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RESEARCH ARTICLE

Clinical Manifestation and Characteristics of COVID-19 in Pregnants: A Retrospective, Single-Center Study

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ABSTRACT

Objectives: Along with the COVID-19 pandemic, pregnant women have experienced COVID-19 symptoms of varying severity. Therefore, we aimed to show the clinical, laboratory, and radiological findings for three different trimesters in pregnant women diagnosed with COVID-19.

Methods: All hospitalized pregnant women with positive SARS-CoV-2 nucleic acid tests were included in this study. The severity of the disease was classified using the NIH Classification of Severity of Disease.

Results: None of the 206 participants were vaccinated. The number of asymptomatic or presymptomatic patients, those with mild, moderate, and severe disease, was 73(35.4%), 59(28.6%), 68 (33.1%), and 6 (2.9%), respectively. The gestational age of symptomatic patients was lower than that of asymptomatic patients (29 vs. 37 weeks) (p= 0.001). The incidence of pneumonia increased with the trimester of pregnancy increased (p<0.001). Sixty-six of the pregnancies (32.0%) ended with term births, and 11 (0.5%) gave premature birth. Three pregnancies resulted in miscarriage (1.4%), and one(0.4%) resulted in intrauterine fetal death. Of the preterm deliveries, nine(64.3%) had pneumonia. There was no significant relationship between the disease severity and delivery time (p=0.075), but a significant relationship between the disease severity and the delivery mode. Expected vaginal delivery occurred in 18 asymptomatic patients (72%), whereas cesarian/section was performed in 75.6% (n=31) of symptomatic patients (p<0.001).

Conclusion: This study reflects the natural course of COVID-19 since our patients were not vaccinated. We think the results will be better with the increase in vaccination rates. *J Microbiol Infect Dis 2022; 12(2):38-47*.

Keywords: *Pregnancy; COVID-19; Pandemic; Pneumonia*

INTRODUCTION

Due to decreased cellular immunity and physical changes, pregnant women are more prone to respiratory diseases, and the risk of developing severe pneumonia is higher than the average population [1]. To date, no studies have shown whether a pregnancy is a risk factor for COVID-19. Previously, Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) epidemics were shown to cause maternal and fetal mortality reaching up to 25-28% [2]. SARS has been strongly associated with spontaneous abortion, preterm delivery, and intrauterine growth retardation during pregnancy [3]. Similarly, the H1N1 pandemic in 2009 was also related to maternal and fetal mortality, this rate was reaching up to 12% [4].

Studies have shown that the rate of severe COVID-19 was about 20%, and one-fourth of those need intensive care units (ICUs). Regardless of the need for hospitalization, the

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rate of progression of critical illness development is given 5.8% [5]. However, according to the Centers for Diseases Control (CDC) report, the hospitalization rate increases up to 30% during pregnancy [6]. Several studies showed that COVID-19 pneumonia was not related to severe maternal and neonatal complications [7]. There is still much unknown about the COVID-19 disease considering three trimesters in pregnancy.

Over the globe, pregnant women have experienced from asymptomatic to severe COVID-19. We aimed to show the course of the clinical, laboratory, and radiological findings for three different trimesters of pregnant women hospitalized with the diagnosis of COVID-19.

METHODS

This study was carried out with the Health Sciences University, Samsun Training and Research Hospital Ethics Committee approval (Decision No: GOKA/2021/5/6) and the permission of the Republic of Turkey Ministry of Health, General Directorate of Health Services, Scientific Research Studies Commission (Decision No: 2021-02-28T15_29_09 and Date: 28.02.2020). Two hundred and six pregnant women with positive SARS-CoV-2 nucleic acid test in pharyngeal and nasal swab samples were hospitalized and treated in the Samsun Training and Research Hospital, Gynecology and Obstetrics Clinic between 01 April 2020 and 01 April 2021. Demographic data such as age, gestational week, comorbidity status, exposure history, hospital admission day after exposure, symptoms, clinical findings, biochemical parameters, and radiological imaging findings at admission time were extracted and evaluated retrospectively. All the data were collected from the electronic hospital information management system. Disease severity was categorized as asymptomatic/presymptomatic, mild disease, moderate disease, severe disease, and critical condition, using the US National Institutes of Health (NIH) classification (Table 1) [8].

