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Effect of Disease Severity on the Clinical Course, Maternal and Perinatal Outcomes in Pregnancy in COVID-19 Infection

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Abstract

Objective: The purpose of the present study was to evaluate the clinical course and maternal and perinatal outcomes of coronavirus disease-2019 (COVID-19) in pregnant women to determine the effects of the severity of the disease on these results.

Materials and Methods: The present study was planned retrospectively, and 303 patients between the ages of 16 and 46 who were admitted by Adana City Training and Research Hospital, Clinic of Gynecology and Obstetrics between 15.03.2020 and 01.10.2021 and diagnosed with COVID-19 with reverse transcription-polymerase chain reaction test, pregnant patients and newborns of those who gave birth among these patients were included in it.

Results: The mean age of pregnant women in the severe and critical disease group was found to be significantly higher than that of pregnant women in the mild disease group. The mean gestational week of the patients who were included in the study was 33.8±6.6 years. It was found that the pregnant women in the severe and critical disease group had a lower gestational week than the pregnant women in the mild disease group, and this difference was significant.

Conclusion: It was determined that maternal age was higher in pregnant women who had severe and critical COVID-19 disease than in those with mild disease. It was determined that the presence of obesity and comorbid disease in pregnant women with COVID-19 did not correlate with the severity of the disease.

Keywords: COVID-19, pregnancy, disease severity, preterm birth, perinatal outcomes

Introduction

Coronavirus disease-2019 (COVID-19) is caused by a highly pathogenic virus from the β-coronavirus group of the Coronaviridea family called severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and was first described in China in 2019. The virus is transmitted among people through droplets as a disease that is easily transmitted and patients usually have mild to moderate symptoms. Severe conditions such as pneumonia and acute respiratory distress syndrome may also develop in some patients [1,2]. The disease may progress more severely in patients who have comorbidities such as underlying heart disease, chronic lung disease, and diabetes [3]. According to World Health Organization data, 659.124.900 people have been diagnosed with COVID-19 since the declaration of a pandemic, and 6.676.181 deaths have occurred due to COVID-19. Around the world, approximately one million people are diagnosed of COVID-19 every day, and approximately 4.000

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people die of of COVID-19 [4]. Very serious restrictions were applied in this respect. Although SARS-CoV-2 was first detected in patients with unexplained pneumonia, it was later shown in studies that it can cause different clinical manifestations, from multi-organ failure, because of the cytokine storm caused by this virus, and it was shown that it can target many tissues. It is now known that it can also cause serious complications and death. Physiological adaptation mechanisms of pregnancy that develop during pregnancy are considered to be a high-risk process because of cardiovascular, immunological, and respiratory changes, and therefore, many studies try to uncover the differences in the clinical course of the disease in pregnancy from that in the normal population. Although some studies speculated that pregnancy is a risk factor affecting the clinical course of COVID-19 negatively, the evidence on this subject is insufficient. In addition, the data in the literature show that the increased severity of COVID-19 in pregnant women significantly increases maternal and fetal complications [5-7]. All the effects of SARS-CoV-2 in pregnancy have not yet been demonstrated. There is a need for collaborative studies to be conducted worldwide to determine the effects of SARS-CoV-2 on implantation, fetal growth and development, and birth and neonatal health [6]. The clinical experience of pregnant women with SARS and Middle East respiratory syndrome (MERS) infections from other coronaviruses in the past caused pregnant women to be identified as a risk group because of more complications and risk of serious disease, and it was recommended that additional precautions must be taken [6,8]. The purpose of the present study was to evaluate the clinical course and maternal and perinatal outcomes of COVID-19 in pregnant women, to determine what kind of effects the severity of the disease causes on these results, and to contribute to the literature by revealing the maternal and fetal negative effects of COVID-19 that occurs during pregnancy, to reduce complications as much as possible and to raise awareness on this issue.

