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The effect of gestational age at the time of diagnosis on adverse pregnancy outcomes in women with COVID-19

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Abstract

Objective: We aimed to investigate the incidence of adverse pregnancy outcomes including preterm birth, preeclampsia (PE), and fetal growth restriction (FGR) in pregnant women with COVID-19 according to the gestational age.

Methods: This retrospective study included 167 pregnant women who were hospitalized with confirmed COVID-19. The patients were divided into three groups according to the time of diagnosis as follows: <12 weeks of gestation (first trimester, $n = 10$), 12–24 weeks of gestation ($n = 28$), and >24 weeks of gestation ($n = 129$). Medical records of the patients were reviewed retrospectively and adverse pregnancy outcomes were analyzed.

Results: A total of 49 (29.3%) patients had an active COVID-19 infection at the time of delivery, while 118 (70.7%) gave birth after the infection was cleared. Twenty-three patients had preterm birth and the gestational age was <34 weeks in only four of these patients. There was no significant difference in the preterm birth, PE, FGR, HELLP syndrome, and gestational diabetes mellitus among the three gestation groups ($p = 0.271$, 0.394, 0.403, 0.763, and 0.664, respectively). Four (2.39%) patients required intensive care unit stay. Maternal death was seen in only one (0.59%) patient.

Conclusion: Our study showed no significant correlation between the gestational age at the time of COVID-19 infection and the frequency of adverse pregnancy outcomes such as preterm birth, PE, FGR, and gestational diabetes mellitus. However, further studies are needed to draw a firm conclusion on this topic.

Key words: COVID-19, gestational age, pregnancy outcome, trimester.

Introduction

Pneumonia of unknown cause was first identified in Wuhan, Hubei province of China in December 2019 and novel coronavirus-2019 (COVID-19) caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) rapidly spread to the world, leading to a devastating pandemic. The World Health Organization (WHO) declared COVID-19 pandemic on March 8th, 2020.[1]

Several studies have shown that COVID-19 has a more severe disease course in elderly, immunocompromised patients, and pregnant women due to hormonal and immune changes.[2,3] Immunological changes during pregnancy seem to be for the benefit of the fetus, although they pose an increased risk for the mother to have viral infections, particularly respiratory system diseases.[4,5] Despite unprecedented events during the pandemic, the relatively low mortality in pregnant women caused by COVID-19 infection has been an interest to many researchers.

Through the spike-like protein on its surface, the SARS-CoV-2 enters the pulmonary epithelial cells by binding to angiotensin-converting enzyme 2 (ACE2) receptors and induces viral replication.[6] The ACE2 is

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a metalloenzyme attached to the cell membranes of the lungs, heart, kidney, and intestines and is expressed abundantly in placenta and reproductive organs.[6] The ACE2 in human placenta is specifically expressed by cytotrophoblasts, syncytiotrophoblasts, extravilloustrophoblasts (EVTs), and vascular smooth muscles and endothelial cells of the primary and secondary villi and decidual cells.[6] The ACE2 forms angiotensin (Ang)-(1-9) through hydrolysis of Ang-1 with a high affinity to Ang-2, enhancing the production of Ang-(1-7).[7] During pregnancy, Ang-2, ACE2, and Ang-(1-7) play a critical role in the blood pressure regulation and development of the fetus.[6] The Ang-(1-7) and ACE2 involve in the angiogenesis, apoptosis, and fetal development in the early period of pregnancy by exerting local effects and regulate uteroplacental blood flow in the late period.[6]

The increased ACE2 expression in the placental tissue is responsible for the placental infection by the SARS-CoV-2 and placental dysfunction, leading to adverse pregnancy outcomes.[8] Previous studies have demonstrated an increased rate of adverse pregnancy outcomes such as preterm birth, premature rupture of membranes (PROM), and cesarean section (C/S) delivery in pregnant women with COVID-19 infection.[9,10] In addition, alterations in the ACE2 ribonucleic acid (RNA) expression in human placental tissues during pregnancy have been reported.[8,11] In a study using single-cell RNA sequencing (first trimester), the ACE2 expression significantly increased in cytotrophoblasts and syncytiotrophoblasts in the maternal-fetal interface with a higher increase at later stages of pregnancy (Week 24).[8]

Considering the fluctuations in the ACE2 expression throughout pregnancy, in the present study, we aimed to investigate the incidence of adverse pregnancy outcomes including preterm birth, preeclampsia (PE), and fetal growth restriction (FGR) in pregnant women with COVID-19 according to the gestational age.