Statistical analysis: Data were analyzed with IBM SPSS 22.0 program. The ANOVA, post-hoc, and Student T-test were used for data with normal distribution. The Kruskal-Wallis and Mann-Whitney U tests were used for quantitative parameters not showing normal distribution. Pearson Chi-Square, Pearson Chi-Square Exact test, Yates' Chi-square, and Fisher's Exact test were used for qualitative data. P-values <0.05 were considered statistically significant.

RESULTS

A total of 261 pregnant who were hospitalized within the specified period were reviewed and 206 pregnant them were enrolled and analyzed. The flow diagram of the study is presented in Figure 1. The patients included in the study were analyzed by grouping according to trimesters. The mean age was 29.0 years and similar within the groups (p=0.920). At the hospital admission, the mean gestational age was 28 weeks. Of the patients, 107 (52%) had a history of direct contact with a patient with a COVID-19. None of the 206 participants were vaccinated. According to the NIH Classification of Severity of Disease (Table 1), the number of asymptomatic or presymptomatic patients; those with mild, moderate, and severe diseases were 73 (35.4%), 59 (28.6%), 68 (33.1%) and 6 (2.9%), respectively. None of the participants had an accompanied critical illness. All the six pregnant with severe diseases were in the third-trimester group (Table 2). Demographic data, symptomatology, and their stratification according to trimesters were given in Table 2. The severity of the diseases is shown in Table 2. Fatigue, cough, nasal congestion, headache, and anorexia were higher in the second trimester (p<0.05). Shortness of breath was significantly higher in the second and third trimesters than in the first trimester (p<0.05).

Sixty-six (32.0%) women gave birth in the term and 11 (0.5%) in pre-term birth. Three (1.4%) pregnancies resulted in miscarriage and one (0.4%) with intrauterine mortality. Of the pre-term patients, nine (64.3%) had pneumonia. Twenty-five women gave vaginal birth at term, and 41 by cesarian/section (C/S). Four patients with severe disease were followed-up in the intensive care unit due to the progression of pneumonia, and two women delivered 37-week and 28-week healthy old babies. No significant difference was found between the severity of the disease and delivery time (p=0.075). But there was a significant relationship between the severity of the disease and the mode of delivery. A normal vaginal delivery (NVD) was preferred in 72% (n=18) of asymptomatic patients, and C/S

delivery in 75.6% (n=31) of symptomatic patients (p<0.001) (Table 3).

Symptomatic patients had a lower gestational age than asymptomatic patients (29 weeks vs 37 weeks) (p= 0.001) (Table 4). The median time of the hospital stay and admission to the hospital after a history of viral contact was higher in symptomatic patients than in asymptomatic arms (p=0.001) (Table 4). Gestational ages were similar for the patients with and without pneumonia (p=0.092). However, the rate of pneumonia increased with increasing trimesters (p<0.001) (Table 5). Admission to the hospital after a history of viral contact and hospital stay was higher in the pneumonia group (p<0.05). Out of a total of 90 patients that were suspected of pulmonary involvement, 74 had pneumonia. Chest tomography was performed in 68 (75.6 %) patients.

Symptomatic patients had significantly lower levels of WBC, neutrophil, lymphocyte, and monocyte counts compared to asymptomatic patients (p<0.05) (Table 4). Platelet counts were also significantly lower in patients with pneumonia. In contrast, Aspartate transaminase, D-Dimer, and C-reactive protein were significantly higher than patients with no pneumonia (p<0.05) (Table 4). Considering the trimesters, inter-group differences in laboratory findings are given in Table 6.

