The clinical findings and outcomes of symptomatic pregnant women diagnosed with or suspected of having coronavirus disease 2019 in a tertiary pandemic hospital in Istanbul, Turkey

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Abstract

Aim: To observe the clinical course of symptomatic pregnant women diagnosed with or suspected of having COVID-19.

Methods: This study analyzed the clinical and laboratory results of 27 patients with real-time polymerase chain reaction (RT-PCR)-confirmed COVID-19 and 25 patients with a suspected COVID-19 diagnosis based on their symptoms and chest computed tomography (CT) findings. The patients’ coagulation parameters and acute-phase reactants were evaluated both before and after treatment. The maternal and neonatal outcomes were also reviewed.

Results: The mean duration of hospitalization was 6.1 ± 3 days. The gestational age of the patients ranged from 6w2d to 40w2d. Thirty-five patients’ CT scan findings suggested viral pneumonia. Four patients delivered vaginally, and 10 patients underwent a cesarean section during the study period. Four of the cesarean deliveries were indicated due to COVID-19 hypoxemia-related fetal distress. Four patients were admitted to the intensive care unit (ICU) after the cesarean section.

Conclusion: Early hospitalization and medical treatment can alleviate symptoms, improve the clinical course and reduce the need for ICU in symptomatic pregnant patients with suspected or confirmed COVID-19. Chest CT scans are a suitable option for suspected but unconfirmed COVID-19 infection.

Key words: chest CT scan, COVID-19, novel coronavirus-2019, pregnancy, SARS-Cov-2.
Introduction

The new coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome 2 (SARS-CoV-2) virus, is an enveloped RNA virus in the betacoronaviridae family that was first detected in Wuhan City, China, in December 2019.1 The virus quickly spread to other countries and became a major health problem that caused severe viral pneumonia and death. The World Health Organization declared COVID-19 a pandemic on 11 March 2020.2 The spread of the virus is thought to occur mainly via respiratory droplets. Although most people infected with the SARS-CoV-2 virus are asymptomatic or have mild symptoms, approximately 5% experience severe viral pneumonia, which requires mechanical ventilation support.3,4

Currently, the gold standard method to diagnose COVID-19 is the real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay, which has some limitations, including difficulty in testing higher numbers of suspected patients, the necessity of maintaining cold chain rules, the occurrence of errors during the sampling process, and a longer duration required for obtaining the test results. In contrast, thorax computed tomography (CT) scanning enables a prompt diagnosis because the appearance of bilateral, peripheral multi-lobar ground-glass opacities or consolidation has a high sensitivity for COVID-19 infection.5,6

Pregnant women are at high risk for COVID-19 and its related complications due to the immune, cardiac and pulmonary changes that take place during pregnancy. Both the data from previous coronavirus infections (Severe Acute Respiratory Syndrome Coronavirus and Middle East Respiratory Coronavirus) and the current lack of data regarding this new coronavirus infection have increased concerns regarding the effects of COVID-19 on pregnant women and their newborns.7,8

There is still a lack of clinical and epidemiological data in the literature regarding pregnancy and COVID-19. Studies of pregnant women with COVID-19 have been small and generally have included only third-trimester pregnancies; consequently, little is known about the clinical progression of the disease in the first and second trimesters and about the effect of the disease on coagulation parameters.9-15 Based on the current literature, the SARS-CoV-2 virus has not been vertically transmitted, and pregnant women with COVID-19 have similar clinical features to non-pregnant patients.

This study aimed to observe the clinical features, laboratory findings, and perinatal and neonatal outcomes of symptomatic hospitalized pregnant women diagnosed with or suspected of having COVID-19 in a tertiary pandemic hospital.

Methods

This retrospective study was conducted at the Obstetrics and Gynecology Department of a tertiary healthcare center in Turkey designated for COVID-19 patients within the scope of national precautions for the COVID-19 outbreak. Ethics approval was obtained from the hospital’s local ethics committee (Approval number 2020/158). The clinical outcomes, sociodemographic characteristics and radiological and laboratory features of 52 pregnant women hospitalized between 25 March and 25 May 2020 due to suspected or diagnosed COVID-19 infection were reviewed; 27 of these women tested positive for COVID-19 infection following a RT-PCR test. The remaining 25 patients were given a suspected COVID-19 diagnosis according to their symptoms and CT scan findings. We excluded patients who were asymptomatic, had negative RT-PCR results and refused hospitalization.