Materials and Methods

This single-center, retrospective study was conducted at Bursa City Hospital, Obstetrics and Gynecology clinic between April 1, 2020, and December 1, 2020. A total of 192 pregnant women who were hospitalized in the infectious diseases ward with confirmed COVID-19 by the real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test were included in the study. The diagnosis of COVID-19 was made based on the definition of the WHO Interim Guidance.[12] The definitive diagnosis was confirmed using RT-PCR, which can qualitatively detect the nucleic acid from the nasopharyngeal/oropharyngeal swabs.[13] The study protocol was approved by the Bursa City Hospital, Ethics Committee (no. 2020-10/5). The study was conducted in accordance with the principles of the Declaration of Helsinki.

All patients who were hospitalized with a confirmed diagnosis of COVID-19 were included. However, patients who did not give birth at the time of study and those having missing delivery data were excluded. The patients were divided into three groups according to the time of diagnosis as follows: <12 weeks of gestation (first trimester, $n = 10$), 12–24 weeks of gestation ($n = 28$), and > 24 weeks of gestation ($n = 129$). Medical records of the patients were reviewed retrospectively and demographic characteristics, clinical signs, and symptoms at the time of admission and laboratory test results were noted. Prescribed treatments were also documented. Gestational age at the time of delivery, type of delivery, indications of delivery, birth weight, postpartum hemorrhage, and other adverse pregnancy outcomes were analyzed. Based on the maternal outcomes, maternal morbidity and mortality rates were also examined.

Adverse pregnancy outcomes were defined as preterm birth, PE, FGR, stillbirth, and spontaneous abortion. The PE diagnosis was made based on at least two high systolic (≥140 mmHg) or diastolic (≥90 mmHg) blood pressure measurements (at 4-h intervals) in a previously normotensive pregnant woman, and also the presence of one or more of the following findings: (i) proteinuria (≥300 mg/24 h; ≥30 mg/mol protein:creatinine ratio; or a dipstick-test result ≥2+); (ii) other maternal organ dysfunction; and (iii) uteroplacental dysfunction (such as FGR, abnormal umbilical artery Doppler waveform analysis, or stillbirth).[14] Preterm birth was defined as a delivery occurring <37 completed weeks of gestation. The FGR was defined as the estimated fetal weight <10th percentile.[15] Abortion was defined as pregnancy loss before 24 weeks of gestation. Stillbirth was defined as any fetal death after 24 weeks of gestation.

Lymphopenia was defined as a peripheral blood lymphocyte count <1500/mm^3, while thrombocytopenia was defined as a platelet count less than 150 000/mm^3.

Statistical analysis

Statistical analysis was performed using the SPSS version 23.0 software (IBM Corp., Armonk, NY, USA).

