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Comparison of clinical features and perinatal outcomes between pre-variant and post-variant periods in pregnant women with SARS-CoV-2: analysis of 1935 cases

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Abstract

Purpose To compare the clinical features and perinatal outcomes of pregnant women with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the pre-variant and post-variant periods.

Methods This prospective cohort study includes pregnant women with SARS-CoV-2 who were followed-up at Ankara City Hospital between 11, March 2020 and 15, September 2021. Demographic features, clinical characteristics and pregnancy outcomes were compared between the pre-variant ($n=1416$) and post-variant ($n=519$) groups.

Results The rates of severe and critical cases significantly increased in the post-variant group (9.7% vs 2%, $p<0.001$). The rates of respiratory support (26.8% vs 7.3%, $p<0.001$), ICU admission (12.9% vs 1.8%, $p<0.001$) and maternal mortality (2.9% vs 0.4%, $p<0.001$) were significantly higher in the post-variant group. A significant increase was observed for pregnancy complications in the post-variant group (45.6% vs 18.8%, $p=0.007$). The rates of preterm delivery (26.4% vs 4.4%, $p<0.001$) and NICU admission (34% vs 18.8%, $p<0.001$) were significantly higher in the post-variant group. Positive, weak, statistically significant correlations were observed between the post-variant period, disease severity and maternal mortality ($r=0.19$, $r=0.12$ and $p<0.001$).

Conclusion Post-variant COVID-19 period was associated with a severe course of the disease and increased rates of adverse obstetric outcomes in pregnant patients.

Keywords COVID-19 · SARS-CoV-2 · Pregnancy · Obstetric complications · Disease severity · COVID-19 variants

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Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been in the center of the world's attention since the beginning of the pandemic. This novel viral disease not only caused significant mortality and morbidity but also resulted in radical changes in our daily lives [1, 2]. Health care systems have been struggling to control the spread of COVID-19 and health care workers have been working under extremely tough conditions to heal infected individuals for approximately 2 years [3, 4]. Although significant progress has been achieved due to effective health policies, lifestyle changes, legal regulations, and widespread vaccination programs, COVID-19 has still not been fully controlled, especially due to the emergence of new variants [5, 6].

Pregnant women with COVID-19 have higher risks for severe disease, need for mechanical ventilation, intensive care unit (ICU) admission, and maternal death [7–11]. Moreover, higher rates of obstetric complications like preterm delivery, preterm premature rupture of membranes, and fetal distress are observed in pregnancies complicated by COVID-19 [12, 13]. There are recent publications in the literature indicating a worse prognosis in pregnant women infected by new SARS-CoV-2 variants [14–22]. However, our knowledge is still limited on the impact of new SARS-CoV-2 variants on maternal COVID-19 prognosis and pregnancy outcomes. For this reason, more data are necessary to achieve more precise results.

This study aims to compare the clinical features and perinatal outcomes of pregnant women with SARS-CoV-2 in the pre-variant and post-variant periods.

Materials and methods

This prospective cohort study includes pregnant women with SARS-CoV-2 who were followed-up at the Department of Obstetrics and Gynecology, Ankara City Hospital between 11, March 2020 and 15, September 2021. All consecutive SARS-CoV-2-positive cases confirmed by real-time polymerase chain reaction (RT-PCR) on nasopharyngeal and oropharyngeal samples were evaluated. Written informed consent was obtained from all participants. The study protocol was approved by the Turkish Ministry of Health and the institutional ethics committee with reference number E2-21-294.

