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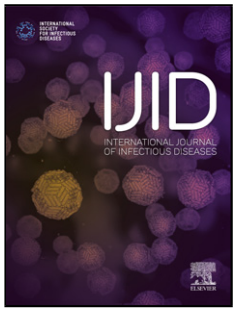

Coronavirus disease 2019 in pregnancy

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Coronavirus disease 2019 in pregnancy

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Abstract

Objectives This study aims to compare clinical course and outcomes between pregnant and reproductive-aged non-pregnant women with COVID-19 and assess the vertical transmission potential of COVID-19 in pregnancy.

Methods Medical records of pregnant and reproductive-aged non-pregnant women hospitalized with COVID-19 from January 15 to March 15, 2020, were retrospectively reviewed. The severity of disease, virus clearance time, and length of hospital stay were measured as the primary interest and the vertical transmission potential of COVID-19 was also assessed.

Results Eighty-two patients (28 pregnant women, 54 reproductive-aged non-pregnant women) with laboratory confirmed COVID-19 were enrolled in this study. Univariate regression indicated no association between pregnancy and the severity of disease (OR 0.73, 95% CI 0.08-5.15; p = 0.76), virus clearance time (HR 1.16, 95% CI 0.65-2.01; p = 0.62), and length of hospital stay (HR 1.10, 95% CI 0.66-1.84; p = 0.71). There were 22 pregnant women delivered 23 live births either by cesarean section (17, 60.7%) or vaginal delivery (5, 17.9%) and no neonate was infected with SARS-CoV-2.

Conclusions Pregnant women have comparable clinical course and outcomes compared with reproductive-aged non-pregnant women when infected with SARS-CoV-2. No evidence supported vertical transmission of COVID-19 in the late stage of pregnancy including vaginal delivery.

Keywords COVID-19, clinical feature, infection, pregnancy, SARS-CoV-2, virus

Coronavirus disease 2019 in pregnancy

Introduction

On March 11, 2020, the coronavirus disease 2019 (COVID-19) caused by the emerging virus, severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) (Zhu et al., 2020), was announced as a pandemic by the World Health Organization (Cucinotta and Vanelli, 2020). As at the writing, there were 191,127 confirmed cases reported globally with a mortality rate of 4.08% (WHO, 2020). Epidemiological study indicated that population of any age were at risk of infection, and the severity was associated with age and comorbidities (Wu and McGoogan, 2020). For example, cancer patients infected with SARS-CoV-2 have shown a higher risk of severe events and mortality rate compared with those without cancer (Liang et al., 2020), and COVID-19 patients with pre-existing digestive diseases were associated with more complications (Mao et al., 2020). The higher vulnerability of those patients is likely caused by a suppressed immune system due to the underlying diseases or the side-effects from treatments, like surgery, chemotherapy, or immunosuppressive agents, among others.

Pregnant women have their special immunological adaptation which is a necessity for maintaining the tolerance of the fetal semi-allograft (Weetman, 2010). The state of the transient suppressed immunity is modulated by suppressing T cells activities, and hence predisposes pregnant women to virus infection (Longman and Johnson, 2007, Pazos et al., 2012). In addition, the physiological changes in respiratory and circulatory systems might worsen clinical outcomes when infected with virus during pregnancy (Rasmussen et al., 2020).

In the 2009 pandemic of H1N1 influenza, pregnancy caused a higher risk of severe pneumonia, ARDS, mechanical ventilation and death when compared with those reproductive-aged non-pregnant (Jamieson et al., 2009). Similar results were also reported in the epidemic of severe acute respiratory distress syndrome (SARS) and Middle East respiratory distress syndrome (MERS), that patients in pregnancy were more likely to develop organ dysfunction and die (Rasmussen and Jamieson, 2020, Schwartz and Graham, 2020, Wang S. et al., 2020). However, in the current COVID-19 outbreak, pregnant women seemingly had fewer maternal and neonatal adverse events than reported in SARS and MERS (Qiao, 2020), but whether pregnant women have a comparable clinical course and outcome compared with non-pregnant women is still unclear.

To facilitate the understanding of pregnancy in COVID-19, we herein reported a retrospective observational study to compare the clinical course and outcomes between pregnant and non-pregnant women, and also summarized the neonatal outcomes, including vertical transmission potential of COVID-19.

Methods

Study design and participants

This is a single-center, retrospective study performed in The Central Hospital of Wuhan, one of the 5 designated hospitals for pregnant women with COVID-19 in the epicenter of the SARS-CoV-2 outbreak in China. We included pregnant women hospitalized with COVID-19 and reproductive-aged (defined as 18 to 41 years old, modified from the previous study (Creanga et al., 2010)) non-pregnant women infected with SARS-CoV-2 as the comparison, from 15 January to 15

March 2020. COVID-19 was diagnosed based on the Chinese Clinical Guidance For COVID-19 Pneumonia Diagnosis and Treatment published and updated by the National Health Commission of China(NHFPC, 2020). All the COVID-19 patients had either positive reverse transcription polymerase chain reaction (RT-PCR) from respiratory samples (Chen H. et al., 2020) or positive serological test of specific IgM antibody to SARS-CoV-2 (The sensitivity and specificity of the serological test for SARS-CoV-2 were 82.7% and 98.6%, respectively) (Zhao J. et al., 2020).
The study was approved by the ethics committee of The Central Hospital of Wuhan (2020-34).

Patients identification and data collection

All patients consecutively admitted in The Central Hospital of Wuhan with the diagnosis of COVID-19 between 15 January to 15 March 2020 were selected from the electronic medical records, and males were excluded. The included females were then classified by age, only those between 18 to 41years were subjected to further analysis. The medical records of the included patients of reproductive age were reviewed by two physicians (QC. X and SR. L) independently to confirm whether the diagnosis of COVID-19 met the criteria according to the guidance published by the National Health Commission of China. All the confirmed cases were then subjected to the pregnant women group or reproductive-aged non-pregnant women group for further analysis.
Data extracted from the patient record included age, time from onset of symptoms to hospital admission, the severity of COVID-19, comorbidities, symptoms at onset, vital signs on admission, laboratory tests, findings on computer tomography (CT), treatments (antivirus regimens, antibiotics, corticosteroids, Gamma globulin), virus clearance time and length of hospital stay (LOS). For the pregnant women, their gestational age on admission, the outcome of pregnancy and information (including birthweight, Apgar scores, and perinatal complications) of neonates were recorded.

