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Original Article

Clinical, Radiological and Laboratory Features and Treatment Responses of COVID-19 Diseases in Pregnant Women

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ABSTRACT

Background SARS-CoV-2 is more contagious than other viruses among populations. Pregnant women are particularly susceptible to respiratory pathogens and severe pneumonia.

Material and Methods Thirty-two pregnant women who were diagnosed with COVID-19 disease by PCR test in our hospital between March 2020 and June 2020 were included in this study. Patients' complaints, comorbid disorders, general physical conditions, radiological, laboratory characteristics, treatment results and maternal and fetus health were recorded retrospectively.

Results The mean age of the patients was 26.6 years. Pregnancy-induced hypertension was evident in 2 patients (6.2%), preeclampsia in 1 patient (3.1%), asthma in 1 patient (3.1%). Mostly detected complaints were cough (34.4%) and fatigue (31.3%). The most frequent abnormal laboratory findings were high fibrinogen level (80.9%), high D-dimer level (71.4%), high CRP level (58.1%). Lymphopenia was found in 15.6% of patients. The maternal and fetal mortality rate was 0%. The rate of improvement in laboratory values in response to the treatment was as follows respectively; sodium (92.3%), lymphocyte count (80%), LDH (62.5%), CRP (61.1%), D-dimer (25%). None of the patients developed spontaneous abortion. Cesarean delivery was performed in 15.6% of patients. 5 newborns were negative for the COVID-19 PCR test two times.

Conclusions Mostly detected complaints in pregnancy patients with COVID-19 disease were cough and fatigue. While evaluating the treatment response, the improvement in sodium level may be more valuable than the improvement in acute phase reactants. The prognosis was quite good in mothers and children treated for this disease. The vertical transition of the disease could not be demonstrated.

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Introduction

Coronaviruses are enveloped, non-segmented, positive-sense ribonucleic acid (RNA) viruses belonging to the family Coronaviridae, order Nidovirales.[1] Pneumonia caused by COVID-19 is a highly contagious and infectious disease declared a health emergency by the World Health Organization.[2-4] Pregnant women are particularly susceptible to respiratory pathogens and severe pneumonia, because of the physiologic changes in the immune and cardiopulmonary systems (e.g. diaphragm elevation, increased oxygen consumption, and oedema of respiratory tract mucosa), which can render them intolerant to hypoxia.[5] Despite some COVID-19 guidelines, some clinical questions about pregnancy and childbirth remain unanswered.[6] The rate of COVID-19 in pregnant women and pregnant women who applied to the hospital for any reason or were newly admitted to the hospital was around 10%. In general, pregnancy does not significantly increase the risk of becoming infected with SARS-CoV-2.[7] The World Health Organization (WHO) has stated that pregnant women or women who are recently pregnant, older, overweight, and have pre-existing medical conditions such as hypertension and diabetes have an increased risk of developing severe COVID-19.[8] In general, there is a consensus that breastfeeding should be encouraged because of its mutual benefits. However, whether the virus can be transmitted through breast milk is not yet known.[9] In present study, we investigated clinical, radiological, laboratory characteristics, treatment results of pregnant women with the covid disease, and its effects on maternal and fetus health.

Material and Methods

Thirty-two patients who were diagnosed as COVID-19 disease by PCR test in our hospital between March 2020 and June 2020 were included in this study. Ethics approval and consent to participate: For this study, approval was obtained from the clinical research ethics committee of the Bursa higher specialized education and research hospital. Ethics committee approval code: 2011-KAEK-25 2020/05-05. Patients' ages, pregnancy weeks, complaints, comorbid diseases, general physical conditions, oxygen saturation level recorded with pulse oximeter, laboratory and radiological findings were recorded retrospectively.

The duration of hospitalization of patients was recorded. Clinical, laboratory responses to the treatment given patients during hospital stay, need for intensive care and mortality rate, if any, were determined. Need for cesarean section (C/S) as a complication of COVID-19 disease was also recorded. If the patients gave birth to children (spontaneous labor or with C/S), the condition of these children and whether covid disease was detected in this children were also recorded.