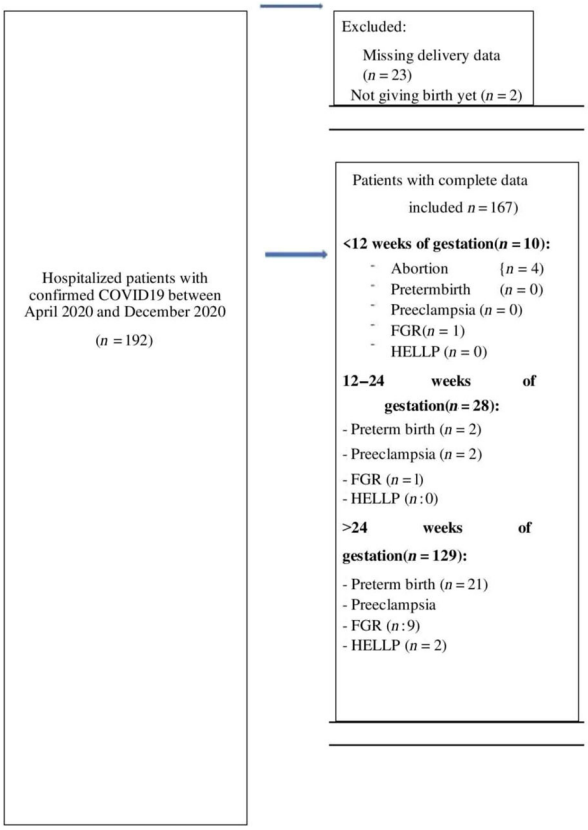

FIGURE 1 Study flow chart

Descriptive data were expressed in mean ± standard deviation (SD), median (min–max), or number and frequency, where applicable. The normality assumption was checked using the Shapiro–Wilk test. The Kruskal–Wallis test was used to compare the groups and significant differences were analyzed using the Dunn *post-hoc* test. The Fisher–Freeman–Halton exact test was used to examine the relationship between categorical variables and gestational age at the time of diagnosis. A p-value of <0.05 was considered statistically significant.

Results

A total of 192 patients who were hospitalized with confirmed COVID-19 were included in the study. However, 23 patients who had incomplete delivery data and two patients who did not give birth at the time of study were excluded. The study flow chart is shown in Figure 1.

TABLE 1 Descriptive data of the patients

Variables	*n*	%	Total *N*
Previous systemic disease	24	14.5	165
Smoking	13	7.9	165
Previous PE	4	2.8	143
Previous preterm birth	10	7.0	143
Abortion	4	2.39	167
COVID-19 at the time of delivery	49	29.3	167
Previous COVID-19 infection	118	70.6	167
Symptom at the time of hospitalization	130	77.8	167
Plaquenil	17	10.2	167
Lopinavir/ritonavir	46	27.5	167
Postpartum favipiravir	14	8.4	167
LMWH	129	77.2	167
NSD	69	42.3	163
C/S	94	57.7	163
FGR	11	6.74	163
PE	20	12.2	163
Preterm birth	23	14.11	163
HELLP	2	1.2	163
GDM	3	1.8	163
Placental abruption	0	0.0	163
Postpartum bleeding	2	1.2	163

Note: Data are given in number and frequency, unless otherwise stated. and Abbreviations: COVID-19, novel coronavirus-2019; C/S, cesarean section; FGR, fetal growth restriction; PE: preeclampsia; GDM, gestational diabetes mellitus; HELLP, hemolysis, elevated liver enzymes, and low platelet count; LMWH, low-molecular-weight heparin; NSD, normal spontaneous delivery.

Of a total of 167 patients included, the mean age was 28.99 ± 5.58 (range, 17–44) years and the mean body mass index was 28.94 ± 4.87 (range, 19.14–46.87) kg/m^2. Two patients had multiple pregnancy, while the remaining patients had a singleton pregnancy.

A total of 49 (29.3%) patients had an active COVID-19 infection at the time of delivery, while 118 (70.7%) gave birth after the infection was cleared. (Table 1).

Of the patients, 24 (14.5%) had a history of chronic diseases, predominantly asthma. Thirteen (7.9%) patients were smokers (Table 1).

At the time of admission, 37 (22.2%) patients were asymptomatic, while dry cough was the most common symptom in 92 (55.1%) patients. Lopinavir/ritonavir was the most frequently used treatment regimen in 46 patients (27.5%). Low-molecular-weight heparin was used in 129 (77.2%) of the patients (Table 1).

The C/S delivery was performed in 94 (57.7%) of the patients, while 69 (42.3%) patients gave birth via vaginal delivery.

Four patients who were diagnosed with COVID-19 in the first trimester of pregnancy experienced abortion.