Outcomes and definitions

The outcomes of interest included: severity of COVID-19, LOS and virus clearance time. The neonates were tested for infection with SARS-CoV-2. Viral clearance was confirmed by serial RT-PCR checking samples from throat swab with those having at least two consecutive negative results taken 24 hours apart considered cleared. The virus clearance time, in days, was calculated starting from the onset of symptoms to the date of the first negative RT-PCR test. The diagnostic criteria for COVID-19 of neonates were the same as for adults, and neonates with at least twice negative RT-PCR tests from throat swab after birth and no evidence of pneumonia were considered as free from SARS-CoV-2 infection. The severity of disease was classified as mild (mild symptoms and without pneumonia on chest imaging), moderate (fever and respiratory symptoms, radiological findings of pneumonia), severe (shortness of breath with respiratory rate $\geq$ 30 breaths/minute, or oxygen saturation $\leq$ 93% at rest, or alveolar oxygen partial pressure/faction of inspiration O_2 (PaO_2/FiO_2) $\leq$ 300 mmHg) and critical (respiratory failure required mechanical ventilation, or shock, or presented other organ failures that need intensive care unit admission) according to the Chinese Clinical Guidance For COVID-19 Pneumonia Diagnosis and Treatment (NHFPC, 2020).

Statistical analysis

Continuous variables were summarized as either means and standard deviations or median and

interquartile range (IQR) as appropriate. Categorical variables were described as frequencies and percentages. The differences between pregnant and reproductive-aged non-pregnant were analyzed by the Fisher's exact test or the Wilcoxon signed-rank test for categorical variables and the Mann-Whitney *U* test for continuous variables. The LOS and virus clearance time were estimated by Kaplan-Meier method and Log Rank Test. Univariable Cox proportional hazard regression and ordinal logistic regression were performed to estimate associations between pregnancy and clinical outcomes and the severity of disease. Hazard ratios (HR), odds ratio (OR) and 95% confidence intervals (CI) were reported. A $p < 0.05$ was considered statistically significant. All analyses were performed using R software version 3.6.2 (R Foundation for Statistical Computing).

Results

Data declaration

At the time of submission of the manuscript (30th March 2020), no studies were identified including data from the present study. During the revision period (17th April to 21st April 2020), an online correspondence (18th April 2020) was published on The New England Journal of Medicine (Chen Lian et al., 2020), which reported 118 pregnant women with COVID-19 in Wuhan, among which 11 cases were from the same hospital of our study.

Patients characteristics

There were 719 patients admitted in the hospital during the study period, among which 339 were male, and 380 were female. 298 females were excluded because of older than 41 years. Eventually, 82 patients enrolled in the study, among that 28 were pregnant women, and 54 were reproductive-aged non-pregnant women (Figure 1). The median age of pregnant women was 30 (IQR, 26.75-32) years that was similar to that of non-pregnant women of 31 (IQR 28-35) years. Comorbidities were not frequently reported in both groups: in pregnant women, 1 (3.6%) had probable gestational hypertension, 2 (7.1%) had probable gestational diabetes, 2 (7.1%) were with chronic hepatitis B, and 1 (3.6%) had hypothyroidism, while in non-pregnant women, 4 (7.4%) patients had diabetes, 2 (3.7%) had chronic hepatitis B and 1 (1.9%) reported hypothyroidism. No cancer, chronic respiratory disease and heart disease were reported.

Pregnant women had a shorter median time from illness onset to admission compared with non-pregnant women (1 day, IQR 1-6.5 vs. 7 days, IQR 5-10; $p < 0.001$). The result might be explained by the waiting time for the SARS-CoV-2 test in patients at priority (like pregnant women, children, and patients in critical situations) was shorter than other patients. The severity of disease was comparable in the two groups, apart from 2 (7.1%) patients in pregnant women presented as mild type, most patients were categorized as moderate pneumonia (24, 85.7% vs. 53, 98.1%) and only 2 (7.1%) patients in pregnant women and 1 (1.9%) in non-pregnant women were classified as severe pneumonia. The major complaints for admission were slightly different, fever and cough were more frequent in non-pregnant women, whereas abdominal pain was the special complaint only reported in pregnant women (Table 1).

Laboratory and radiological presentations

More leukocytosis ($> 9.5\times10^9$/L) (10, 35.7% vs. 2, 3.7%; $p < 0.001$) and elevated C reactive

protein (> 0.6 mg/dl) (17, 68% vs. 14, 25.9%; $p = 0.001$) was detected in pregnant patients than in non-pregnant women, while there was no statistical difference in procalcitonin. Baseline hemoglobin level (117.5 g/L, IQR 106.75-129.00, vs. 126.00 g/L, IQR 121.25-135.50; $p = 0.018$) and albumin level (35.50 g/L, IQR 34.00-38.65 vs. 43.00 g/L, IQR 41.00-43.85; $p < 0.001$) were lower in patients with pregnancy compared with those reproductive aged non-pregnant women. Elevated alanine aminotransferase was observed in 2 (3.7%) non-pregnant women, while did not report in pregnant women (p = 0.80). A small number of patients in both groups had elevated creatine (≥ 75 μmol/L) (1, 3.8% vs. 5, 9.3%; $p = 0.683$), lactate dehydrogenase (≥ 220 U/L) (4, 16% vs. 1, 2.4%; $p = 0.116$), and creatine kinase (≥ 140 U/L) (3, 12.5% vs. 2, 4.8%; $p = 0.51$), without statistical significances. Apart from two pregnant patients, all others had typical changes on chest CT with multiple patchy ground-glass shadows (Table 2).