Results

Patients' ages ranged from 17 to 39. The mean age of them was 26.6±5.7 years (mean±SD). Four patients (12.5%) had comorbid diseases. Pregnancy-induced hypertension was evident in 2 patients (6.2%), preeclampsia in 1 patient (3.1%), asthma in 1 patient (3.1%). The gestational weeks of the patients ranged from 8 to 38 (mean 21.3±10.2). The seven patients (21.9%) had no complaints in the anamnesis and signs. The other 25 (78.1%) had complaints. No sputum was detected in any patient. The incidence of other complaints was shown in Table 1. The general clinical condition of 31 patients (96.9%) was good at presentation.

Table 1. Rates of complaints detected in COVID-19 patients.

Complaints	n (%)
Cough	11 (34.4)
Fatigue	10 (31.3)
Headache	5 (15.6)
Joint pain	5 (15.6)
Sore throat	4 (12.5)
Dyspnea	4 (12.5)
Fever	3 (9.4)
Anorexia	2 (6.3)
Diarrhea	2 (6.3)
Nausea	2 (6.3)
Anosmi	2 (6.3)
Taste inability	1 (3.1)
Taste inability+ anosmi	1 (3.1)
Chest pain	1 (3.1)
Vomiting	1 (3.1)
Palpitation	1 (3.1)

Table 2. Laboratory findings of pregnant patients with COVID-19 on admission.

Parameters	Mean (min:max)	Patient number higher than normal n (%)	Patient number lower than normal n (%)
WBC count (/mm^3)	6,989 (4,000:11,900)	4 (12.5)	-
Platelet count (/mm^3)	210,968 (46,000:391,000)	-	5 (15.6)
Hemoglobin (g/dL)	11.4 (5.9:13.9)	-	18 (56.3)
Leucocyte count	5,200 (2,400:8,600)	2 (6.3)	-
Leucocyte (%)	69 (40.9:85)	7 (21.9)	2 (6.3)
Lymphocyte count	1,568 (470:3,000)	-	5 (15.6)
Lymphocyte (%)	23.1 (7.7:48)	2 (6.3)	10 (31.3)
Eosinophil count	0.06 (0:0.57)	2 (6.3)	-
Eosinophil (%)	0.8 (0:4.7)	-	-
Basophil count	0.01 (0:0.08)	-	-
Basophil (%)	0.25 (0.1:0.9)	-	-
CRP (mg/L)	14 (3.1:143)	18 (58.1)	-
Ferritin (ng/mL)	137.3 (7.6:3133)	1 (3.4)	6 (18.8)
D-dimer (ng/mL)	1.38 (0.21:5.47)	20 (71.4)	-
LDH (U/L)	220.2 (122:734)	8 (27.6)	3 (9.4)
Troponin (ng/mL)	2.4 (2:7.8)	-	-
Fibrinojen (mg/dL)	455 (139:688)	17 (80.9)	-
Creatinine (mg/dL)	0.47 (0.28:0.69)	-	-
AST (U/L)	19.2 (11:35)	-	-
ALT (U/L)	14.8 (2:53)	-	-
Sodyum (mEq/L)	135.5 (126:141)	-	13 (41.9)
Potasyum (mEq/L)	3.9 (3.07:4.65)	-	2 (6.5)

Only one patient (3.1%) had a moderate clinical condition. In addition, only one patient (3.1%) had a low oxygen saturation level of 92%, and all the other patients had normal oxygen saturation levels.

Laboratory findings of pregnant patients with COVID-19 are shown in Table 2. Fibrinogen level was studied in 21 patients, and its level was high in 17 patients (80.9%). Laboratory abnormalities are in order according to the frequency of occurrence; high fibrinogen level (80.9%), high D-dimer level (71.4%), increased C-reactive protein (CRP) level (58.1%), low haemoglobin level (56.3%), low sodium level (41.9%), low lymphocyte (31.3%), high lactate dehydrogenase (LDH) level (27.6%), low lymphocyte count (15.6%), low platelet count (15.6%). It was interesting that only one patient had high ferritin levels. Ferritin levels were found below average in 6 patients (18.8%) *(Table 2)*.