Ankara City Hospital is one of the leading pandemic centers in Turkey dealing with highly complicated COVID-19 patients. Sahin et al. regularly updated their experience on pregnant COVID-19 patients and shared their findings with the literature with three published studies [23–25]. The present study is the latest update of this group. The first variant case in Ankara City Hospital was detected on 20, February 2021. Due to cost-effective issues, variant classification is not a routine part of clinical practice in Turkey. However, the majority of variant cases evaluated for research purposes were the Delta variants. For this reason, the authors divided the patients into two groups based on the determined periods to assess the impact of COVID-19 variants on pregnant women: (1) pre-variant group, (2) post-variant group. Maternal age, previous obstetric history, prepregnancy body-mass-index (BMI), comorbid diseases, gestational age at diagnosis, pregnancy trimester at diagnosis, initial symptoms, close contact with a confirmed or suspected case, abnormal vital signs at admission to hospital, pregnancy-specific medications, COVID-19 therapy, disease severity, respiratory support, ICU admission, maternal mortality, hospitalization rate, length of hospital stay, initial hemoglobin (Hg), hematocrit (Hct), leukocyte, neutrophil, lymphocyte, neutrophil-to-lymphocyte ratio (NLR), platelet, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin, interleukin 6 (IL-6), ferritin, blood urea nitrogen (BUN), creatinine, liver enzymes, lactate dehydrogenase (LDH), D-dimer, creatine kinase MB (CK-MB), troponin, hypokalemia rate, radiologic imaging findings, pregnancy complications, delivery status, time interval between diagnosis and delivery, route of delivery, cesarean indications, labor anesthesia, spontaneous labor rate, preterm delivery rate, gestational age at delivery, birth weight, 1–5 min Apgar scores, neonatal intensive care unit (NICU) admission, neonatal SARS-CoV-2 positivity and SARS-CoV-2 positivity in breastmilk were recorded for both groups. Demographic features, clinical characteristics, laboratory test results, radiologic imaging findings, obstetric and neonatal outcomes were compared between the groups. Furthermore, a correlation analysis was performed between disease severity, maternal mortality, and the post-variant period. All cases were managed according to the current scientific consensus by a multidisciplinary team and the severity of COVID-19 was assessed according to the national guideline [26–29]. Presence of any sign and symptom for COVID-19 without lower respiratory system involvement was defined as mild COVID-19. Evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SaO2) ≥ 94% on room air at sea level was defined as moderate COVID-19. Respiratory frequency > 30 breaths per minute, SaO2 < 94% on room air at sea level,ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/ FiO2) < 300, or lung infiltrates > 50% was defined as severe COVID-19. Presence of respiratory failure, septic shock, and/or multiple

organ dysfunction was defined as critical COVID-19. All cases were managed according to the Turkish Ministry of Health, General Directorate of Public Health, COVİD-19 (SARS-CoV-2 infection) Guideline, Scientific Committee Report. The multidisciplinary team consisted of obstetricians, maternal–fetal medicine specialists, neonatologists, infectious disease specialists and radiologists [26–29].

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS.22, IBM SPSS Statistics for Windows, Version 22.0 Armonk, NY: IBM Corp.). Descriptive analyses were presented as means and standard deviations for normally distributed values. Median and interquartile values were used for variables that were not normally distributed. Student's t test was used for comparing mean values between the groups. Mann–Whitney U test was performed to compare the median values between the groups. Categorical variables were presented by numbers and percentages. The chi-square test was used to compare categorical variables between the groups. Correlation analysis was performed by the Spearman test. A two-tailed p value < 0.05 was regarded as statistically significant.

Results

There were 1416 and 519 patients in the pre-variant and post-variant groups, respectively. None of the patients included in the study were vaccinated for COVID-19. A comparison of demographic features and clinical characteristics between the pre-variant and post-variant groups is summarized in Table 1. Comorbidities such as obesity was observed significantly more often in the pre-variant group (23.1% vs 17.1%, $p = 0.005$). The rate of asymptomatic cases was significantly lower in the post-variant group (40.1% vs 30.1%, $p < 0.001$). The rate of oxygen saturation $\leq 93\%$ was significantly higher in the post-variant group. On the other hand, the rate of fever was significantly higher in the pre-variant group. The rate of pregnancy-specific medications was significantly higher in the post-variant period due to an increase in the administration of antenatal corticosteroids ($p < 0.05$). Moreover, the rate of COVID-19 therapy was significantly higher in the post-variant group (55.1% vs 68.4%, $p < 0.001$).. The rates of severe and critical cases significantly increased in the post-variant group (9.7% vs 2%, $p < 0.001$). Moreover, the rates of respiratory support (26.8% vs 7.3%, $p < 0.001$), ICU admission (12.9% vs 1.8%, $p < 0.001$) and maternal mortality (2.9% vs 0.4%, $p < 0.001$) were significantly higher in the post-variant group. However, the hospitalization rate was significantly lower in the post-variant group (55.9% vs 23.3%, $p < 0.001$).