Treatments and outcomes

Twenty-one (75%) patients with pregnancy received antivirus therapy, all except one (20, 71.4%) received ribavirin alone. By contrast, all non-pregnant women received antivirals, in which 19 (35.2%) received ribavirin, 11 (20.4%) received umifenovir, 17 (31.5%) received ribavirin and umifenovir combination and 7 (13.0%) received triple combination by adding interferon-alpha inhalation to ribavirin and umifenovir.

Similar percent of patients (24, 85.7% vs. 47, 87%) in both groups received antibiotics prophylactic therapy. Patients without pregnancy used more combination antibiotics with cephalosporin and quinolone than that in pregnant women (32, 59.3%), while single cephalosporin therapy was the major antibiotics regimen in pregnant women (20, 71.4%). In addition, reproductive-aged non-pregnant women also received more corticosteroids (21, 38.9% vs. 4, 14.3%; $p = 0.041$) and immunoglobulin (19, 35.2% vs. 3, 10.7%; $p = 0.035$) therapy when compared with pregnant patients (Table 2).

In terms of clinical outcomes, no fatal case was reported in both groups and there were no significant association between pregnancy and virus clearance time (HR 1.16, 95% CI 0.65-2.01; $p = 0.62$), LOS (HR 1.10, 95% CI 0.66-1.84; $p = 0.71$) and severity of disease (OR 0.73, 95% CI 0.08-5.15; $p = 0.76$) (Figure 2).

Maternal and neonatal outcomes

The median gestational age on admission was 38 (IQR, 36.5-39) weeks, with 3 (10.7%) in the first trimester, 1 (3.6%) in the second trimester and 24 (85.7%) in the third trimester. All pregnant women in the first and second trimester terminated pregnancy due to concerns of side-effects from drugs, radiological examination and COVID-19, and the decisions were made by themselves after discussion with their families. Two pregnant women in early third trimester continued pregnancy (30, and 33 gestational weeks, respectively) at the time of writing, while the others (22, 78.6%) delivered 23 live births (included two twins) either by cesarean section (17, 60.7%) or vaginal delivery (5, 17.9%).

One patient had preterm labor in 35 gestational weeks but had a birthweight of 2940 g healthy neonate. Only one of the twins had a birthweight less than 2500 g (2350 g), and the median birthweight of neonates was 3130 (IQR, 2915-3390) g. No fetal death, neonatal death, or neonatal

asphyxia was observed. All the neonates received at least two subsequent tests of RT-PCR of 24 to 48 hours apart for SARS-CoV-2 infection, and none of them had a positive result. Furthermore, there did not show any evidence that supported pneumonia diagnosis (Table 3).

Discussion

One of the major concerns for obstetricians during the outbreak of COVID-19 is whether pregnant women would have worse outcomes compared with non-pregnant women of similar ages when infected with SARS-CoV-2. Studies reported that pregnant women were at a higher risk of getting infections with H1N1 influenza and SARS-CoV and were also associated with poorer clinical outcomes, like required mechanical ventilation, organ dysfunction, ICU admission and death, in comparison to reproductive aged non-pregnant women (Creanga et al., 2010, Jamieson et al., 2009, Lam et al., 2004). However, in our study, we did not find an association between pregnancy and outcomes (included the severity of disease, virus clearance time and LOS). Similar results were also reported in a recently published case series (Chen H. et al., 2020).

Pregnant women infected with other respiratory viruses, e.g. H1N1 influenza, SARS-CoV, were reported with more fetal adverse events, for example, miscarriages in the early trimester, fetal distress, intrauterine growth restriction, etc. (Rasmussen and Jamieson, 2020). In our study, 4 patients had their pregnancy terminated in the first and second trimester, which prevented analysis of the effect of SARS-CoV-2 infection in earlier stages of pregnancy. Apart from the two patients with ongoing pregnancy, all the other pregnant women in the third trimester in our study delivered 23 live births without documented perinatal complications, except one had a preterm birth. Recently, a high rate of pregnancy complications was reported in a case series with 10 SARS-CoV-2 infected pregnant women, 5 of them received emergency caesarean section because of fetal distress (3, 30%, premature rupture of the membrane (1, 10%) and stillbirth (1, 10%), even though the severity of COVID-19 in these patients were majorly classified as mild to moderate, with only one developed severe pneumonia (Liu et al., 2020). By contrast, another study enrolled 16 pregnant women with COVID-19 and 45 pregnant women without infection in their third trimester, the results did not indicate any increased risks of perinatal complications in SARS-CoV-2 infected women, including the occurrence of severe preeclampsia, premature rupture of membranes, fetal distress, meconium-stained amniotic fluid, premature delivery, neonatal asphyxia, and postpartum hemorrhage (Zhang et al., 2020). The controversial results might be caused by selection bias in small sample size studies, therefore, the effect of COVID-19 in pregnancy warrants further studies.

Another vital question for COVID-19 in pregnancy is whether it could be vertically transmitted from mother to neonate, or not, as previously reported for SARS (Lam et al., 2004). A recent review summarized 38 pregnant women and their newborns in China, and no evidence for vertical transmission were identified (Schwartz, 2020). Among the included literature, one study enrolled 9 pregnant women with COVID-19 in the late stage of pregnancy (Chen H. et al., 2020). These researchers tested SARS-CoV-2 in amniotic fluid, cord blood, neonatal throat swab, and breastmilk samples, and all results were negative. However, the study failed to answer whether it was possible to get the infection during vaginal delivery, because all the neonates were born with cesarean section. In our study, we included 5 neonates who were born vaginally, and none of them had the evidence for COVID-19, which added clinical evidence to the safety of vaginal delivery.