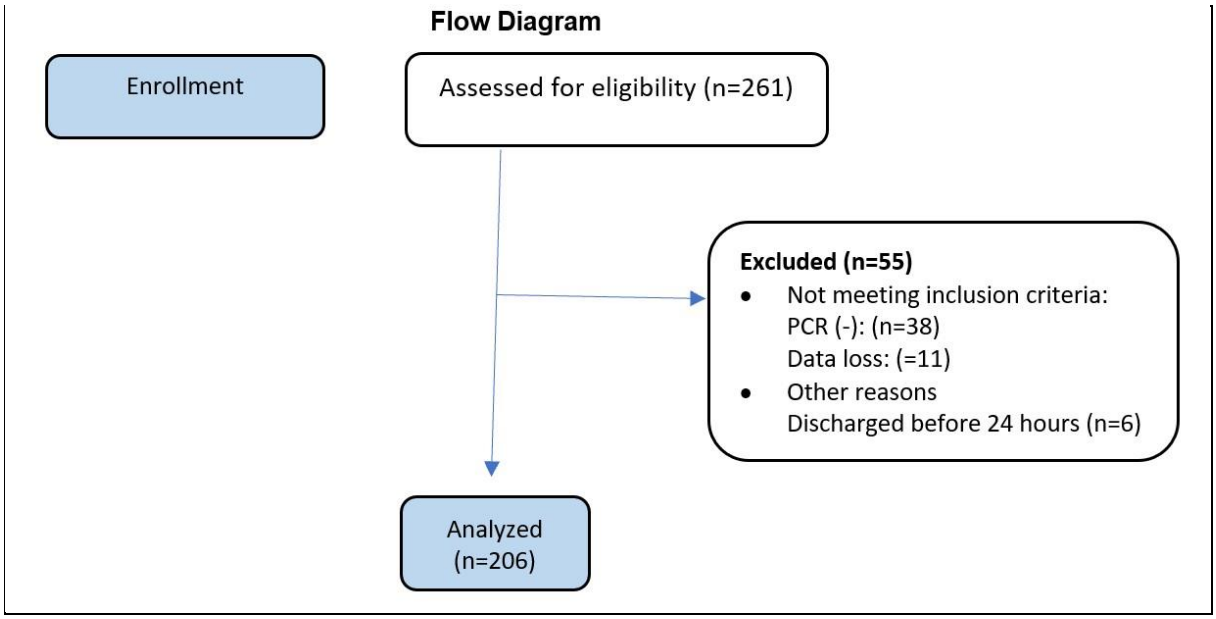

Figure 1 Flow diagram for study participants

Table 1. Disease severity classification according to the National Institute of Health Classification.

Severity	Symptoms
Asymptomatic or Presymptomatic	Positive for SARS-CoV-2 with no symptom
Mild Illness	Any signs and symptoms (fever. cough. sore throat. headache) without shortness of breath. dyspnea. or abnormal imaging
Moderate Illness	Evidence of lower respiratory tract disease by clinical assessment or imaging and an oxygen saturation (SpO_2) >93% on room air at sea level
Severe Illness	Respiration rate >30 breaths per minute. SpO2 = 93% on room air at sea level.the ratio of arterial partial pressure oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 or lung infiltrates > 50%
Critical Illness	Respiratory failure. septic shock. and/or multiple organ dysfunction