The sociodemographic characteristics and medical histories of the patients were obtained upon admission. Gestational age was calculated according to the date of the patients’ last menstrual period. After routine physical and obstetric examinations that included obstetric ultrasonography, the patients were transferred to the COVID-19 quarantine service and hospitalized in isolated patient rooms. CT scans were performed after covering the entire abdomen with a lead blanket to protect the fetus from the radiation. Thoracic CT scan findings were reviewed from radiologists’ reports accessed from the computer-based database. Written informed consent for radiologic imaging and medical therapy was obtained from all patients. Nasal and pharyngeal swabs for the RT-PCR tests were performed, and the samples were transferred to national virology laboratories for results following cold chain rules.

Coagulation parameters (including activated partial thromboplastin time, prothrombin time, fibrinogen, international normalized ratio, and D-dimer), platelet, red blood cell, lymphocyte and neutrophil counts, kidney and liver function tests, and hemoglobin, hematocrit, C-reactive protein (CRP), ferritin and...
procalcitonin levels, were evaluated at admission and again at 2-day intervals during the hospital stay. Both admission and discharge values for D-dimer, fibrinogen, ferritin, procalcitonin and CRP are presented. The participants were categorized according to their gestational age as first-, second- or third-trimester pregnancies.

All patients received oxygen support, enoxaparin, and hydroxychloroquine treatment. Other antiviral and antibiotic medications (i.e., oseltamivir, azithromycin, lopinavir/ritonavir, favipiravir, and ceftriaxone) were administered based upon the clinical conditions of the patients. The applied medical treatment protocols were as follows: hydroxychloroquine, 400 mg p.o. every 12 h on the first day and 200 mg p.o. every 12 h on the following days; oseltamivir, 75 mg p.o. twice a day; favipiravir, 1600 mg p.o. every 12 h on the first day and 600 mg p.o. twice a day on the following days; lopinavir 200 mg / Ritonavir 50 mg two capsules p.o. twice a day; azithromycin 500 mg p.o. on the first day and 250 mg p.o. on the following days; ceftriaxone 1 gr i.v. every 12 h. The duration of medical treatment was determined by infectious disease specialists based on the clinical conditions of the patients and laboratory results.

Labor and delivery were conducted according to the national safety guidelines with all healthcare workers wearing personal protective equipment. The neonatal outcomes of the patients delivered during follow-up were evaluated, including neonatal ICU admission, fetal weight, cord blood pH, first- and fifth-minute Apgar score, and the RT-PCR results of neonatal oropharyngeal and nasal swab samples. Newborn babies were isolated from their mothers in the neonatal care unit and were given collected breastmilk.

Statistical analysis

The data analysis was performed with SPSS software (IBM SPSS Statistics for Windows, Version 20.0 IBM Corp.). The categorical variables are presented as the numbers and frequencies. Continuous variables are shown as the mean, the standard deviation and the minimum and maximum values. The paired-sample t-test and Wilcoxon Signed Rank test were used to compare the D-dimer, fibrinogen, ferritin, procalcitonin and CRP levels both before and after treatment. $\chi^2$ and Fisher’s exact tests were used to evaluate the association between RT-PCR test results and clinical symptoms. A P-value of <0.05 was considered statistically significant.

Results

The mean age of the patients was 30 ± 5.7 years. The demographic characteristics and laboratory results of the patients are presented in Tables 1 and 2. The mean duration of hospitalization was 6.1 ± 3 days. Five, 24, and 23 of the cases were in the first, second and third trimesters of pregnancy, respectively. The median gestational age of the patients was 26 weeks (range: 6w2d–40w2d).