However, another study investigated 19 neonates born to mothers with COVID-19 in Wuhan, in which 3 neonates were reported as SARS-CoV-2 positive (Zeng et al., 2020). Because strict infection control and prevention procedures were implemented during the delivery, and all infants with COVID-19 were confirmed early on the second day of life, which led the author to conclude that the potential vertical transmission still cannot be ruled out. Moreover, it is important to note that evidence for no vertical transmission to date all based on the late stage of pregnancy, whether intrauterine vertical transmission could happen during the first or second trimester is still unclear.

Pregnant patients with COVID-19 received less treatment compared to non-pregnant women in our study. The reluctant therapy might be explained by the concern of adverse effects in the fetus that could be generated by certain drugs, like interferon-alpha (Hiratsuka et al., 2000, Liang and Acharya, 2020). Except for the 4 cases of pregnant women that underwent the medical abortion, all the other pregnant women received medications after delivery. Twenty out of 21 pregnant patients used ribavirin as the antiviral for the treatment of COVID-19. Although all be prudently used after delivery or after the decision to terminate the pregnancy, the long-term reproductive toxicity of ribavirin should also be taken into consideration (Narayana et al., 2005). In terms of antivirus regimens in non-pregnant women, there seems did not have any standardized treatment with four antivirals regimens. The phenomenon could be explained by the quickly updated recommendation by The National Health Commission of China during the study period. Within two months, there were seven versions of recommendation. Regarding to corticosteroids, apart from one pregnant woman received dexamethasone for fetal lung maturity at 35 gestational week, the other three pregnant women all received methylprednisolone due to complaints of dyspnea and rapid progressions on chest radiography. By contrast, most reproductive-aged non-pregnant women received methylprednisolone without clear clinical indications. Although the Chinese Thoracic Society recommended using corticosteroids prudently during the outbreak of COVID-19 (Zhao J. P. et al., 2020), the rate of corticosteroids using was still high and lack of indications, as reported in previous studies (Wang Dawei et al., 2020, Zha et al., 2020). Moreover, the virus clearance time was not associated with corticosteroids using in our study (HR 0.69, 95% CI 0.42-1.14; p = 0.15), which is consistent with a recently published study (Zha et al., 2020). In general, decisions of treatment for COVID-19 in pregnant women should be more prudent until sufficient clinical evidence appeared.

There are several limitations in our study. First, the majority of the included patients were presented as mild to moderate, which limited the interpretation of the results. Besides, there were five hospitals in Wuhan during the outbreak designated to accommodate pregnant women with COVID-19, which might generate selection bias because more severe patients might be admitted to other hospitals, other than the study hospital. Although a recent epidemiological study included 118 pregnant women reported similar results as our study, comprehensive research of pregnant women with COVID-19 is still warranted. Second, some of the patients with the clinical diagnosis were confirmed with the specific antibody (IgM). Although the reported sensitivity and specificity were good enough, the potential to introduce selection bias should still be taken into consideration, because the test might exclude true COVID-19 patients due to the low concentration of antibody. Moreover, in the beginning, due to the limited test agents, only those with clinical diagnosis had the chance to receive the serological test, therefore those without obvious abnormalities on chest

radiology or clinical symptoms have been excluded, and subsequently generated selection bias. Third, all the delivered pregnant women were infected with SARS-CoV-2 in the late stage of pregnancy, which failed us to assess the probability of vertical transmission during the early trimesters. Additionally, due to the nature of the retrospective study, we failed to test samples of the placenta, amniotic fluid, and vaginal mucosa, that diminished the power of the conclusion of no vertical transmission potential. Last, we used virus clearance time as one of the clinical outcomes, but the RT-PCR of SARS-CoV-2 from respiratory samples was not routinely performed due to the lack of agents in the beginning of the outbreak in the epicenter. The test of RT-PCR for SARS-CoV-2 was ordered by attending physicians only if there were clues of improvement of COVID-19 according to patients' symptoms and examination results, the subsequent tests for patients with a previous positive result were scheduled on the next 2-3 days which might cause a prolonged documented virus clearance time than reality. However, the two groups were under the same situation, that means the virus clearance time is still comparable. In spite of these limitations, study compared pregnant women with reproductive-aged non-pregnant women is necessary and valuable, which can substantially add important new information for doctors during the pandemic of COVID-19.

In conclusion, in this observational study, both pregnant and non-pregnant women infected with SARS-CoV-2 had good outcomes. There were no associations between pregnancy and severity of COVID-19, virus clearance time, and LOS. Regarding vertical transmission, in this small group of cases, no evidence supported vertical transmission of COVID-19 in the late stage of pregnancy including vaginal delivery. However, due to the limited data, the potential of vertical transmission is still uncertain and warranted for further study.

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Conflict of interest

Non to declare.

References

Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet (London, England) 2020;395(10226):809-15.

Chen L, Li Q, Zheng D, Jiang H, Wei Y, Zou L, et al. Clinical Characteristics of Pregnant Women with Covid-19 in Wuhan, China. The New England journal of medicine 2020.

Creanga AA, Johnson TF, Graitcer SB, Hartman LK, Al-Samarrai T, Schwarz AG, et al. Severity of 2009 pandemic influenza A (H1N1) virus infection in pregnant women. Obstetrics and gynecology 2010;115(4):717-26.

Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta bio-medica : Atenei Parmensis 2020;91(1):157-60.

Hiratsuka M, Minakami H, Koshizuka S, Sato I. Administration of interferon-alpha during pregnancy: effects on fetus. Journal of perinatal medicine 2000;28(5):372-6.

Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. 2009;374(9688):0-458.

Lam CM, Wong SF, Leung TN, Chow KM, Ho LC. A case-controlled study comparing clinical course and outcomes of pregnant and non-pregnant women with severe acute respiratory syndrome. Bjog An International Journal of Obstetrics & Gynaecology 2004;111(8):771-4.

Liang H, Acharya G. Novel corona virus disease (COVID-19) in pregnancy: What clinical recommendations to follow? Acta obstetricia et gynecologica Scandinavica 2020;99(4):439-42.

Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. The Lancet Oncology 2020;21(3):335-7.

Liu Y, Chen H, Tang K, Guo Y. Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy. The Journal of infection 2020.