The radiological examination was requested in 5 of the patients. Thoracic CT was performed in 4 patients, and a posterior-anterior chest X-ray was performed in 1 patient. On thorax CT, only one patient had bilateral multifocal, peripheral, basal dominant significant ground-glass opacities and consolidations *(Figure 1)*. The other 4 had no infiltration.

Treatment protocols for these pregnant patients with COVID-19 were listed in Table 3. Hydroxychloroquine (HCQ) treatment alone was the most common treatment protocol (78.1%). One patient had to be given tocilizumab treatment after HCQ treatment. Antiviral treatment was not given to 2 patients *(Table 3)*. One patient (3.1%) needed intensive care, and none died. Length of stay in the hospital (LOS) ranged from 3 to 20 days. The average LOS was 6.1 days.

Table 3. Treatment protocol.

Protocol	n (%)
Hyroxychloroquine	25 (78.1)
Hyroxychloroquine+azithromycin	2 (6.3)
Lopinavir+ritonavir	1 (3.1)
Azithromycin	1 (3.1)
Hyroxychloroquine+tocilizumab	1 (3.1)
Without drug treatment	2 (6.3)

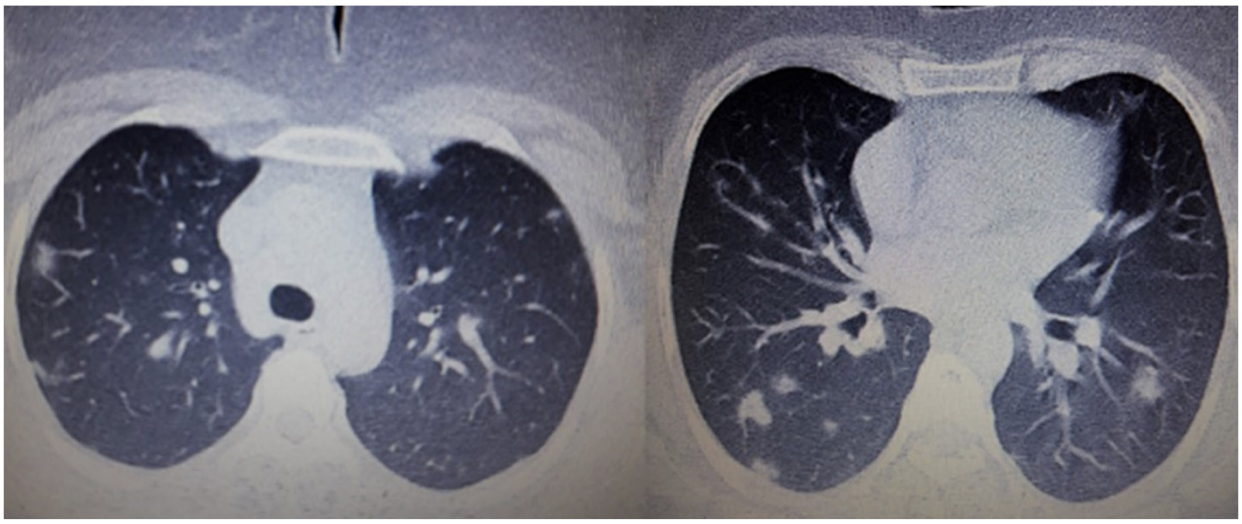

Figure 1. Thorax CT: bilateral, multifocal, peripheral, basal-predominant ground-glass opacities and consolidations.