TABLE 2 Numerical data of the patients according to the gestational age groups

	Gestational age at the time of diagnosis (week)									
	<12 weeks			12–24 weeks			>24 weeks			
Variable	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	p^a
Age, years	10	27.90	5.26	28	29.14	5.78	129	29.05	5.78	0.757
BMI, kg/m^2	9	25.10a	4.40	26	29.59b	4.35	128	29.08b	4.91	0.037
Fever	10	37.13	1.17	28	36.64	0.57	123	36.86	0.80	0.449
WBC ($10^3/\mu L$)	10	7.44	3.45	28	7.54	3.05	126	8.24	2.51	**0.050**
Hb (g/dL)	10	11.53	1.81	28	10.77	1.24	126	11.36	1.35	0.073
Platelet count ($10^3/\mu L$)	10	249.80	86.65	27	217.07	36.17	126	209.99	69.73	0.137
Lymphocyte count ($10^3/\mu L$)	10	1.45	0.78	28	1.68	0.74	126	1.41	0.60	0.226
AST (IU/L)	9	21.94	10.07	27	17.84	6.57	124	21.04	9.60	0.216
ALT (U/L)	9	17.78	10.37	28	19.75	19.33	124	19.98	28.95	0.656
LDH (IU/L)	6	277.00	174.2	20	174.50	47.43	84	195.37	50.32	0.050
CRP (mg/L)	7	6.71	5.46	27	21.78	24.46	116	24.49	28.62	0.088
Ferritin (μg/L)	8	37.28	34.51	26	48.16	44.46	113	59.00	76.53	0.658
Procalcitonin (μg/L)	7	0.13	0.18	22	0.05	0.03	87	0.09	0.08	**0.021**
D-dimer (μg FEU/mL)	9	1.13	2.48	27	1.07	0.96	114	1.55	1.07	**<0.001**
PT (s)	10	8.86	0.86	24	8.15	0.31	107	7.93	0.41	**<0.001**
aPTT (s)	10	30.51	4.55	24	28.48	4,07	106	30.45	4.50	0.002
INR	10	0.88	0.32	24	0.91	0.03	106	0.89	0.04	**0.002**

Note: Different lowercase letters represent significant differences. There is a significant difference between the weeks with different lowercase letters.; Abbreviations: ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; Hb, hemoglobin; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin time; WBC, white blood cell.; [a]Kruskal-Wallis test and Dunn post-hoc test.
Bold values are indicates statistical significance at $p < 0.05$.

Twenty (12.2%) patients had PE and two (1.2%) patients had HELLP syndrome. Eighteen patients with PE were in the late-onset PE group (≥35th week of gestation). One of the patients with HELLP became pregnant with in vitro fertilization (IVF) and received COVID-19 treatment at 31st week of gestation. At the time of diagnosis, she was 22 years old and was intubated due to COVID-19. The C/S was performed for HELLP and she developed peripheral arterial thrombosis in later stages. The other patient with HELLP was a 25-year-old pregnant who was at 28th week of gestation and was transferred to the intensive care unit (ICU) for severe COVID-19 infection. At 39th week of gestation, this patient underwent C/S delivery. Another patient was a 36-year-old patient who became infected with COVID-19 at 28th week of gestation and re-admitted with severe PE and intrauterine fetal death at 35th week of gestation.

Of all patients, 23 (14.11%) had preterm birth. The gestational age was <34 weeks in only four (17.3%) patients. Delivery was performed in nine (39.1%) patients during the COVID-19 positivity. Eight (34.7%) of the patients with preterm labor had PE and another (4.37%) patient had HELLP syndrome. Eleven (6.74%) patients had FGR.

Numerical data of the patients according to the gestational age groups are summarized in Table 2. Accordingly, the median D-dimer level was the lowest and highest in the <12 weeks of gestation group and the >24 weeks of gestation group, respectively ($p < 0.001$). The procalcitonin levels were higher in the >24 weeks of gestation group than the other two groups ($p = 0.021$). In addition, the median white blood cell (WBC) count was significantly higher in the >24 weeks of gestation group than the other two groups ($p = 0.050$).. The LDH level was higher in the <12 weeks of gestation group than the 12–24 weeks of gestation group ($p = 0.050$). The prothrombin time (PT) and international normalized ratio (INR) levels were the highest and the lowest in the <12 weeks of gestation group and > 24 weeks of gestation group, respectively ($p = 0.001$ and 0.002).