Longman RE, Johnson TR. Viral respiratory disease in pregnancy. Curr Opin Obstet Gynecol 2007;19(2):120-5.

Mao R, Liang J, Shen J, Ghosh S, Zhu LR, Yang H, et al. Implications of COVID-19 for patients with pre-existing digestive diseases. The lancet Gastroenterology & hepatology 2020.

Narayana K, D'Souza UJ, Narayan P, Kumar G. The antiviral drug ribavirin reversibly affects the reproductive parameters in the male Wistar rat. Folia morphologica 2005;64(2):65-71.

NHFPC. New coronavirus pneumonia prevention and control program (7th edn). Mar 04, 2020.http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989/files/ce3e6945832a438eaae415350a8ce964.pdf (accessed Mar 22, 2020; in Chinese). 2020.

Pazos M, Sperling RS, Moran TM, Kraus TA. The influence of pregnancy on systemic immunity. Immunologic Research 2012;54(1-3):254-61.

Qiao J. What are the risks of COVID-19 infection in pregnant women? Lancet (London, England) 2020;395(10226):760-2.

Rasmussen SA, Jamieson DJ. Coronavirus Disease 2019 (COVID-19) and Pregnancy: Responding to a Rapidly Evolving Situation. Obstetrics & Gynecology 2020;Publish Ahead of Print.

Rasmussen SA, Smulian JC, Lednicky JA, Wen TS, Jamieson DJ. Coronavirus Disease 2019 (COVID-19) and Pregnancy: What obstetricians need to know. American journal of obstetrics and gynecology 2020.

Schwartz DA. An Analysis of 38 Pregnant Women with COVID-19, Their Newborn Infants, and Maternal-Fetal Transmission of SARS-CoV-2: Maternal Coronavirus Infections and Pregnancy Outcomes. Arch Pathol Lab Med 2020.

Schwartz DA, Graham AL. Potential Maternal and Infant Outcomes from (Wuhan) Coronavirus 2019-nCoV Infecting Pregnant Women: Lessons from SARS, MERS, and Other Human Coronavirus Infections. Viruses 2020;12(2).

Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. Jama 2020.

Wang S, Guo L, Chen L, Liu W, Cao Y, Zhang J, et al. A case report of neonatal COVID-19 infection in China. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2020.

Weetman AP. Immunity, thyroid function and pregnancy: molecular mechanisms. Nature reviews

Endocrinology 2010;6(6):311-8.
WHO. Coronavirus disease 2019 (COVID-19) Situation Report. Mar 16, 2020. https://wwwwhoint/docs/default-source/coronaviruse/situation-reports/20200318-sitrep-58-covid-19pdf?sfvrsn=20876712_2 (accessed Mar 16, 2020) 2020.
Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. Jama 2020.
Zeng L, Xia S, Yuan W, Yan K, Xiao F, Shao J, et al. Neonatal Early-Onset Infection With SARS-CoV-2 in 33 Neonates Born to Mothers With COVID-19 in Wuhan, China. JAMA pediatrics 2020.
Zha L, Li S, Pan L, Tefsen B, Li Y, French N, et al. Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19). The Medical journal of Australia 2020.
Zhang L, Jiang Y, Wei M, Cheng BH, Zhou XC, Li J, et al. [Analysis of the pregnancy outcomes in pregnant women with COVID-19 in Hubei Province]. Zhonghua fu chan ke za zhi 2020;55(0):E009.
Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2020.
Zhao JP, Hu Y, Du RH, Chen ZS, Jin Y, Zhou M, et al. Expert consensus on the use of corticosteroid in patients with 2019-nCoV pneumonia. Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases 2020;43(3):183-4.
Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. The New England journal of medicine 2020;382(8):727-33.

Figure 1: Flow chart of study inclusion process.

Figure 2: Kaplan–Meier curves and log-rank test of length of hospital stay and virus clearance time in pregnant and reproductive aged non-pregnant women with coronavirus disease 2019 (COVID-19).

Table 1. Baseline characteristics of pregnant and non-pregnant reproductive aged women with coronavirus disease 2019 (COVID-19)

To be continued.

Characteristics	Pregnant women (n = 28)	Non-pregnant women (n = 54)	*p*
Baseline			
Age (years)	30 (26.75-32)	31.00 (28.00-35.00)	0.097
Time from illness onset to hospital admission (days)	1.00 (1.00-6.50)	7.00 (5.00-10.00)	< 0.001
Severity of disease			
Mild	2 (7.1)	0 (0.0)	0.062
Normal pneumonia	24 (85.7)	53 (98.1)	..
Severe	2 (7.1)	1 (1.9)	..
Comorbidities			
Hypertension	1 (3.6)	0 (0.0)	0.599
Diabetes	2 (7.1)	4 (7.4)	..
Chronic hepatitis B virus infection	2 (7.1)	2 (3.7)	..
Hypothyroidism	1 (3.6)	1 (1.9)	..
Symptoms			
Fever	5 (17.9)	29 (53.7)	0.004
Malaise	1 (3.6)	3 (5.6)	1
Cough	7 (25.0)	32 (59.3)	0.007
Dyspnea	2 (7.1)	6 (11.1)	0.856
Abdominal pain	5 (17.9)	0 (0.0)	0.007
Signs			
Respiratory rate	20 (18-22)	20 (18-20)	0.239
Heart rate	84 (80-91)	82 (77.25-99.5)	0.537
Systolic pressure (mmHg)	113 (109-128)	120.00 (112.5-125)	0.534
Diastolic pressure (mmHg)	70.5 (64.75-77.25)	74.5 (69.25-79.75)	0.067
Peripheral oxygen saturation (%)	98 (97-98)	98 (97-99)	0.868
Laboratory tests			
White blood cell count (×109/L)	7.54 (6.58-10.26)	4.69 (3.87-5.77)	< 0.001
< 3.5	0 (0.0)	8 (14.8)	< 0.001
3.5-9.5	18 (64.3)	44 (81.5)	..
> 9.5	10 (35.7)	2 (3.7)	..
Neutrophil count (×109/L)	5.87 (4.62-8.62)	2.88 (1.99-3.57)	< 0.001
Lymphocyte count (×109/L)	1.29 (0.91-1.71)	1.54 (1.09-2.03)	0.148
< 1.0	8 (28.6)	14 (25.9)	0.906
≥ 1.0	20 (71.4)	40 (74.1)	..