Table 2. Distribution of age and symptoms of pregnant women by trimesters

Variables	Total (n=206) (100%)	First trimester (n=34) (16.5%)	Second trimester (n=40) (19.4%)	Third trimester (n=132) (64.1%)	P-value
Age (years)	29.0±5.8	29.3±5.6	29.1±5.8	28.9±5.9	0.920
Hospital admission time(days)	5.4+3.7	4.5+2.9	5.5+3.1	5.6+4.0	0.346
Comorbidity	12(%5.8)	1(%2.9)	2(%5)	9(%6.8)	
COPD	7(3.4)	1(2.9)	1(2.5)	5(3.8)	
Asthma	2(1)	0	1	1(0.8)	0.670
HT	1(0.5)	0	0	1(0.8)	
DM	2(0.5)	0	0	2(1.5)	
Disease severity					
Asymptomatic	73(35.4)	12(35.3)	8(20)	53(40.2)	
Mild	59(28.6)	20(58.8)	18(45)	21(15.9)	0.0001 [a]
Moderate	68(33.1)	2(5.9)	14(35)	52(39.4)	
Severe	6(2.9)	-	-	6(4.5)	
Critical	-	-	-	-	
Fatigue	82 (39.8)	12(35.3)	23(57.5)	47(35.6)	0.039
Cough	79 (38.3)	10(29.4)	22(55)	47(35.6)	0.044
Shortness of breath	55 (26.7)	3(8.8)	13(32.5)	39(29.5)	0.034
Anorexia	44 (21.3)	8(23.5)	16(40)	20(15.2)	0.003
Myalgia	43 (20.9)	9(26.5)	12(30)	22(16.7)	0.130
Fever	34 (16.5)	4(11.8)	6(15)	24(18.2)	0.641
Headache	28 (13.6)	6(17.6)	10(25)	12(9.1)	0.028
Back pain	19 (0.92)	6(17.6)	5(12.5)	8(6.1)	0.089
Taste loss	15 (0.73)	4(11.8)	4(10)	7(5.3)	0.32
Loss of smell	14 (0.68)	4(11.8)	4(10)	6(4.5)	0.239
Diarrhea	7 (0.34)	1(2.9)	2(5)	4(3)	0.851
Nasal congestion	6 (0.29)	0(0)	4(10)	2(1.5)	0.022
Runny nose	5 (0.24)	1(2.9)	3(7.5)	1(0.8)	0.055
Throat ache	4 (0.2)	1(2.9)	1(2.5)	2(1.5)	0.831

*According to the US National Institutes of Health (NIH) classification. [a] Pearson Chi-square (Exact test).

Table 3. Evaluation of the patients according to the severity of symptoms and delivery time.

Variables		Severity of disease				P-value
		Asymptomatic	**Mild**	**Moderate**	**Severe**	
According to birth time (n, %)	Preterm delivery	4(28.6)	1(7.1)	7(50.0)	2(14.3)	0.075
	Delivery in term	28 (42.4)	11(16.6)	25 (37.8)	2 (3.0)	
		Asymptomatic	Symptomatic patients			
Preferred type of birth * (n, %)	NVD	18 (72.0)	7 (28.0)			0.001
	C/S	10 (24.4)	31 (75.6)			

Data are expressed as median (min-max), *This group consists of term pregnancy (>37 weeks).

Table 4. Comparison of clinical data and laboratory findings of asymptomatic and symptomatic patients.

Variables	Asymptomatic cases (n=73)	Symptomatic patients* (n=133)	P-Value
Gestational age (weeks)	37 (5-40)	29 (5-41)	0.001
Admission to hospital after a history of viral contact	1 (1-5)	3 (1-9)	0.001
Hospital stay (days)	3 (1-14)	6 (1-32)	0.001
Hemoglobin (g/dL)	11.1 (8.9-14.1)	11.8 (9.4-13.4)	0.979
WBC ($x10^3$/µl)	9.6 (3.2-29.6)	7.6 (0.7-23.2)	0.001
Neutrophil ($x10^3$/µl)	7 (1.5-27.3)	5.2 (0.5-11.8)	0.001
Lymphocyte ($x10^3$/µl)	1.4 (0.3-3.1)	1.1 (0.2-3.3)	0.007
Monocytes ($x10^3$/µl)	0.6 (0.2-5.9)	0.5 (0-1.5)	0.008
Thrombocyte ($x10^3$/µl)	199-1990	195.5(114-353)	1.000
AST (IU/L)	18 (10-49.5)	20.3 (10-241)	0.192
ALT (IU/L)	13 (4-78)	15 (4.5-90.2)	0.221
CK (IU/L)	35 (9-458)	35 (12-218)	0.846
BUN	15 (7.2-38)	15 (5.9-40)	0.213
Creatinine (mg/dl)	0.4 (0.19-0.78)	0.43 (0.28-2.8)	0.526
Fibrinogen (mg/dl)	401 (372-519)	422 (330-584)	0.979
D-Dimer (mg/L)	1.15 (0.2-8.1)	1.285 (0.19-7.52)	0.843
Ferritin (ng/ml)	43.3 (11.5-209)	50.78 (2-755)	0.712
CRP (mg/L)	11.25 (0.6-155)	12.165 (0.3-174)	0.807
LDH (IU/L)	212 (124-416)	187 (117-473)	0.450