Materials and Methods

The present study was planned retrospectively, and 303 patients between the ages of 16 and 46 who were admitted by Adana City Training and Research Hospital, Clinic of Gynecology and Obstetrics between 15.03.2020 and 01.10.2021 and diagnosed with COVID-19 with reverse transcription-polymerase chain reaction (RT-PCR) test, pregnant patients and newborns of those who gave birth among these patients were included in it. This study was approved by University of Health Sciences Turkey, Adana City Training and Research Hospital, Clinical Research Ethics Committee (date: 04.11.2021, meeting number: 92, decision no: 1628). Patients' ages, gestational weeks, body mass index (BMI) scores, troponin, C-reactive protein (CRP), procalcitonin, ferritin, D-dimer, urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), sodium, potassium, hemoglobin, platelet, leukocyte, neutrophil, lymphocyte, and their laboratory findings including monocytes, international normalized ratio, fibrinogen values, presence of chronic disease, symptoms, gestational week, whether or not the patient gave birth during hospitalization, if she did, the type and timing of the delivery, indications for cesarean section, hospitalization in the intensive care unit, oxygen support, mechanical ventilation or ECMO, whether the patient received support, the presence of pneumonia findings in lung imaging, stillbirth, maternal death, 1st and 5th minute APGAR scores of newborns, RT-PCR results in swab samples taken from newborns within the first 24 hours were obtained by examining patient files in an electronic environment. The pregnant patients with COVID-19 who were taken into custody were examined by dividing them into two categories as the mild disease group and the severe and critical disease group. The data used in the study were analyzed comparatively between these two groups. In this study, the severity scale defined by Wu and McGoogan [9] was used as a reference. In this definition, the mild disease group was defined as patients with asymptomatic or mild symptoms, the severe disease group was defined as patients with tachypnea (respiratory rate 30/min), hypoxia (SPO_2 93 and below in room air or PaO_2/FiO_2 <300 mmHg), patients with more than 50% lung involvement in imaging, and the critical disease group was defined as patients with respiratory failure, septic shock, or multiorgan failure. Among the patients, asymptomatic patients and those with oxygen saturation over 93% and showing mild signs of disease without the need for oxygen support were in the mild disease group, those with severe dyspnea symptoms and oxygen saturation was 93% and below, those who received oxygen support with mechanisms such as a nasal cannula, mask with reservoir, high flow oxygen, continious positive airway pressure, bilevel positive airvay pressure, and patients who received mechanical ventilation and respiratory support were evaluated in the severe and critical disease group.

Statistical Analysis

The Statistical Package for the Social Sciences 23.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and minimum-maximum were appropriate). The Shapiro-Wilk test was used to determine whether the parameters in the study showed normal distribution, and the chi-square and Fisher's exact tests were used to compare the categorical expressions. The Mann-Whitney U test was used for the parameters that did not show normal distribution and the logistic regression test was used for the mortality findings of the patients. The statistical significance level was taken as 0.05 in all tests.

Results

It was found that 273 (90%) of the 303 pregnant patients who were diagnosed with COVID-19 included in the study had mild disease and 30 (10%) had severe and critical disease findings. The mean age of the pregnant women was 29.0±6.2 years. The mean age of the pregnant women in the severe and critical disease group was found to be significantly higher than that of the pregnant women in the mild disease group (p=0.010; p<0.05) (Table 1).

The mean gestational week of the patients who were included in the study was 33.8±6.6. It was found that the pregnant women in the severe and critical disease group had a lower gestational week than the pregnant women in the mild disease group, and this difference was significant (p=0.004; p<0.05) (Table 2).

It was found that 205 (68.3%) of the patients who were included in the study gave birth. When the patients who gave birth were examined in terms of preterm birth, delivery types, and first- and fifth- minute APGAR scores of newborns, the rate of preterm birth was found to be significantly higher in pregnant women in the severe and critically ill group than in the mild disease group (p<0.001). The frequency of cesarean delivery was significantly higher in the severe and critical disease group than in the mild disease group (p=0.001; p<0.05) (Table 3).

When the patients who were included in the study were examined in terms of laboratory findings, Troponin, Procalcitonin, Ferritin, CRP, AST, ALT, and LDH values were significantly higher in pregnant women in the severe and critical disease group when compared to the pregnant women in the mild disease group, and the lymphocyte count was

Table 1. Demographic characteristics of patients

	Mild illness (number of patients=273)	Severe and critical illness (number of patients=30)	Total (number of patients=303)	p[a]
	Mean ± standard deviation	Mean ± standard deviation	Mean ± standard deviation	
Age	28.7±6.2	31.8±5.7	29.0±6.2	**0.010***[, a]
BMI	28.9±4.7	30.0±0.4	29.0±4.8	0.245[a]
Body mass index grup	**Number of patients (%)**	**Number of patients (%)**	**Number of patients (%)**	
18.5≤ weak	1 (0.4)	-	1 (0.3)	0.419[b]
25-30 normal	162 (61.4)	18 (60)	180 (61.2)	
30-34.9 slightly fat	76 (28.8)	7 (23.3)	83 (28.2)	
35-39.9 fat	17 (6.4)	2 (6.7)	19 (6.5)	
40≥ morbidly obese	8 (3.0)	3 (10)	11 (3.7)	
Chronic diseases	**Number of patients (%)**	**Number of patients (%)**	**Number of patients (%)**	
Diabetes mellitus	5 (1.8)	-	5 (1.7)	0.455[b]
Hypertension	16 (5.9)	3 (10)	19 (6.3)	0.375[b]
Hypothyroidism	1 (0.4)	-	1 (0.3)	0.740[b]
Asthma	4 (1.5)	-	4 (1.3)	0.505[b]
Cardiovascular disease	2 (0.7)	-	2 (0.7)	0.638[b]