| Table 1 Sociodemographic, clinical characteristics and laboratory results of the study population |
|---------------------------------------------------------------|
| **Minimum** | **Maximum** | **Mean** | **SD** |
| Age (years) | 18 | 42 | 30.0 | 5.7 |
| BMI (kg/m²) | 19.6 | 46.8 | 28.3 | 4.8 |
| Hospitalization (days) | 2 | 20 | 6.1 | 3.0 |
| Gravidity | 1 | 10 | 3.1 | 2.1 |
| Parity | 0 | 8 | 2.9 | 2.0 |
| Gestational Age (weeks/days) | 6w2d | 40w2d | 26w1d | 8w6d |
| RBC (x10⁹/mm³) | 2.6 | 5.1 | 3.9 | 0.4 |
| WBC (cells/mm³) | 3390 | 26 810 | 8902.8 | 4149.1 |
| Lymphocyte (cells/mm³) | 240 | 3270 | 1442.5 | 614.8 |
| Neutrophil (cells/mm³) | 1030 | 22 640 | 6511.1 | 3805.8 |
| Platelet (cells/mm³) | 117 000 | 406 000 | 216 576.9 | 64 858.6 |
| Hemoglobin (gr/dL) | 6.5 | 14.9 | 11 | 1.5 |
| Hematocrit (%) | 21 | 44.2 | 33.0 | 4.2 |
| aPTT (sn) | 21.4 | 49.5 | 35.7 | 4.3 |
| PT (sn) | 10.9 | 15.9 | 13.1 | 1.3 |
| INR | 0.8 | 1.2 | 0.9 | 1.1 |

aPTT, activated partial thromboplastin time; BMI, body mass index; d, days; INR, international normalized ratio; PT, prothrombin time; RBC, red blood cell; SD, standard deviation; w, weeks; WBC, white blood cell.
Twenty-seven of the patients had RT-PCR-confirmed diagnoses of COVID-19. The remaining 25 symptomatic patients’ CT findings suggested viral pneumonia. The distribution of symptoms was as follows: fever, 17.3%; cough, 73%; fatigue, 36.5%; sore throat, 13.4%; shortness of breath, 40.3%; loss of smell and taste, 5.7%; abdominal pain and diarrhea, 7.6%; and headache, 9.6%. There was no significant difference between RT-PCR test positive and negative patients in terms of clinical symptoms including fever ($P = 0.621$), cough ($P = 0.279$), headache ($P = 0.575$), shortness of breath ($P = 0.609$), sore throat ($P = 0.267$), fatigue ($P = 0.071$), loss of smell and taste ($P = 0.507$) and diarrhea ($P = 0.262$).

Pulmonary CT scanning was performed in 40 of the patients. The pulmonary CT scan images showed ground-glass opacity in 80%, patch-like shadows in 55%, fiber shadows in 15%, pleural effusion in 15%, atelectasis in 17.5%, a crazy-paving sign in 2.5% and a halo sign in 2.5%.

The frequencies of patients who were administered oseltamivir, lopinavir/ritonavir, favipiravir, azithromycin and ceftriaxone in addition to hydroxychloroquine treatment were 19.2%, 11.5%, 5.8%, 21.2% and 5.8%, respectively. However, 28 (54.9%) patients were administered hydroxychloroquine treatment alone.

Four patients delivered vaginally, and 10 patients underwent a cesarean section during the study period. Four of the cesarean deliveries were performed due to fetal distress after a sudden decrease in maternal oxygen saturation related to COVID-19 disease. Eight patients had preterm deliveries (four early preterm and four late preterm deliveries) during the study period.

Four of the delivered patients were admitted to the ICU following cesarean section. All of these patients were admitted with cough and shortness of breath. The laboratory results, clinical features and pulmonary CT scan images of these patients are presented in Table 3 and Figure 1. Case 4 had a contact history with a COVID-19 patient. On the third day of hospitalization, a sudden decrease on her oxygen saturation was observed while she was under nasal oxygen support and hydroxychloroquine treatment and an emergency cesarean delivery was performed due to hypoxemia related fetal distress. Case 6 was diagnosed preeclampsia during follow-up due to higher blood pressure levels and 5 g proteinuria in her 24-h urine analysis. She received alpha methyldopa, MgSO4, betamethasone and hydroxychloroquine treatment. On the fifteenth day of hospitalization, she had a cesarean delivery due to maternal hypoxemia and severe preeclampsia.

Case 12 underwent cesarean delivery on the third day of hospitalization due to suddenly decreased oxygen saturation up to 70% under nasal oxygen support. Case 14 had a 27-week in vitro fertilization pregnancy and was diagnosed preeclampsia the month before her admission. Her blood pressure was 170/110, and her oxygen saturation was 60% at admission. An emergency cesarean section was performed due to maternal hypoxemia and severe preeclampsia.

Throat swab samples were obtained from all newborn babies within 24 h of birth; none were positive.
for COVID-19. Table 4 shows the maternal and neonatal data of patients delivered during the study period.

While the CRP and procalcitonin levels significantly decreased after treatment, there were no significant differences before or after treatment in terms of the fibrinogen, ferritin, and D-dimer levels (Table 5).