Characteristics	Pregnant women (n = 28)	Non-pregnant women (n = 54)	*p*
Hemoglobin (g/L)	117.5 (106.75-129)	126 (121.25-135.5)	0.018
Platelet count (×109/L)	175.00 (154-233)	210 (164.75-249)	0.235
< 100	2 (7.1)	0 (0.0)	0.22
≥ 100	26 (92.9)	54 (100)	..
D-dimer (mg/L)	2.80 (1.36-4.29)	0.26 (0.13-0.42)	< 0.001
< 0.5	2 (7.7)	40 (75.5)	< 0.001
≥ 0.5	24 (92.3)	13 (24.5)	..
Fibrinogen	2.88 (2.64-3)	2.18 (2.03-2.5)	< 0.001
Alanine aminotransferase (U/L)	9.8 (7.05-12.15)	13.00 (10.0-18.3)	0.006
< 40	27 (100)	52 (96.3)	0.80
≥ 40	0 (0.0)	2 (3.7)	..
Albumin (g/L)	35.5 (34-38.65)	43.00 (41-43.85)	< 0.001
Creatine (μmol/L)	43.25 (35.6-52.72)	53.25 (48.4-62.85)	0.001
< 75	25 (96.2)	49 (90.7)	0.683
≥ 75	1 (3.8)	5 (9.3)	..
Lactate dehydrogenase (U/L)	146 (127-182)	140 (118.25-163.75)	0.233
< 220	21 (84.0)	41 (97.6)	0.116
≥ 220	4 (16.0)	1 (2.4)	..
Creatine kinase (U/L)	46 (35.75-74.5)	65 (45-75)	0.34
< 140	21 (87.5)	40 (95.2)	0.51
≥ 140	3 (12.5)	2 (4.8)	..
Procalcitonin (ng/ml)	0.06 (0.04-0.13)	0.04 (0.03-0.05)	<0.001
0.1-0.5	22 (95.7)	53 (100)	0.665
> 0.5	1 (4.3)	0 (0)	..
C Reactive Protein (mg/dl)	1.81 (0.44-4.84)	0.12 (0.03-0.61)	< 0.001
> 0.6	17 (68)	14 (25.9)	0.001
Radiological findings			
Pneumonia	26 (92.9)	54 (100)	0.74

Table 1. Continued

Treatments and outcomes	Pregnant women (n = 28)	Non-pregnant women (n = 54)	*p*
Treatments			
Antivirals			
Ribavirin	20 (71.4)	19 (35.2)	< 0.001
Umifenovir	1 (3.6)	11 (20.4)	..
Ribavirin+Umifenovir	0 (0.0)	17 (31.5)	..
Interferon alpha inhalation	0 (0.0)	7 (13.0)	..
Antibiotics	24 (85.7%)	47 (87%)	
Cephalosporins	20 (71.4)	9 (16.7)	< 0.001
Quinolone	4 (14.3)	6 (11.1)	..
Cephalosporins + quinolone	0 (0)	32 (59.3)	..
Corticosteroids	4 (14.3)	21 (38.9)	0.041
Gamma globulin	3 (10.7)	19 (35.2)	0.035
Outcomes			
Hospitalization	7 (25)	0 (0)	< 0.001
Discharge	21 (75)	54 (100)	..
Death	0 (0)	0 (0)	..
Virus clearance time (days)	12 (8-26.5)	18 (12-25)	0.613
Length of hospital stay (days)	14 (12-22.25)	18 (10.25-22)	0.635

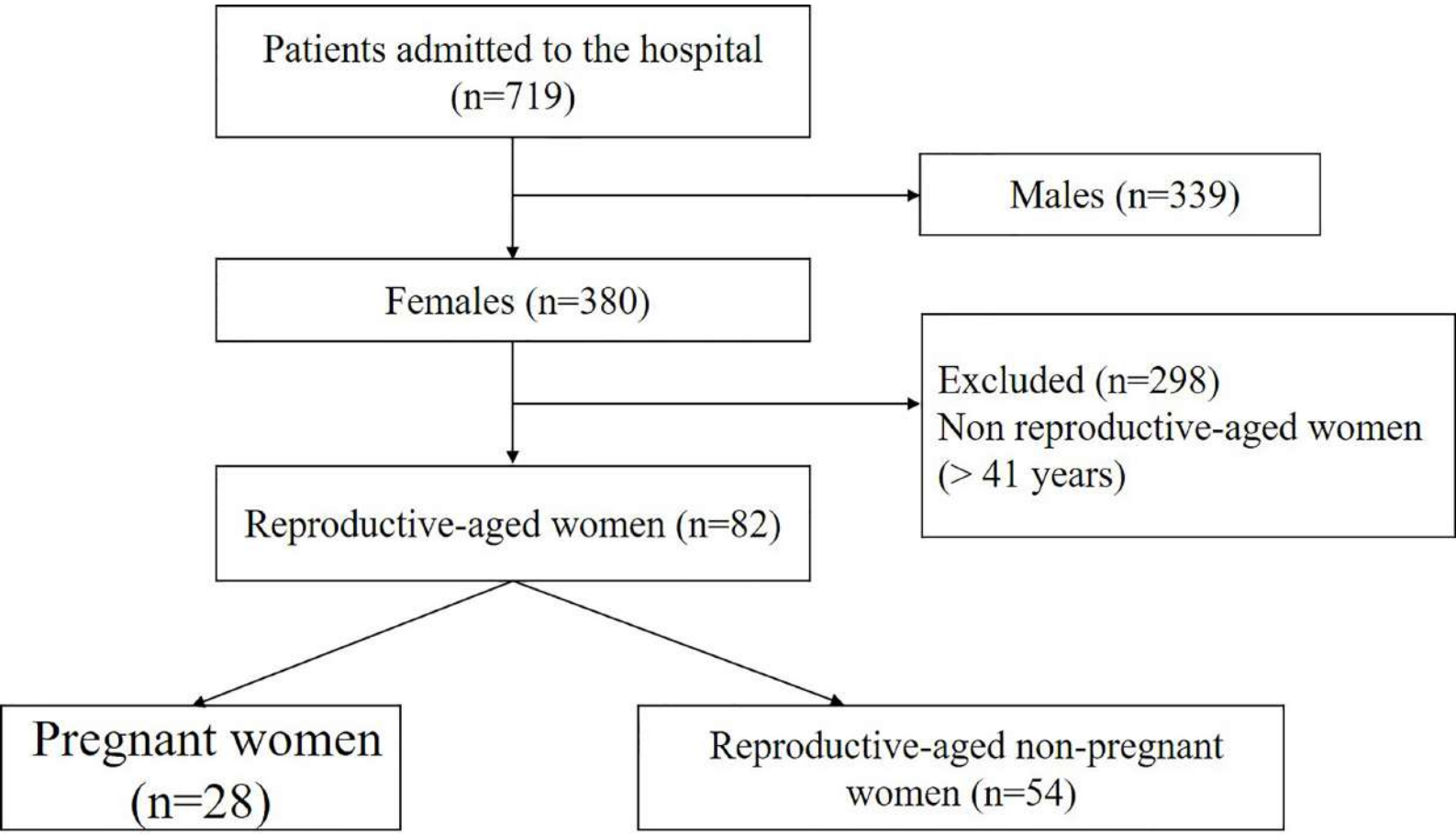
Table 2. Treatments and clinical outcomes in pregnant and non-pregnant reproductive aged women with coronavirus disease 2019 (COVID-19).