Comparison of initial laboratory test results and radiologic imaging findings between the pre-variant and post-variant groups is shown in Table 2. Higher values for leukocyte, neutrophil, CRP, ferritin, liver enzymes, LDH, D-dimer, and troponin were observed in the post-variant group. Lymphocytopenia and hypokalemia rates were also significantly higher in the post-variant group. Although the rates of radiologic imaging and suspicious radiologic findings consistent with COVID-19 were similar between the groups, a significant increase was observed for pulmonary computerized tomography angiography in the post-variant group ($p < 0.05$).

A comparison of obstetric and neonatal outcomes between the pre-variant and post-variant groups is shown in Table 3. A significant increase was observed for pregnancy complications in the post-variant group (45.6% vs 18.8%, $p = 0.007$). Prominent increases were observed for miscarriage, cholestasis of pregnancy, gestational diabetes, preterm labor, and placental abruption ($p < 0.05$). The rates of cesarean section performed for worsening in maternal health condition and general anesthesia increased significantly in the post-variant group ($p < 0.05$). Furthermore, the rates of preterm delivery (26.4% vs 4.4%, $p < 0.001$) and NICU admission (34% vs 18.8%, $p < 0.001$) were significantly higher in the post-variant group.

The correlation of the post-variant period with disease severity and maternal mortality is shown in Table 4. Positive, weak, statistically significant correlations were observed between the post-variant period, disease severity, and maternal mortality ($r = 0.19$ for disease severity, $r = 0.12$ for maternal mortality, and $p < 0.001$ for both).

Discussion

Severe COVID-19, ICU admission, maternal mortality, and obstetric complication rates were significantly higher in the post-variant group compared to the pre-variant group in the present study. These results indicated a worse prognosis for pregnant women in the post-variant period. Although the experience of physicians dealing with pregnant women with COVID-19 has increased significantly since the beginning of the pandemic, COVID-19 still appears to be a major threat to the pregnant population.

Various mutations have been observed in the SARS-CoV-2 genome over time. Although the majority of them have no significant effect on the course of COVID-19, some variants have raised serious concern due to their rapid emergence. These variants are defined as variants of concern. Alpha (B.1.1.7 lineage), Beta (B.1.351 lineage), Delta (B.1.617.2 lineage), and Gamma (P.1 lineage) were the most common variants reported in the literature. These variants are more transmissible and they have the potential for a worse prognosis [30–32]. The impact of new SARS-CoV-2 variants on pregnant women has been investigated in recent studies [14–20, 33]. A national population-based prospective

Table 1 Comparison of demographic features and clinical characteristics between the pre-variant and post-variant groups