Discussion

Although some data have been published since the beginning of the COVID-19 pandemic, the literature on pregnant patients is scant. Della Gatta et al.’s16 systematic review evaluated just 50 patients with an RT-PCR-confirmed diagnosis. The median maternal age was 30 years, and the median gestational age at diagnosis was 36 weeks. Of the 48 patients who were delivered, there were only two vaginal births, and 39% of the patients had a preterm delivery; just two of the patients were in the second trimester. In our study, most pregnant patients were in their thirties, and nearly half were in the second trimester. Twenty-seven patients had an RT-PCR-confirmed diagnosis of COVID-19. However, all remaining patients were symptomatic and had positive CT findings that

| Table 3 Clinical characteristics and blood test results of patients admitted to the ICU |
|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Blood test results at hospitalization | Blood test results at discharge | Hospitalization at ICU (days) | Age (years) |
| WBC (cells/mm³) | 10,800 | 10,230 | 9,140 | 20,580 |
| Neutrophil (cells/mm³) | 9,110 | 8,030 | 7,350 | 18,140 |
| Lymphocyte (cells/mm³) | 910 | 1,530 | 1,090 | 1,780 |
| Platelet (cells/mm³) | 223,000 | 164,000 | 186,000 | 335,000 |
| D-Dimer (μg FEU/mL) | 0.74 | 0.69 | 0.04 | 1.79 |
| Fibrinogen (mg/dL) | 574 | 467 | 555 | 574 |
| INR | 0.98 | 1.00 | 0.96 | 1.06 |
| Ferritin (μg/L) | 94 | 25 | 59 | 8 |
| Procalcitonin (ng/mL) | 0.68 | 0.04 | 0.24 | 0.12 |
| CRP (mg/L) | 153 | 17 | 113 | 45 |
| Blood test results at discharge | | | | |
| WBC (cells/mm³) | 6,180 | 6,890 | 13,810 | 4,390 |
| Neutrophil (cells/mm³) | 3,440 | 4,390 | 10,990 | 2,890 |
| Lymphocyte (cells/mm³) | 1,950 | 1,960 | 1,710 | 940 |
| Platelet (cells/mm³) | 445,000 | 137,000 | 397,000 | 274,000 |
| D-Dimer (μg FEU/mL) | 0.87 | 0.26 | 0.48 | 4.56 |
| Fibrinogen (mg/dL) | 527 | 483 | 401 | 401 |
| INR | 1.12 | 0.94 | 1.3 | 1.07 |
| Ferritin (μg/L) | 75 | 37 | 24 | 378 |
| Procalcitonin (ng/mL) | 0.03 | 0.02 | 0.05 | 0.05 |
| CRP (mg/L) | 15 | 13 | 10 | 9 |
| Hospitalization at ICU (days) | 15 | 2 | 10 | 3 |
| Age (years) | 32 | 35 | 32 | 33 |
| Gravidity | 3 | 2 | 3 | 1 |
| Parity | 1 | 1 | 1 | 0 |
| BMI (kg/m²) | 27.5 | 35.8 | 30.4 | 29.7 |
| SaO₂ at admission (%) | 95 | 97 | 94 | 60 |
| Chronic disease | — | Ascending aortic aneurysm | — | — |
| Complaint at admission | Cough, shortness of breath | Cough, shortness of breath | Cough, shortness of breath | Cough, shortness of breath |
| RT-PCR result | Positive | Negative | Positive | Negative |
| Duration Between hospitalization and ICU admission (days) | 3 | 15 | 3 | 0 |

BMI, body mass index; CRP, C-reactive protein; CT, computed tomography; ICU, intensive care unit; INR, international normalized ratio; RT-PCR, real-time reverse transcriptase-polymerase chain reaction; WBC, white blood cell.
suggested viral pneumonia. Ten out of 14 patients had cesarean deliveries; eight patients had preterm deliveries and 4 were late preterm deliveries beyond 34 weeks. In only four patients, the cesarean indication was fetal distress from severe COVID-19-related hypoxemia. The other cesarean deliveries were due to non-COVID-19-related indications. Similarly, only two of Della Gatta et al.’s patients were admitted to the ICU. These results confirm that the outcomes of COVID-19 pregnancies are generally favorable.