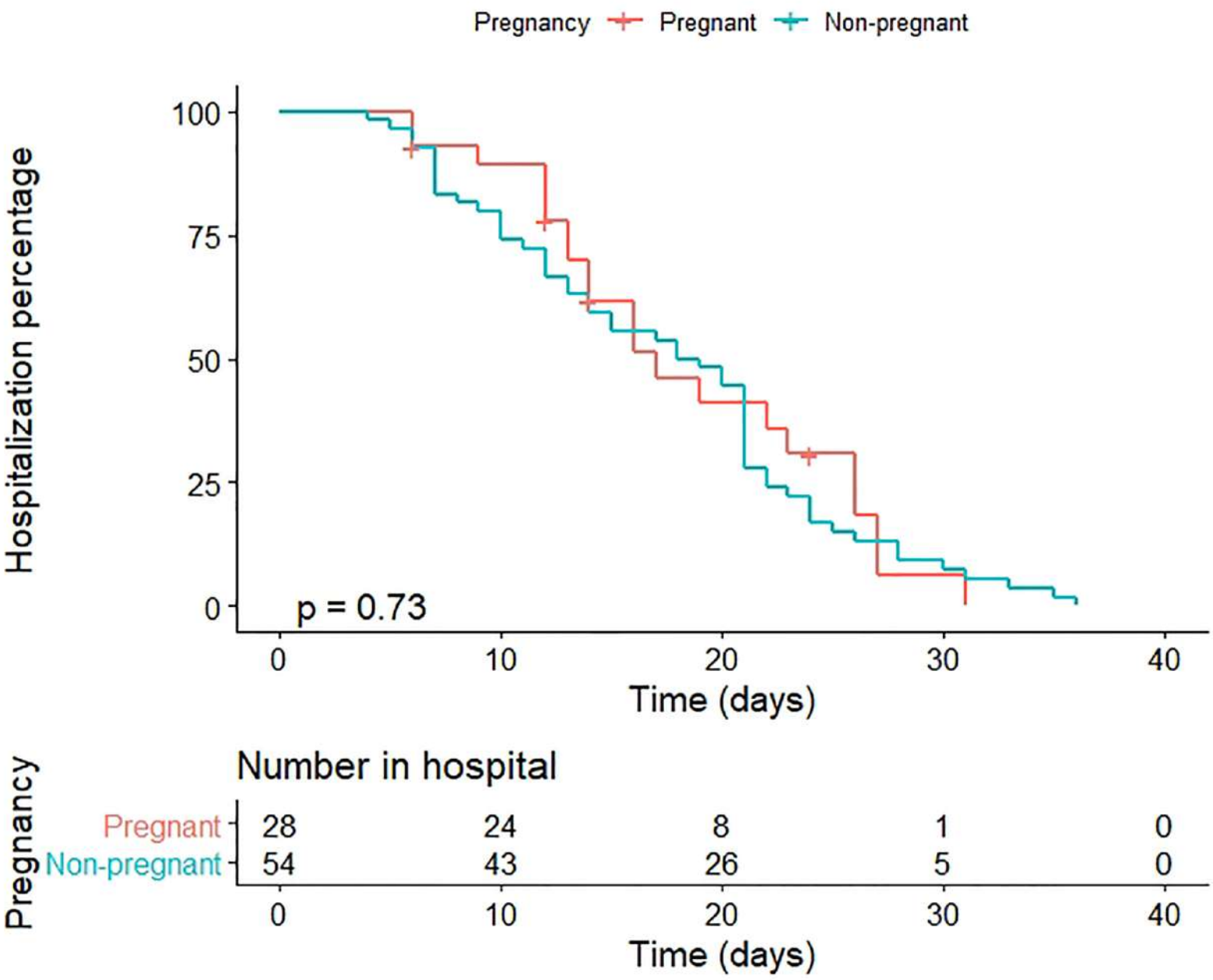
Table 3. Maternal and neonatal characteristics and outcomes