Data are expressed as median (min-max), *Symptomatic patients cover mild, moderate, and severe diseases, AST: Aspartate aminotransferase. ALT: Alanine aminotransferase. CK: Creatine-kinase. BUN: Blood Urea Nitrogen. CRP: C-Reactive Protein. LDH: Lactate dehydrogenase

Table 5. Comparison of the clinical data and laboratory findings of patients with and without pneumonia.

Variables	Asymptomatic and mild illness (without pneumonia) (n=132)	Moderate and severe illness (with pneumonia) (n=74)	p
Gestational age (weeks)	29.5 (5-41)	34 (11-40)	0.092
1st trimester	32	2	
2nd trimester	26	14	<0.001
3rd trimester	74	58	
Admission to hospital after a history of viral contact	2 (1-9)	3 (1-9)	0.002
Hospital stay (days)	3 (1-16)	7 (1-32)	0.001
Hemoglobin (g/dL)	11.8 (8.9-14.1)	11.5 (9.4-13.4)	0.922
WBC ($x10^3$/µl)	8.75 (0.7-29.6)	7.4 (1.3-15)	0.021
Neutrophil ($x10^3$/µl)	6.3 (1.5-27.3)	5.1 (0.5-11.6)	0.016
Lymphocyte ($x10^3$/µl)	1.25 (0.3-3.3)	1.1 (0.2-3.1)	0.048
Monocytes ($x10^3$/µl)	0.55 (0.1-5.9)	0.4 (0-1.3)	0.000
Thrombocyte ($x10^3$/µl)	213.5 (199-353)	173 (114-187)	0.006
AST (IU/L)	19 (10-49.5)	21.9 (11-241)	0.035
ALT (IU/L)	12.9 (4-78)	16 (4.5-90.2)	0.077
CK (IU/L)	38 (9-458)	31.6 (12-200)	0.123
BUN	15 (7.2-38)	14.9 (5.9-40)	0.191
Creatinine (mg/dl)	0.4 (0.19-0.8)	0.43 (0.28-2.8)	0.300
Fibrinogen (mg/dl)	427 (330-534)	422 (363-584)	0.558
D-Dimer (mg/L)	1.03 (0.19-8.1)	1.5 (0.4-5.6)	0.011
Ferritin (ng/ml)	50.56 (2-755)	49.8 (5.47-598)	0.576
CRP (mg/L)	10.95 (0.3-174)	18.2 (0.52-168)	0.024
LDH (IU/L)	189 (124-416)	197 (117-473)	0.486

Data are expressed as median (min-max), AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CK: Creatine-kinase, BUN: Blood Urea Nitrogen, CRP: C-Reactive Protein, LDH: Lactate dehydrogenase

Table 6. Distribution of laboratory findings by groups.