Another different finding was the distribution of symptoms. Our study had fewer fevers than previously reported (17.3% vs. 48%, respectively), while cough was the main complaint of prior patients. This discrepancy may be related to our early treatment protocol with hydroxychloroquine and antiviral therapy. All of the newborn babies in our investigation were negative for COVID-19, which was similar to Della Gatta et al.’s results. According to Yang et al., fever was the main complaint in 87% of their 114 pregnant cases, which differed from our results. Adverse outcomes, including stillbirth (1.2%) and neonatal death, were reported in only 1.2% of these patients. While 21.3% of Della Gatta et al.’s participants had preterm deliveries, the preterm delivery rate in our study was 15.3%. We also had four preterm deliveries that were unrelated to COVID-19. Among the four preterm deliveries due to COVID-19-related hypoxemia, two of them were late preterm deliveries and the others were early preterm deliveries.

We used chest CT scanning to confirm the presence of COVID-19 disease because the detection rate of RT-PCR is relatively low and may be related to improper sampling techniques. Chest CT played an important role in the diagnosis and management of our patients; it was used in 40 of our reviewed patients and has a good diagnostic value for COVID-19-related pneumonia. In contrast, the RT-PCR analysis has some limitations, including false-negative results due to inappropriate sample collection or procedural errors. It was also time-consuming to start medication at the beginning of a pandemic. This limitation of RT-PCR led us to the nearly routine use of chest CT for the early diagnosis and hospitalization of pregnant patients.
patients. Ground-glass opacity is the earliest manifestation that has been reported in up to 98% of COVID-19 patients\textsuperscript{18} and was present in 80% of our patients. In a different series, multifocal, patchy or segmental consolidations were also identified in 2–64% of patients.\textsuperscript{18} Patch-like shadows were the second most common finding in our COVID-19 patients. The crazy-paving sign, which is attributed to alveolar edema and acute interstitial inflammation, has been reported in 5–36% of COVID-19 patients.\textsuperscript{19} We found this sign in only 2.5% of our patients. This discrepancy may be related to the severity of the patients’ conditions, as we began medication upon hospitalization; as a result, we had few patients with severe conditions who required ICU hospitalization.

In their retrospective study that included 140 patients diagnosed with COVID-19, Liu\textit{ et al.}\textsuperscript{20} investigated the prognostic value of inflammatory markers, including interleukin-6, CRP and procalcitonin, and found that interleukin-6 and CRP can effectively assess the disease severity and predict its outcome. To our knowledge, there are no published data regarding the efficacy of inflammatory markers in pregnant COVID-19 patients. In our study, CRP and procalcitonin levels significantly decreased after medical treatment with hydroxychloroquine.

COVID-19 increases the risk of intravascular thrombosis, and a prophylactic dose of a low-molecular weight heparin (LMWH) is recommended for patients hospitalized due to COVID-19.\textsuperscript{21} Because prophylactic LMWH is a routine clinical treatment for all pregnant patients hospitalized for more than 2 days, we were able to begin enoxaparin treatment immediately. Although there is not yet enough evidence to support our suspicion, we believe that LMWH treatment may facilitate the early recovery of pregnant patients with COVID-19.

Vertical transmission of the SARS-CoV-2 virus has not been demonstrated, but little is known about the risk of adverse fetal and neonatal outcomes in patients infected during their first and second trimesters. Our study included 5 first trimester and 24 s-trimester patients who will be closely monitored, and the outcome of these pregnancies may shed light on this issue along with cumulative data from around the world.

One strength of this study was that it included a higher number of first- and second-trimester pregnant patients with COVID-19 than other published studies. In addition, the evaluation of acute-phase reactants and coagulation parameters both before and after treatment also contributed to the literature. The study’s
retrospective design and lack of data regarding RT-PCR results for cord blood in newborns and mother’s breastmilk samples are limitations of this study.

In conclusion, we believe that our results offer a positive contribution to currently available data for the diagnosis and treatment of pregnant COVID-19 patients. Although pregnant women with COVID-19 are no more likely than their nonpregnant counterparts to develop severe pneumonia or to die, early hospitalization and treatment are mandatory to relieve symptoms, to shorten the hospitalization period and to lower the rate of progression to severe pneumonia. Chest CT is a good diagnostic tool in patients who require rapid disease confirmation, as RT-PCR is time-consuming; CT scanning also carries a negligible risk of false-negative results. Finally, the oxygen saturation of all COVID-19 patients should be closely monitored because severe hypoxemia may quickly progress. CRP and procalcitonin are also helpful for monitoring these patients.

Disclosure

All of the authors declare that they have no conflict of interest.

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