*p<0.05, [a]Mann Whitney U test, [b]Chi-square test, BMI: Body mass index

Table 2. Pregnancy characteristics of the patients

	Mild illness (number of patients=273)	Severe and critical illness (number of patients=30)	Total (number of patients=303)	p[a]
	Mean ± standard deviation	Mean ± standard deviation	Mean ± standard deviation	
Gestational week	34.1±6.7	30.4±5.2	33.8±6.6	**0.004****
Trimester	**Number of patients (%)**	**Number of patients (%)**	**Number of patients (%)**	
1. Trimester[+]	7 (2.6)	-	7 (2.3)	0.460
2. Trimester[++]	31 (11.0)	5 (16.7)	35 (11.6)	
3. Trimester[+++]	236 (86.4)	25 (83.3)	261 (86.1)	
Multiparity presence	**Number of patients (%)**	**Number of patients (%)**	**Number of patients (%)**	
Nullipar	54 (19.8)	4 (13.3)	58 (19.1)	0.394
Multipar	219 (80.2)	26 (86.7)	245 (80.9)	

**p<0.001, [a]Mann-Whitney U test, [+]0-14, [++]14-28, [+++]28 above

significantly lower (p=0.002; p=0.002; p<0.001; p=0.001; p<0.001; p<0.001; p<0.001; p=0.030, respectively) (Table 4).

Discussion

It is considered that COVID-19, which first emerged in China in December 2019 and turned into a serious pandemic all over the world, will cause various clinical differences in pregnant patients when compared to the normal population, with the effect of physiological and immunological adaptation mechanisms brought by pregnancy. The diagnosed patients follow a clinical course ranging from asymptomatic to severe disease requiring respiratory support and even death.

In this study, the mean age of the pregnant women was 29.0±6.2 years. The mean age of the pregnant women was

Table 3. Pregnancy outcomes and examination of newborns

	Mild illness (number of patients=273)	Severe and critical illness (number of patients=30)	Total (number of patients=303)	p[a]
Patients giving birth	185 (68.5)	20 (66.7)	205 (68.3)	0.836[b]
Preterm/term[+]				
Preterm	62 (33.5)	17 (85)	79 (38.5)	**<0.001**[**, b]
Term	123 (66.5)	3 (15)	126 (61.5)	
Type of birth				
C/S	115 (62.2)	20 (100)	135 (65.9)	**0.001**[**, b]
Vaginal birth	70 (37.8)	-	70 (34.1)	
1. Minute APGAR (mean ± standard deviation)	7.97±0.5	7.58±1.1	7.91±0.6	0.092[a]
5. MinuteAPGAR (mean ± standard deviation)	9.39±0.6	9.05±1.2	9.34±0.7	0.476[a]

**p<0.001, [a]Independent Student's t-test, [b]Chi-square test, [+]Less than 37 weeks, C/S: Cesarean section

Table 4. Laboratory findings

	Mild illness (number of patients=273)	Severe and critical illness (number of patients=30)	Total (number of patients=303)	p[a]
	Mean ± standard deviation	Mean ± standard deviation	Mean ± standard deviation	
Troponin	4.87±6.7	8.0±9.2	5.2±7.0	**0.002****
Procalcitonin	0.16±1.2	3.42±12.5	0.49±4.2	**0.002****
Urea	14.9±5.7	16.0±9.8	15.1±6.2	0.504
Creatinine	0.45±0.1	0.43±0.1	0.44±0.1	0.200
Ferritin	51.9±109.6	113.3±177.5	58.1±19.2	**<0.001****
C-reactive protein	34.8±43.8	72.9±84.5	38.6±50.5	**0.001****
Sodium	137.2±7.9	137.1±3.7	137.2±7.6	0.270
Potassium	4.02±0.4	3.90±0.4	4.0±0.4	0.094
Aspartate transferaminase	32.3±26.2	57.1±56.9	34.8±31.4	**<0.001****
Alanine transferaminase	21.4±23.7	47.7±60.0	24.0±30.2	**<0.001****
Lactate dehydrogenase	257.9±109.6	366.9±33.6	268.9±116.8	**<0.001****
Leukocyte	9127.3±3730.9	9680.0±3696.5	9182.0±3725.1	0.374
Neutrophil	6999.6±3352.5	7866.7±3451.9	7085.5±3366.7	0.108
Lymphocyte	1399.7±728.8	1146.7±616.3	1374.6±721.5	**0.030***
Monocyte	620.9±322.6	580±346.8	616.8±324.7	0.215
INR	1.30±5.8	0.93±0.05	1.26±5.5	0.194
Fibrinogen	482.7±334.1	471.7±144.6	481.6±320.1	0.579
D-dimer	2789.5±6295.2	2128.7±1737.3	2723±5996.8	0.289
Hemoglobin	11.2±1.6	11.5±1.3	11.2±1.5	0.534
Thrombocyte	226.7±157.9	254.2±130.6	229.4±155.5	0.294