Variables	First trimester	Second trimester	Third trimester	P[a]	P[b]	P[c]	P[d]
Hemoglobin (g/dL)	12.1 (11.5-14.1)	11.85 (10.4-12.6)	11.1 (8.9-13.4)	0.169			
WBC (x10^3/µl)	8.19 (3.0-15.8)	6.5 (3.2-23.2)	8.9 (0.7-29.6)	0.019	0.295	0.078	0.002
Neutrophil (x10^3/µl)	5.15 (1.5-11.8)	4.95(1.8-9.3)	6.55 (0.5-27.3)	0.001	0.591	0.021	0.001
Lymphocyte (x10^3/µl)	1.0 (0.3-3.1)	1.0 (0.3-3.2)	1.3 (0.2-3.3)	0.007	0.918	0.023	0.008
Monocytes (x10^3/µl)	0.5 (0.2-2.1)	0.5 (0.1-1.0)	0.5 (0-5.9)	0.104			
Thrombocyte (x10^3/µl)	241.5 (211-353)	164 (114-187)	189 (173-204)	0.020	0.034	0.021	0.157
AST (IU/L)	18.5 (10-49.5)	20 (13-71.5)	20 (10-241)	0.180			
ALT (IU/L)	15.9 (6-78)	15 (7-90.2)	13.6 (4-57.8)	0.060			
CK (IU/L)	34.5 (16.5-128)	35.6 (14-97)	35 (9-458)	0.764			
BUN	17 (11-38)	13.9 (8.2-34)	14.9 (5.9-40)	0.002	0.000	0.002	0.429
Creatine (mg/dl)	0.44 (0.3-0.78)	0.39 (0.28-0.56)	0.44 (0.19-2.8)	0.010	0.012	0.919	0.004
Fibrinogen (mg/dl)	391 (330-492)	406.5 (338-443)	454 (372-584)	0.024	0.697	0.035	0.026
D-Dimer (mg/L)	0.82 (0.19-7.52)	0.845 (0.3-6.35)	1.62 (0.2-8.1)	0.000	0.685	0.000	0.000
Ferritin (ng/ml)	63 (8.3-755)	45.9 (2-390)	43.6 (3.87-598)	0.442			
CRP (mg/L)	5.725 (0.3-174)	11.22 (0.5-146)	18.2 (0.52-168)	0.000	0.022	0.000	0.050
LDH (IU/L)	139 (117-196)	182 (142-429)	232 (124-473)	0.007	0.026	0.008	0.064

Data are expressed as median (min-max), a. Between 1st, .2nd, and 3rd-trimester groups; b. Between 1st and 2nd-trimester groups; c. Between 1st and 3rd-trimester groups; d. Between 2nd and 3rd-trimester groups; AST. Aspartate aminotransferase; ALT. Alanine aminotransferase; CK. Creatine kinase; BUN. Blood Urea Nitrogen; CRP. C-Reactive Protein; LDH. Lactate dehydrogenase.

DISCUSSION

In this retrospective study, we determined a partial correlation between the trimester of pregnancy and the severity of the disease in patients who had COVID-19 during pregnancy. In this single-center study, evaluating completely unvaccinated patients and covering the highest number of pregnant COVID-19 positive participants in our country, may contribute to the literature due to its homogeneous distribution according to trimesters.

None of the pregnants was lost in the present study, possibly due to the low number of comorbidities. Screening during hospital admissions for routine pregnancy check-ups might explain the high number of asymptomatic patients. There are conflicting data on whether COVID-19 is more mortal than SARS-CoV or MERS-CoV. Some studies showed that the mortality of COVID-19 is somewhat higher than the others, but some advocate similar mortality rates [9, 10]. A recent survey showed that pulmonary comorbidities, hypertension, and diabetes have increased maternal complications [11]. In our study, of the patients, 64.1% had no pulmonary symptoms, and only six had severe diseases. Some similar studies showed that COVID-19 pneumonia did not cause severe maternal and neonatal complications [7, 12]. It has been shown that 88% of PCR-positive pregnant women are asymptomatic [13].

In a multicenter study in which data on approximately 11,000 cases of COVID-19 were presented, the mortality rate of 1062

pregnant patients was given at 0.8% [14]. Another study of 706 pregnant women reported a 1.6% mortality rate regardless of the trimesters [15]. Similarly, Blitz et al. reported 15% maternal mortality in patients followed up in ICUs, and 25 of those needed invasive mechanical ventilation [16]. The clinical course of COVID-19 is better in younger women than in older men [17].