Categorical data of the patients according to the gestational age groups are presented in Table 3. Accordingly, there was no significant difference in the symptoms at the time of diagnosis, except for nasal congestion ($p = 0.043$). During follow-up, there was no significant difference in the preterm birth, PE, FGR, HELLP syndrome, and gestational diabetes mellitus (GDM) among the three gestation groups ($p = 0.271$, 0.394, 0.403, 0.763, and 0.664, respectively).

Of all patients included, only four (2.39%) required ICU stay. Maternal death was seen in only one

TABLE 3 Categorical data of the patients according to the gestational age groups

	Gestational age at the time of diagnosis (week)						
	<12 weeks ($n = 10$)		12–24 weeks ($n = 28$)		>24 weeks ($n = 129$)		
Variable	*n*	%	*n*	%	*n*	%	p^a
Previous systemic disease	2	20.0	4	14.8	18	14.1	0.771
Smoking	2	20.0	3	11.1	8	6.3	0.131
COVID-19 infection							
At time of delivery	2	20.0	0	0.0	47	36.4	**<0.001**
Previous infection	8	80.0	28	100.0	82	63.6	
Symptom at the time of hospitalization	6	60.0	23	82.1	101	78.3	0.347
Cough	4	40.0	15	53.6	73	56.6	0.629
Dyspnea	1	10.0	8	28.6	43	33.3	0.321
Loss of smell and taste	1	10.0	4	14.3	29	22.5	0.550
Fatigue	4	40.0	10	35.7	56	43.4	0.772
Diarrhea	0	0.0	2	7.1	14	10.9	0.696
Sore throat	1	10.0	8	28.6	28	21.7	0.506
Nasal congestion	0	0.0	1	3.6	25	19.4	**0.043**
NSD	5	83.3	9	32.1	55	42.6	0.070
CS	1	16.7	19	67.9	74	57.4	
PE	0	0.0	2	7.1	18	14.0	0.394
Preterm birth	0	0.0	2	7.1	21	16.3	0.271
HELLP	0	0.0	0	0.0	2	1.6	0.763
GDM	0	0.0	0	0.0	3	2.4	0.664
Placental abruption	0	0.0	0	0.0	0	0.0	-
Postpartum bleeding	0	0.0	0	0.0	2	1.6	-
FGR	1	16.7	1	3.7	9	7.3	0.403
Pneumonia							
No	9	90.0	21	75.0	74	57.4	0.070
Mild	0	0.0	6	21.4	36	27.9	
Moderate	0	0.0	0	0.0	14	10.9	
Severe	1	10.0	1	3.6	5	3.9	

Note: Data are given in number and frequency, unless otherwise stated.; Abbreviations: COVID-19, novel coronavirus-2019; C/S, cesarean section; FGR, fetal growth restriction; GDM, gestational diabetes mellitus; HELLP, hemolysis, elevated liver enzymes, and low platelet count; NSD, normal spontaneous delivery; PE, preeclampsia.; [a]Fisher–Freeman–Halton exact test and Bonferroni correction Z-test. and Bold values are indicates statistical significance at $p < 0.05$.

(0.59%) patient. This patient was a 32-year-old pregnant woman who was at 11 weeks of pregnancy. She was hospitalized for COVID-19. On Day 9 of hospitalization, the patient was transferred to the ICU and intubated due to severe pneumonia and myocarditis. Two days later, curettage was performed for missed abortion. Her clinical status worsened after the procedure and septicemia developed. She died on Day 9 of intubation.

Discussion

In the present study, we investigated the incidence of adverse pregnancy outcomes in pregnant women with COVID-19 according to the gestational age at the time of diagnosis. The study results showed no significant difference in the adverse pregnancy outcomes such as preterm birth, PE, FGR, GDM, and HELLP syndrome among the three pregnancy groups.

