indications for caesarean section included history of caesarean sections, fetal distress, or social factors. All the 17 neonates were negative for SARS-CoV-2, including three neonates delivered naturally. In addition, in our previous study, the breast milk, vaginal secretions, and intrauterine tissue samples (cord blood and amniotic fluid) were all negative for SARS-CoV-2.[21] Although very limited sample size, it is reasonable to infer that uncomplicated spontaneous vaginal delivery is safe.[31] However, the indication of cesarean section should be moderately relaxed, especially for those who are already in labor but are not able to achieve vaginal delivery within a short time. From our study results, we propose that the indication of cesarean section for pregnant women with COVID-19 should be relaxed for reducing the length of stay of women in obstetrics and minimizing the risk of cross infection, which is consistent with the previously report.[23] Delivery should take place on a negative-pressure isolation ward. Otherwise, the occupational exposure of healthcare workers increases the risk of infection especially at the beginning of outbreak owing to inappropriate and insufficient preventive measures. N95 mask, goggles, and medical protective suit are requisite for healthcare workers.

The long-term prognosis of COVID-19 for pregnant women and fetuses is an issue of great concern to obstetricians. Several human viruses could cause birth defects, including rubella virus,[32] varicella-zoster virus,[33] parvovirus B19[34] and human cytomegalovirus (CMV).[35]Although the receptor of SARS-CoV-2, angiotensin-converting enzyme 2 (ACE2), was highly expressed in maternal-fetal interface cells.[36] More placenta microscopical examination revealed infrequent

occurrence of mother-to-fetus SARS-Cov-2 transmission.[37] There were no dates about impact of SARS-CoV-2 on fetal malformation during pregnancy. The most important period of fetal heart development were in the first trimester, exposure to various adverse factors in the early pregnancy has a greater impact on the fetus.[38] Here, we followed up to three pregnant women who recovered from the COVID-19 until they gave birth. Adverse perinatal outcomes were not observed in two cases, but one case whose baby was detected with fetal multiple heart malformations 1 month after discharge. In our study, pregnancy women with COVID-19 may not have teratogenic effects on the fetus. The advanced age of pregnant women and previous other adverse factors may be the cause of fetal malformations. Placental pathology of pregnant women with SARS infection showed villous infarct,[39] and COVID-19 case also showed acute inflammatory pathology (AIP) including histologic chorioamnionitis, which is agree with the pathology of placenta in our study. Since the virus replicates in the human body and produces a systemic inflammatory response, these pathologies of the placenta are probably caused by inflammation. In our cases, for a pregnant women who recovered with from mild type of COVID-19 in first trimester may have good perinatal outcome.

In summary, pregnant women with COVID-19 had high premature birth rate, while other adverse perinatal outcomes were not observed. Besides, there is no neonatal infection and vertical transmission of COVID-19 detected. However, due to the limited sample size and short observation time, the further multi-center and large-scale trials studies are needed.

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Conflicts of Interest

None declared.

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