Variables	Pre-variant group ($n=1416$)	Post-variant group ($n=519$)	p value
Maternal age (years) (mean ± SD) (min–max)	28.47 ± 5.63 (17–47)	29.37 ± 5.55 (18–45)	0.22
Advanced maternal age (≥ 35 years) (*n*, %)	219 (15.4%)	96 (18.5%)	0.11
Gravidity (median)(IQR, min–max)	2 (2, 0–10)	2 (2, 0–12)	0.12
Parity (median) (IQR, min–max)	1 (2, 0–7)	1 (2, 0–9)	0.76
Living child (median) (IQR, min–max)	1 (2, 0–7)	1 (2, 0–6)	0.68
Previous miscarriage (median) (IQR, min–max)	0 (0, 0–6)	0 (1, 0–6)	0.07
Prepregnancy BMI (kg/m^2) (mean ± SD)(min–max)	26.75 ± 5.34 (18–45)	26.78 ± 5.18 (21–42)	0.97
Comorbid disease (*n*, %)	326 (23.1%)	89 (17.1%)	0.005
Obesity (*n*, %)	169 (11.9%)	6 (1.2%)	< 0.001
Hypothyroidism (*n*, %)	72 (5.1%)	37 (7.1%)	0.08
Hypertension (*n*, %)	20 (1.4%)	12 (2.3%)	0.17
Asthma (*n*, %)	19 (1.3%)	15 (2.8%)	0.02
Diabetes mellitus type 2 (*n*, %)	12 (8.5%)	2 (0.3%)	0.28
Rheumatological disease (*n*, %)	10 (0.7%)	4 (0.7%)	0.88
Cardiovascular disease (*n*, %)	8 (0.5%)	2 (0.3%)	0.62
Diabetes mellitus type 1(*n*, %)	5 (0.3%)	2 (0.3%)	0.92
Epilepsy (*n*, %)	4 (0.3%)	6 (1.1%)	0.017
Renal disease (*n*, %)	3 (0.2%)	3 (0.5%)	0.19
ITP (*n*, %)	2 (0.1%)	0 (0%)	0.79
Thalessemia minor (*n*, %)	2 (0.1%)	0 (0%)	0.79
Gestational age at diagnosis (weeks) (mean ± SD) (min–max)	25.59 ± 11.13 (4–41)	26.36 ± 9.65 (5–40)	0.12
Pregnancy trimester at diagnosis			
First (*n*, %)	311 (22%)	84 (16.2%)	0.001
Second (*n*, %)	433 (30.6%)	161 (31%)	
Third (*n*, %)	672 (47.5%)	274 (52.8%)	
Initial symptoms			
Asymptomatic (*n*, %)	567 (40.1%)	156 (30.1%)	< 0.001
Symptomatic (*n* ,%)	849 (59.9%)	363 (69.9%)	
Cough (*n*, %)	392 (27.7%)	180 (34.7%)	0.04
Myalgia (*n*, %)	350 (24.7%)	140 (27%)	0.86
Dyspnea (*n*, %)	233 (16.4%)	155 (29.9%)	< 0.001
Headache (*n*, %)	127 (8.9%)	38 (7.1%)	0.07
Anosmia (*n*, %)	109 (7.7%)	15 (2.9%)	< 0.001
Sore throat (*n*, %)	103 (7.3%)	40 (7.7%)	0.91
Nausea–vomiting (*n*, %)	103 (7.3%)	45 (8.7%)	0.58
Ageusia (*n*, %)	86 (6.1%)	14 (2.7%)	0.001
Fever (*n*, %)	83 (5.8%)	45 (8.7%)	< 0.001
Nasal congestion (*n*, %)	79 (5.6%)	17 (3.3%)	0.015
Diarrhea (*n*, %)	53 (3.7%)	17 (3.3%)	0.41
Chest pain (*n*, %)	31 (2.2%)	22 (4.2%)	0.03
Close contact with a confirmed or suspected case (*n*, %)	188 (13.3%)	61 (11.8%)	0.36
Abnormal vital signs at admission to hospital			
Tachycardia (heart rate ≥ 100/min) (*n*, %)	327 (23.1%)	151 (29.1%)	0.007
Fever (body temperature ≥ 38 °C) (*n*, %)	83 (13.3%)	45 (8.7%)	< 0.001
Tachypnea (respiratory rate ≥ 20/min) (*n*, %)	45 (3.2%)	42 (8.1%)	< 0.001
Oxygen saturation ≤ 93% (*n*, %)	48 (3.4%)	88 (17%)	< 0.001
Pregnancy-specific Medications (*n*, %)	67 (4.7%)	87 (16.8%)	< 0.001
Tocolytic agent (*n*, %)	32 (2.2%)	11 (2.1%)	0.62
Antenatal corticosteroid (*n*, %)	67 (4.7%)	87 (16.8%)	< 0.001