Previous studies using human placenta have shown the increased decidual arteriopathy, maternal vascular malperfusion (MVM), inflammation, and fibrinoid deposition in patients recovered from COVID-19.[16,17] These pathological alterations have been associated with oxygenation abnormalities and adverse pregnancy outcomes.[17] In addition, MVM has been shown to be linked to hypertensive diseases and severe preterm PE.[18,19]The SARS-CoV-2 has been thought to cause inflammatory syndrome in the placenta, resulting in preterm birth, PROM, fetal distress, and stillbirth.[20]

Upon entry into the human body, SARS-CoV-2 spike binds to ACE2 receptor through its receptor-binding domain. In a study examining ACE2 RNA in

placental tissues obtained from all three trimesters, the ACE2 expression in the term placental tissues was not as high as in the first and second trimester placentas.[11] Unlike syncytiotrophoblasts, EVTs play a central role in the placental barrier and vertical transmission of pathogens from mother to fetus.[21,22] In a study examining the first-trimester placental tissues, the ACE2 positivity was found to be higher in the cytotrophoblasts and syncytiotrophoblasts, while it was higher in the EVTs at 24 weeks of pregnancy.[23] The ACE2 + TMPRSS2 + early trophectoderm were strongly correlated with viral invasion, epithelial cell proliferation, and cell adhesion.[23] In the light of these data, the gestational age at the time of COVID-19 diagnosis may be associated with adverse pregnancy outcomes.

In the secondary analysis of the multi-center, multinational study on COVID-19 conducted by the World Association of Perinatal Medicine (WAPM), the association between maternal and pregnancy characteristics and the risk of adverse perinatal outcomes in pregnancies with laboratory confirmed COVID-19 was evaluated. The authors reported that gestational age at the time of diagnosis and early gestational age at the time of infection were the independent risk factors of adverse perinatal outcomes such as abortion, stillbirth, and neonatal death.[24] Unlike this study, we found no significant difference in the adverse pregnancy outcomes among the three pregnancy groups.

There is a limited number of data regarding the effect of COVID-19 in the first trimester of pregnancy on spontaneous abortion and adverse pregnancy outcomes in the literature. In a retrospective study conducted in an IVF center in Canada, the effect of COVID-19 pandemic on early was investigated in the first-trimester pregnancies.[25] In this study, no significant difference in the number of first-trimester miscarriage, biochemical pregnancies, or total miscarriage rate was observed between the pandemic and prepandemic groups. However, this study excluded symptomatic patients. In another Italian study, whether SARS-CoV-2 infection was a risk factor for early pregnancy loss in the first trimester of pregnancy was investigated.[26] This study included both women with spontaneous abortion and women with ongoing pregnancy. Past or current infection was identified based on RT-PCR of nasopharyngeal swabs and immunoglobulin G and M antibodies in blood samples. The authors found no significant difference in the incidence of COVID-19 between the two groups. However, severe cases of COVID-19 were excluded from this study. In this study, four (2.3%) patients of the first trimester pregnancies had spontaneous abortion. In the multi-center WAPM study, this rate was 2.3%.[27] Unlike previous studies, only 22.2% of the patients in the first trimester were asymptomatic in our study.

The Ang-(1-7) has vasodilatory properties and plays a key role in the regulation of renin-angiotensin-aldosterone system.[28,29] Besides the kidneys, the placenta and uterus also contribute to the increased ACE2 expression and activity during pregnancy, which is involved in the regulation of blood pressure.[30] Several studies demonstrated that low ACE2 and Ang-(1-7) levels were associated with FGR and PE.[31,32] The Ang-(1-7)/Ang-2 ratio was also found to be independently linked to PE.[33] Furthermore, there is a growing number of studies suggesting the increased rate of PE in pregnant women with COVID-19.[34] As a heterogeneous hypertensive disorder of pregnancy, PE is characterized by hypertension, proteinuria, thrombocytopenia, and renal failure caused by endothelial damage due to placental oxidative stress and anti-angiogenic factors.[35,36] Since COVID-19 and PE share similar pathophysiological mechanisms and symptoms of both conditions may overlap, the differential diagnosis can be challenging in patients presenting with hypertension, proteinuria, and elevated liver enzymes.[36] In a prospective study, Mendoza et al.[37] reported that severe COVID-19 patients had PE-like syndrome and that uterine artery pulsatility index (UtAPI) and soluble fms-like tyrosine kinase-1/placental growth factor (sFlt-1/PlGF) were helpful to distinguish these conditions from each other. In another report, Coronado-Arroyo et al.[38] suggested that SARS-CoV-2 infection was a proinflammatory state, even in asymptomatic patients, which could be a risk factor for PE development. In the current study, 20 (12.1%) of our patients had PE. We observed no significant difference in the developing PE among the pregnancy groups classified according to the gestational age. Thirteen patients had PE in later stages of pregnancy. Seven patients underwent delivery at the time of COVID-19 treatment. Similar to previous studies, the differential diagnosis of PE-like syndrome related to COVID-19 and true PE was unable to be made. Therefore, PE-like syndrome should be kept in mind in pregnant women with COVID-19 and differential diagnosis should be performed.