In a study from the China Center for Disease Control and Prevention (CDC), symptomatic patients were evaluated in the general population. In that study, the mild and moderate disease was observed in 80% of the patients, whereas severe illness was 15% and critical disease was 5% [18]. Unlike that study, our results showed that the sum of mild to moderate diseases was 95.5% and severe illness was 4.5%. No critical disease was observed in our participants. Similarly, Chen et al. evaluated 118 pregnant, and they reported 92% mild and moderate-severe disease and only 8% severe disease [17]. Similarly, several studies have shown that pregnancy does not affect the course of COVID-19, negatively [16-21]. Our results are compatible with these reports.

Our results show that the most common symptoms in the second trimester, unlike the other two trimesters, are fatigue (57.5%), cough (55.0%), shortness of breath (32.5%), anorexia (40.0%), and myalgia (30.0%) ($p<0.05$). In general population, the most common symptoms were fatigue 68.4%, myalgia (61%), headache (56.5%), loss of smell (45%), loss of taste, and anorexia; fatigue, headache, sore throat, nausea, loss of appetite, loss of taste and loss of smell were reported more frequently in women [22]. In a recent review of first and second-trimester pregnancies, 60% of pregnant women were symptomatic, with fever (39%), cough (33%), shortness of breath (24%), nausea, and vomiting (12%), and the loss of taste (26%) has been reported [23]. Zhu et al. showed no difference between pregnant and non-pregnant [24]. Due to several reasons such as age, gender, comorbidities, geographical features, and study setup, COVID-19 symptomatology may vary.

COVID-19 is a systemic disease that affects the hematopoietic system. Numerous studies showed that lymphopenia is a prognostic indicator for COVID-19 disease [25-27]. Our hematology results are compatible with the literature [9,17].

On the other hand, some studies showed that COVID-19 infection in pregnancy was associated with high mortality. The delivery with C/S has been emphasized as a factor that increases mortality and morbidity due to inadequate antenatal care, insufficient healthcare conditions, pandemic conditions restricting access to obstetric care, and limitations in reaching ICU and mechanical ventilators [28, 29]. In our study, NVD was preferred in asymptomatic patients, but the C/S ratio was higher than NVD in symptomatic pregnancies. It has been shown that the risk of intrapartum transmission of COVID-19 to the newborn is also low in vaginal delivery [30]. No 2019-nCoV infection was found in newborns of pregnant women with COVID-19 [31]. However, C/S delivery can be preferred to minimize the virus density in delivery rooms during the NVD with COVID-19 and the exposure risk for healthcare workers. Another reason for choosing the C/S is that it allows the opportunity for pregnancy termination at the most appropriate time, which is essential in reducing the risk of premature birth and asphyxia of the newborn and early treatment and rehabilitation of maternal pneumonia. The mode of delivery and presence of critical illness should be evaluated together, and an appropriate delivery method should be determined.

The most common undesirable outcome in patients with pneumonia is deliveries before 37 weeks of gestation and mode of C/S [2]. In our patients, the premature birth rate was higher in patients with pneumonia, and the C/S ratio was significantly higher in symptomatic patients. The reason for this was the choice to deliver the baby under elective conditions before hypoxia becomes a threat to the pregnant woman and the fetus with the progression of the disease.

Our study has several limitations. This study has a retrospective design and we have handled data from a single center. In addition, this virus, which we are faced with multiple mutations in a short time, can appear with serious changes in clinical presentations with each mutation. There is a need for studies to be carried out in selected groups based on a certain variant, and these studies should be repeated in the process.

CONCLUSION

This study demonstrates the natural course of COVID-19 in unvaccinated pregnant women. In the follow-up of the patients, there was no maternal mortality. Increased awareness of the pandemic, some measures, including effective filiation, early diagnosis, isolation, and therapeutic management, can reduce maternal and fetal morbidity and mortality. In addition, with the increase in vaccination rates, the clinical presentation of COVID-19 disease would be more moderate.

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