*p<0.05, **p<0.00, [a]Mann-Whitney U test, INR: International normalized ratio

found to be significantly higher in the severe and critical disease groups than in the mild disease group. In a review that included 62 studies conducted by Lassi et al. [10], COVID-19 was examined in 2 categories as severe and non-severe, and it was found that 85.6% of pregnant women had non-severe COVID-19 and the remaining 14.4% had severe COVID-19. The study reported that pregnant women with severe COVID-19 were approximately 3.7 years older and had a higher risk of severe COVID-19 among women in a higher age group (>35 years) [10]. In another review of 33 studies including 385 patients, 95.6% of patients had mild disease, 3.6% had severe disease, and 0.8% had critical disease [11].

In the non-pregnant population, obesity was associated with severe COVID-19 disease, and several case series and cohort studies involving pregnant patients showed increased severity of COVID-19 in pregnant women with high BMI scores and obesity [12]. No significant differences were detected between the mild disease and severe and critical disease groups in terms of BMI scores. In a study that was conducted with pregnant patients in Italy, the mean BMI score of the patients was found to be 22.8, the mean BMI score of women with severe disease was found to be 30, and it was reported that the BMI of patients with severe disease was significantly higher than those with mild disease [13]. In a case series study conducted by Andrikopoulou et al. [14] in New York, mild disease was detected in 52% and severe disease in 47%, and it was found that there was no significant difference between the two groups regarding age and obesity.

In most previous studies, BMI scores were calculated by considering the weight of the patients before pregnancy or in the early gestational weeks, and the data on the weight of the patients in our study were obtained at the time of hospitalization. We think that the reason why our study was incompatible with the data given in the literature that BMI increases the severity of the disease was because of this.

It was reported in many previous studies that severe COVID-19 is more common in adults over 60 years of age, immunocompromised patients, and those with chronic diseases such as diabetes, hypertension, and chronic lung disease [15]. No significant differences were detected between the groups in terms of chronic disease findings. In a meta-analysis of pregnant patients with COVID-19, severe COVID-19 was associated with increased maternal age, high BMI scores, any pre-existing maternal disease, chronic hypertension, preeclampsia, gestational diabetes, and pregestational diabetes [2]. In a case series study conducted with 158 pregnant women by Andrikopoulou et al. [14], it was found that pregnant patients with moderate or severe disease had an underlying chronic disease and were diagnosed with asthma. The data obtained in our study regarding comorbidities do not match the literature data. The reason for this may be some hereditary differences because of ethnic origin as well as a lack of data because of deficiencies in the anamnesis of the patients.

In the present study, it was found that the pregnant women in the severe and critical disease group had a lower gestational week than the pregnant women in the mild disease group. In all studies conducted so far, there were not enough data on first- and early second-trimester pregnant patients, many data were obtained from patients in the third trimester. For this reason, according to the data in the literature, the data on whether gestational week affects the severity of the disease is not yet sufficient to comment on this issue.

The pregnancies of 3 (1%) of the 303 patients who were included in the current study resulted in abortion. Although there are some studies reporting data showing that the rate of miscarriage increased in other previous coronavirus (SARS, MERS) outbreaks, there was no evidence in the literature showing that COVID-19 increased the risk of miscarriage [16]. Among the patients who gave birth, 135 (65.9%) were delivered by cesarean section and 70 (34.1%) were delivered by normal vaginal delivery (NVD). Twenty patients who underwent cesarean section were in the severe and critical disease group, and none of the patients who gave birth with NVD had severe or critical disease findings. It was found that cesarean delivery rates differed according to the country where the study was conducted. In a systematic review conducted by Huntley et al. [17], the cesarean section rate was reported as 42.9% in Italy, 44.4% in the USA, and 92.2% in China. In the study, it was suggested that the difference in these rates was caused by the acceptance of COVID-19 as an independent cesarean indication in the data from China [17]. High cesarean rates may be caused by one of the following factors: concerns that pregnancy may increase the severity of the disease, fetal or neonatal transmission may increase with NVD, fetal distress may occur because of systemic inflammatory response in the mother, and thoughts such as reducing transmission to healthcare personnel. However, the role of cesarean section in reducing these risks has not been proven. In a study conducted by Khoury et al. [18] in New York in 5 centers, the rate of cesarean section was reported to be 52.4% in pregnant women with severe COVID-19 and 91.7% in critically ill patients, and a significant increase was reported between COVID-19 severity and cesarean rates. In a meta-analysis conducted by Lassi et al. [10], 48.4% of the patients gave birth with cesarean section, and the risk of cesarean section was found to be 1.39 times higher in severe cases.