Laboratory response rates to treatment for COVID-19 disease were shown in Table 4. The rate of improvement in laboratory values in response to the treatment was as follows respectively; sodium (92.3%), lymphocyte count (80%), LDH (62.5%), CRP (61.1%), D-dimer (25%). Ferritin level was elevated in only one patient and returned to normal with treatment *(Table 4)*. None of the patients developed spontaneous abortion. Cesarean section was delivered in 5 patients (15.6%). 2 had pregnancy-induced hypertension, 1 had preeclampsia, 1 had placenta previa, and 1 had a non-reactive contraction in NST. 2 patients (6.3%) had preterm cesarian delivery at 35 weeks gestation. Five newborns were negative for the COVID-19 PCR test two times.

Table 4. Laboratory response rates to treatment for COVID-19 disease.

Parameters	n (%)
Leukocyte	3 (75)
Lymphocyte	4 (80)
Platelet	3 (60)
CRP	11 (61.1)
Ferritin	1 (100)
D-dimer	5 (25)
LDH	5 (62.5)
Fibrinogen	4 (23.5)
Sodium	12 (92.3)
Potassium	1 (50)

Discussion

SARS-CoV-2 is more contagious than other viruses among populations. Pregnant women could be more susceptible to COVID-19 infection than the general population. Our study mostly detected cough complaints (34.4%) and fatigue (31.3%). Pain in different parts of the body (headache, joint pain and chest pain) was also detected in a substantial proportion of the patients (34.4%). Anosmia or/ and taste inability complaints were seen at a rate not negligible (12.5%). However, contrary to expectations, fever symptoms were detected at a very low rate (9.4%). In the study of Yan J *et al.*[5], fever was the most common sign detected in 50.9% of patients, cough in 28.4%, fatigue in 12.9%. In another study, fever was detected in 84% of patients and cough in 28%.[10] Shortness of breath was seen in 18% of pregnant patients in a study[10], but it was in 12.5% in this study. The rate of asymptomatic patients in our study was 21.9%, similar to the rate (23.3%) found in their research.[5]

In this study, the most frequent abnormal laboratory findings were high fibrinogen level (80.9%), high D-dimer level (71.4%), high CRP level (58.1%). While lymphopenia was found in two-thirds of patients in previous studies,[3,5,11-13] this rate was relatively low in our study at 15.6%. Interestingly, the rate of a low percentage of lymphocytes (31.3%) was higher than the low rate of lymphocytes count (15.6%). There was thrombocytopenia in 5 patients (15.6%); it was 13% in a recent study.[10] Interestingly, ferritin level was

high in only one patient, and ferritin levels were found below the expected values in 6 (20.7%) of 20 patients who evaluated ferritin levels. Leucocytosis was detected in 21.9% of patients, and this rate was higher in another study, such as 80%.[10]

Since the patients were pregnant, only five patients could be evaluated radiologically for fear of radiation side effects. Only 1 of these patients had pneumonia with diffuse infiltrations in both lungs *(Figure 1)*. In the study of Yan J *et al.*[5], there were abnormal radiologic findings in 96.3% of cases.

Recent studies have identified remdesivir and chloroquine as potential candidate drugs for the treatment of COVID-19.[14] Chloroquine phosphate is a ubiquitous antimalarial quinolone compound with broad-spectrum antiviral and immunomodulating activity. It has been shown to block coronavirus infection by increasing the endosomal pH required for cell fusion and interrupting the glycosylation of cellular receptors of SARS-CoV in cell culture.[14] In this study, hydroxychloroquine treatment alone was the most preferred form of treatment (78%). And this form of treatment was sufficient in the treatment of the majority of patients. However, despite HCQ treatment in 1 patient, when clinical laboratory improvement could not be achieved, tocilizumab treatment had to be given. With HCQ treatment, only one patient developed liver enzyme elevation as a side effect and improved when we stopped taking the drug.