Table 1 (continued)

Variables	Pre-variant group ($n=1416$)	Post-variant group ($n=519$)	p value
COVID-19 Therapy (n, %)	780 (55.1%)	355 (68.4%)	< 0.001
Low-molecular weight heparin (n, %)	*723 (51.1%)*	360 (69.4%)	< 0.001
Hydroxychloroquine (n, %)	162 (11.4%)	49 (9.4%)	0.04
Systemic corticosteroid (n, %)	113 (7.9%)	115 (22.4%)	< 0.001
Favipiravir (n, %)	*82 (5.8%)*	50 (9.6%)	0.03
Lopinavir-ritonavir (n, %)	78 (5.5%)	26 (5%)	0.26
Convalescent plasma (n, %)	37 (2.6%)	3 (0.6%)	0.02
Azithromycin (n, %)	30 (2.1%)	29 (5.6%)	0.001
N-acetylcysteine (n, %)	24 (1.7%)	37 (7.1%)	< 0.001
rHuIL-1Ra (n, %)	20 (1.4%)	13 (2.5%)	0.22
Colchicine (n, %)	6 (0.4%)	17 (3.3%)	0.007
High-dose vitamin C (n, %)	5 (0.3%)	30 (5.8%)	< 0.001
Remdesivir (n, %)	4 (0.3%)	2 (0.4%)	0.53
Tocilizumab (n, %)	1 (0.07%)	2 (0.4%)	0.16
Dornase alpha (n, %)	1 (0.07%)	1 (0.2%)	0.92
Antibiotherapy for other pathogens (n, %)	280 (19.7%)	159 (30.6%)	< 0.001
COVID-19 severity			
Mild (n, %)	1322 (93.4%)	398 (77.4%)	< 0.001
Moderate (n, %)	65 (4.6%)	66 (12.8%)	
Severe (n, %)	14 (1%)	22 (4.3%)	
Critic (n, %)	15 (1%)	28 (5.4%)	
Respiratory support (n, %)	103 (7.3%)	139 (26.8%)	< 0.001
Nasal oxygen therapy (n, %)	76 (5.4%)	70 (13.5%)	< 0.001
High-flow nasal cannula (n, %)	12 (0.8%)	22 (4.2%)	
Oxygen mask with reservoir bag	8 (0.5%)	28 (5.4%)	
Invasive mechanical ventilation (n, %)	7 (0.4%)	27 (5.2%)	
ICU admission (n, %)	26 (1.8%)	67 (12.9%)	< 0.001
Maternal mortality (n, %)	6 (0.4%)	15 (2.9%)	< 0.001
Hospitalization rate (n, %)	792 (55.9%)	121 (23.3%)	< 0.001
Length of hospital stay (mean ± SD) (min–max)	3.15 ± 3.76 (1–35)	4.64 ± 8.21 (1–54)	0.03

COVID-19, Coronavirus disease 19; BMI, body-mass index; ICU, ıntensive care unit; IQR, ınter-quartile range; ITP, ımmune thrombocytopenic purpura; SD, standard deviation; rHuIL-1Ra, recombinant human IL-1 receptor antagonist