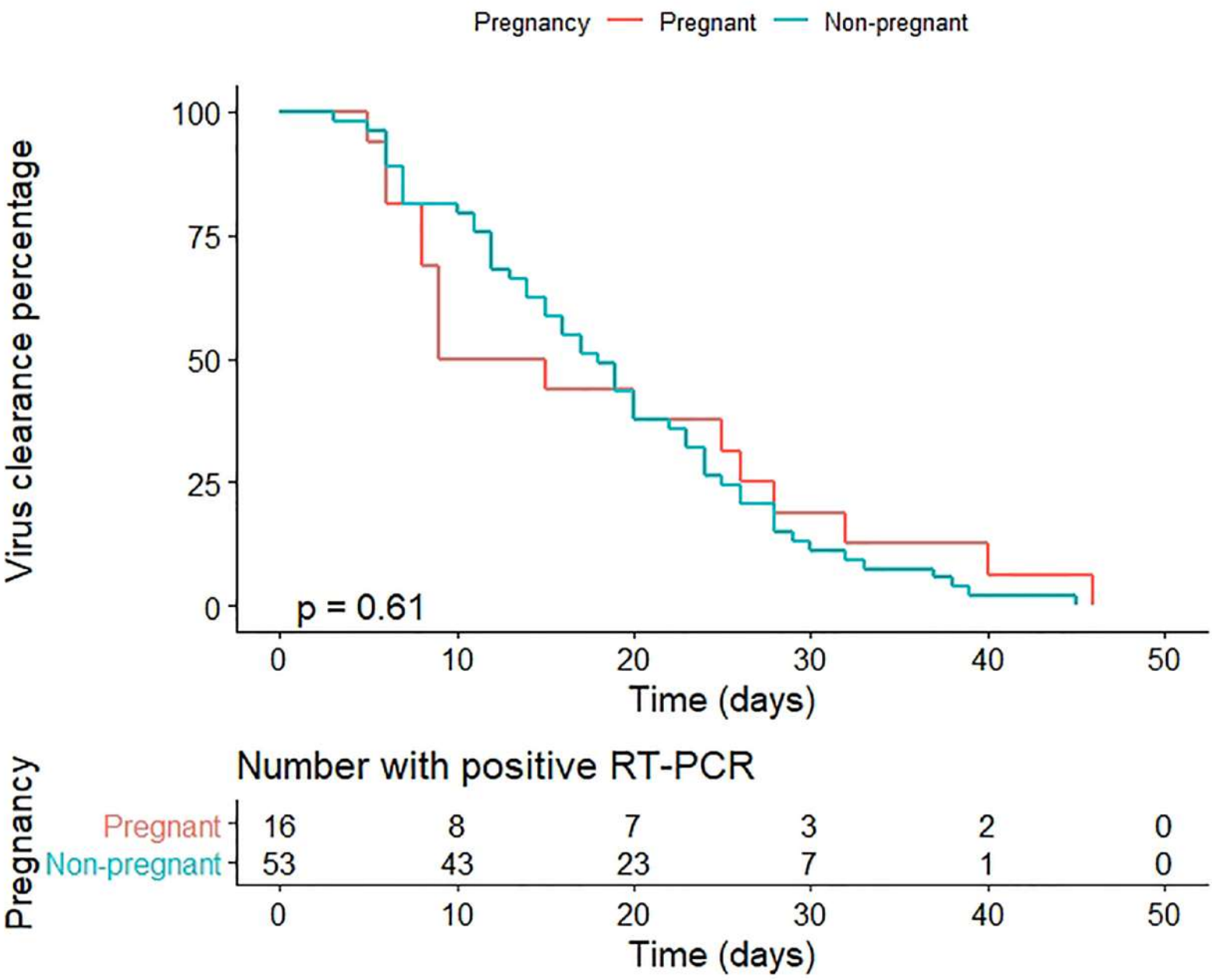
Characteristics and outcomes	
Maternal (n = 28)	n (%) or Median (IQR)
Gestational age on admission (weeks)	38 (36.5-39)
First trimester	3 (10.7)
Second trimester	1 (3.6)
Third trimester	24 (85.7)
From admission to delivery (days)	1 (1-6)
Outcome of pregnancy	
Cesarean section	17 (60.7)
Vaginal delivery	5 (17.9)
Medical abortion	4 (14.3)
Continued pregnancy	2 (7.1)
Neonatal (n = 23)	n (%) or Median (IQR)
SARS-CoV-2 infection	0 (0)
Premature delivery	1 (4.35)
Birthweight (g)	3130 (2915-3390)
Low birthweight (< 2500 g)	1 (4.35)
Apgar score (1 minute)	10 (10-10)
Apgar score (5 minute)	10 (10-10)
Severe neonatal asphyxia	0 (0)
Live birth	10 (100)
Neonatal intensive care unit admission	0 (0)
Neonatal death	0 (0)

Highlights

- Most pregnant women with SARS-CoV-2 infection present as mild to moderate type.
- Pregnant women have comparable clinical course and outcomes compare with reproductive-aged non-pregnant women infected with SARS-CoV-2.
- No evidence supports vertical transmission of COVID-19 including vaginal delivery.


Patients admitted to the hospital (n=719)
Males (n=339)
Females (n=380)
Excluded (n=298)
Non reproductive-aged women (> 41 years)
Reproductive-aged women (n=82)
Pregnant women (n=28)
Reproductive-aged non-pregnant women (n=54)


Pregnancy
Pregnant
Non-pregnant
Hospitalization percentage
100
75
50
25
0
p = 0.73
0
10
20
30
40
Time (days)
Number in hospital
Pregnancy
Pregnant
Non-pregnant
28
24
8
1
0
54
43
26
5
0
0
10
20
30
40
Time (days)


Pregnancy
Pregnant
Non-pregnant
Virus clearance percentage
100
75
50
25
0
p = 0.61
0
10
20
30
40
50
Time (days)
Number with positive RT-PCR
Pregnancy
Pregnant
Non-pregnant
16
8
7
3
2
0
53
43
23
7
1
0
0
10
20
30
40
50
Time (days)