The laboratory values that improved at the highest rate with treatment respectively were; sodium (92.3%), lymphocyte count (80%), leucocyte count (75%), LDH (62.5%), and CRP (61.1%). The recovery rate in D-dimer levels only remained at 25%. Also, the fibrinogen response rate remained at low levels of 23.5%. These results suggest that improvements in sodium, lymphocyte, leucocyte, LDH, and CRP values are quite sensitive while determining the response to treatment. In contrast, improvements in D-dimer and fibrinogen levels are not satisfactory. It has already been reported in previous studies that D-dimer levels are difficult to interpret, as the values are usually raised in pregnancy, such that only 84%, 33%, and 1% of women in the first, second, and third trimesters, respectively would have normal results based on conventional thresholds.[15] While evaluating the treatment response, the results of this study suggest that the improvement in sodium level may be more valuable than the improvement in acute phase reactants.

In the present study, the general clinical condition of almost all patients (96.9%) was good at presentation except for one. All mothers and infants showed good outcomes. One of the patients (3.1%) was taken to the intensive care unit and had to be given tocilizumab. None of the patients died. Similar results were found in the literature.[5,6] A case series of 12 pregnant women with SARS-CoV reported three maternal deaths in China.[16]

A total of 5 patients had C/S, which was thought to be a complication of COVID-19 disease. The reason for cesarean delivery in 2 of these patients was pregnancy-induced hypertension, preeclampsia in 1, placenta previa in 1 and nonreactive nonstress test in the other one. It has been reported that viral pneumonia in pregnant women is associated with an increased risk of preterm birth, fetal growth restriction (FGR), and perinatal mortality.[17] Based on the nationwide population-based data, it has been indicated that pregnant women with viral pneumonia other than COVID-19 (n=1,462) have an increased risk of preterm birth, FGR, and having a newborn with low birth weight and Apgar scores <7 at 5 minutes compared with those without pneumonia (n=7,310).[18] Our study suggests that the risk of spontaneous abortion is not increased in pregnant women with COVID-19 infection. This result is similar to the result of the study of Yan J *et al.*[5] The present study's findings also suggest that COVID-19 disease may increase the risk of preterm delivery before 37 weeks gestation. The rate of spontaneous abortion was 12.5% in the study of Yan J *et al.*[5] The fact that the PCR test for COVID-19 was negative in all five born children in our study created an impression that there was no vertical transition of this disease as in the study of Yan J *et al.*[5] Two recent research letters reported that three children had negative viral nucleic acid results. Still, the possibility of vertical transmission was thought as the immunoglobulin G, and immunoglobulin M tests were positive.[19,20] However, Yan J *et al.*[5] evaluated amniotic fluid, cord blood, and neonatal pharyngeal swab samples at birth to ascertain the possibility of vertical transmission, and their results indicated that SARS-CoV-2 was negative in all of the above

biological samples, suggesting that no intrauterine fetal infection occurred because of SARS-CoV-2 infection. In the study by Yu *et al.*[21], three neonates were tested for SARS-CoV-2, of whom two were negative. One neonate was positive, but the viral nucleic acid tests of the placenta and cord blood, in this case, were negative.[21]

Conclusion

The findings we obtained in our study were as follows: Mostly detected complaints in pregnancy patients with COVID-19 disease were cough and fatigue. HCQ treatment alone in covid treatment was successful; Improvement in sodium, lymphocyte, LDH, and CRP values in determining response to treatment is probably valuable. While evaluating the treatment response, the improvement in sodium level may be more valuable than the improvement in acute phase reactants. Prognosis was quite good in mothers and children treated for this disease. COVID-19 disease may increase the risk of preterm delivery before 37 weeks. Vertical transition of the disease could not be demonstrated.

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Conflict of Interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: AS, ET, NK; Study Design: AEC, AS, NK; Supervision: YU, SYG, OD; Fundings and Materails: SD, AK, US, AS, ET, NK; Data Collection and/or Processing: SYG, OD, AK; Statistical Analysis and/or Data Interpretation: US, YU, SD; Literature Review: AEC, US, AK, SD; Manuscript Preparation: SYG, OD, ET; Critical Review: AK, AEC, AS.

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