Previous studies have demonstrated that the upregulation of ACE2/Ang-(1-7)/mitochondrial assembly (MAS) prevents preterm birth.[39] The SARS-CoV-2 has

been proposed to induce inflammatory syndrome in human placenta, thereby, leading to preterm birth and PROM.[20] In the literature, the rate of preterm birth varies between 15.2 and 27.6%.[27,40] In a study, Kayem et al.[41] reported that 27.6% of the patients had preterm birth, while 11.6% of the patients had delivery between 21st and 31st weeks of pregnancy. In our study, 13.9% ($n = 23$) patients had preterm birth and the gestational age was <34 weeks in only 17.3% ($n = 4$) patients. Delivery was performed in 39.1% ($n = 9$) at the time of the COVID-19 infection.

In previous studies, alterations in the placental tissues of the third-trimester pregnancy materials obtained from COVID-19 survivors, compatible with PE and FGR, were observed.[18,19] However, studies investigating placental tissues of the COVID-19 survivors who were first diagnosed during the first or second trimester of pregnancy are scarce. Therefore, further studies investigating placental tissues of COVID-19 survivors who were first diagnosed with COVID-19 during the early pregnancy are needed to gain a better understanding of the possible association between the disease itself and adverse pregnancy outcomes.

In the present study, we found a significant difference in the laboratory parameters among the groups. D-dimer is an indicator of fibrinolysis and plays a key role in the diagnosis of thromboembolism. In previous studies, increased D-dimer levels were associated with severe COVID-19.[42] In the current study, however, we found no significant difference between the rate of mild, moderate, or severe pneumonia among three groups. On the other hand, D-dimer levels were higher in the >24 weeks of gestation group. This can be attributed to the fact that women who gave birth were included in the >24 weeks of gestation group and D-dimer levels tend to increase physiologically.[43] In addition, procalcitonin is a useful marker in the diagnosis of bacterial sepsis and in the distinction of other pathologies. Dockree et al.[44] reported that procalcitonin levels were similar between the pregnant and non-pregnant women and found no significant correlation between the gestational age, maternal age, and body mass index. However, in the present study, we found higher procalcitonin levels in the >24 weeks of gestation group.

Nonetheless, there are some limitations to the present study. First, the number of asymptomatic patients is relatively low, as the majority of the patients were symptomatic or had a contact history with confirmed COVID-19 cases. Therefore, further studies including both symptomatic and asymptomatic pregnant women would provide more accurate information regarding the adverse maternal and fetal outcomes. Second, the number of patients with COVID-19 during the first trimester of pregnancy is relatively low to draw firm conclusions on the effect of COVID-19 on adverse pregnancy outcomes. Third, neonatal outcomes were unable to be documented which could have enhanced the strength of the results.

In conclusion, although the incidence of adverse pregnancy outcomes such as PE, preterm birth, and FGR increased in pregnant women with COVID-19, no statistically significant difference was observed according to the gestational age groups. Further large-scale, prospective studies including pregnant women who were first diagnosed with COVID-19 during the first trimester of pregnancy are needed to confirm these findings and to establish a definitive conclusion on this topic.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

Conceptualization, methodology, software, formal analysis, data collection, data interpretation: Gültekin A. Aydın, Serhat Ünal, and Hilal G. T. Özsoy. Writing and original draft: Gültekin A. Aydın. Review and editing, supervision: Gültekin A. Aydın, Serhat Ünal, and Hilal G. T. Özsoy. All authors read and approved the final manuscript.

Data Availability Statement

Data available on request from the authors.

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