It was found that the rate of preterm birth in the severe and critical disease groups was significantly higher than in the mild disease group. In the study conducted by Metz et al. [19], 1.219 pregnant COVID-19 patients were evaluated, and it was reported that the risk of preterm birth increased in severe

and critically ill patients when compared to asymptomatic patients.

Only 1 (0.3%) of the patients who were included in this study had positive RT-PCR results in their babies. This patient was admitted to the clinic with the diagnosis of PROM at 29 weeks of gestation, tocolysis was applied to the patient for 1 day, but the delivery could not be prevented, and the patient delivered by NVD. Based on these findings, although it is considered that RT-PCR positivity in the baby may have occurred with ascending transmission rather than vertical transmission, vertical transmission could not be excluded. There are many articles in the literature arguing that there is no vertical transition, as well as many publications containing data on vertical transition [20-22].

It was also found that troponin, procalcitonin, ferritin, CRP, ALT, AST, and LDH values in the blood samples taken at the time of hospitalization of the pregnant women who were included in the study were significantly higher in the severe and critical disease group than in the mild disease group. However, lymphocytopenia was also found to be significantly higher in the severe and critically ill group than in the mild disease group. Although the mean D-dimer values were above the upper reference value in all patient groups, no significant differences were detected between the groups. In a cohort that examined inflammatory biomarkers in pregnant patients with COVID-19, it was reported that especially lymphocytopenia and high CRP levels were associated with disease severity and mortality, and lymphopenia was associated with the possibility of receiving oxygen support. It was also reported in the same study that although D-dimer values were above the upper reference value, they were not associated with oxygen demand and did not cause any significant changes in the clinical course [23]. In a study by Zhou et al. [24] with patients in the normal population, high D-dimer values were reported to be associated with poor prognosis. It was concluded in another systematic review that D-dimer elevation is associated with mortality, as in many similar studies [25]. Pregnancy increases the risk of thromboembolism, and D-dimer values increase physiologically, especially in the third trimester. For this reason, the prognostic role of D-dimer in pregnant women with COVID-19 is controversial, and the data obtained from the publications so far do not provide sufficient evidence that high D-dimer affects the prognosis negatively in pregnant women with COVID-19 [26].

Study Limitations

The limitations of the current study were that only hospitalized pregnant patients were evaluated and outpatients were not included in the study, and insufficient data on the clinical prognosis of COVID-19 at early weeks of gestation were not presented because of the low number of first- and second-trimester patients.

Conclusion

The present study will contribute to many issues regarding the clinical course of the disease and maternal and fetal outcomes based on the data on pregnant patients with COVID-19, which has become a serious healthcare concern all over the world. We tried to contribute to the literature in terms of minimizing maternal and fetal complications by showing how it affects maternal and perinatal outcomes. We believe that further studies are needed to determine the negative impacts and unidentified aspects of COVID-19 on maternal and newborn health with prospective studies to be conducted with larger patient populations.

Ethics

Ethics Committee Approval: This study was approved by University of Health Sciences Turkey, Adana City Training and Research Hospital, Clinical Research Ethics Committee (date: 04.11.2021, meeting number: 92, decision no: 1628).

Informed Consent: Since all information was obtained from the hospital automation system, informed consent was not required from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ş.E.B., N.Y., E.B., Design: Ş.E.B., N.Y., E.B., Data Collection or Processing: Ş.E.B., N.Y., H.E.S., A.R.Ş., E.B., E.G., A.G., A.A., R.A.O., Analysis or Interpretation: Ş.E.B., N.Y., H.E.S., A.R.Ş., E.B., E.G., A.G., A.A., R.A.O., Literature Search: Ş.E.B., N.Y., H.E.S., A.R.Ş., E.B., E.G., A.G., A.A., R.A.O., Writing: Ş.E.B., N.Y., H.E.S., A.R.Ş., E.B., E.G., A.G., A.A., R.A.O.

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