cohort study from Italy including 3306 pregnant women with confirmed SARS-CoV-2 infection reported increased rates of oxygen support requirement and ICU admission among cases with pneumonia during the Alpha variant period compared to the wild-type period [14]. A case report from Belgium presented placentitis and acute placental insufficiency in a pregnant woman infected by the Alpha variant [15]. Another single-center retrospective cohort study from the United States compared the pregnancy outcomes between cases admitted to hospital before and after the Delta variant periods. The mentioned study reported that cases diagnosed after the spread of the Delta variant were more symptomatic and their gestational age at diagnosis was earlier [16]. Similarly, a single-center retrospective cohort study from another tertiary center from the United States compared the outcomes of pregnant women diagnosed in the pre-Delta variant period with those diagnosed in the Delta period indicating increased rates of critical illness and adverse perinatal outcomes [17]. A multicenter prospective cohort study from the United States including 1515 pregnant women reported increased COVID-19-related morbidity after the predomination of the Delta variant especially in populations with lower vaccine acceptance [18]. A retrospective observational cohort study from India comparing pregnant and postpartum women according to the first and second waves of SARS-CoV-2 infection reported higher rates of severe COVID-19, admission to ICU, and maternal mortality [19]. Finally, correspondence from the United Kingdom underlined the more severe course of COVID-19 for pregnant and peripartum women in the second wave of the pandemic compared to the first wave [20]. The findings of the present study were consistent with the current literature. However, to the best of our

Table 2 Comparison of initial laboratory test results and radiologic imaging findings between the pre-variant and post-variant groups

Variables	Pre-variant group ($n=1416$)	Post-variant group ($n=519$)	p value
Hb (g/dl) (mean ± SD) (min–max)	11.88 ± 1.43 (4.7–16.4)	11.82 ± 1.48 (7.5–16)	0.22
Hct (%) (mean ± SD) (min–max)	35.98 ± 4.27 (26.2–47.1)	35.96 ± 6.48 (23.4–46.2)	0.89
Hb < 10 g/dl (n, %)	137 (9.7%)	53 (10.2%)	0.43
Leukocyte ($10^3/mm^3$) (mean ± SD) (min–max)	7412.40 ± 2889.65 (1240–28,510)	8494.32 ± 3648.56 (2750–25,180)	< 0.001
Leukocytosis (> 11,000/mm^3) (n, %)	145 (10.2%)	102 (19.7%)	< 0.001
Neutrophil ($10^3/mm^3$) (mean ± SD) (min–max)	5476.82 ± 2629.86 (1070–25,430)	6541.19 ± 3253.63 (990–23,890)	< 0.001
Neutrophil percentage (%) (mean ± SD) (min–max)	75.74 ± 10.84 (62–90.8)	76.03 ± 9.20 (35.5–94.9)	0.94
Neutrophilia (> 7700/mm^3 or > 70% of leukocytes) (n, %)	218 (15.4%)	136 (26.2%)	< 0.001
Lymphocyte ($10^3/mm^3$) (mean ± SD) (min–max)	1330.67 ± 576.97 (140–4650)	1094.37 ± 467.24 (100–2970)	< 0.001
Lymphocyte percentage (%) (mean ± SD) (min–max)	22.40 ± 9.51 (1.8–51.8)	13.38 ± 8.75 (1.7–53)	0.002
Lymphocytopenia (< 1000/mm^3 or < 8% of leukocytes) (n, %)	433 (30.6%)	271 (52.2%)	< 0.001
Neutrophil to lymphocyte ratio (mean ± SD) (min–max)	5.51 ± 3.39 (1.2–25.28)	6.32 ± 4.72 (1–51.9)	0.42
Platelet ($10^3/mm^3$) (mean ± SD) (min–max)	225.69 ± 68.55 (19–708)	227.32 ± 101.48 (28–778)	0.71
ESR (mm/h) (mean ± SD) (min–max)	41.10 ± 23.64 (2–113)	47.76 ± 22.58 (3–99)	0.23
CRP (mg/dl) (mean ± SD) (min–max)	22.78 ± 32.76 (1–419)	34.14 ± 42.06 (2–264)	< 0.001
Procalcitonin (ng/ml) (mean ± SD) (min–max)	0.16 ± 2.87 (0–96.85)	0.24 ± 1.72 (0–28.63)	0.58
IL-6 (pg/ml) (mean ± SD) (min–max)	73.15 ± 134.19 (0–22,524)	176.74 ± 86.97 (0–5500)	0.51
Ferritin (ng/ml) (mean ± SD) (min–max)	50.04 ± 269.21 (10–9130)	99.78 ± 354.60 (2–6263)	0.004
BUN (mmol/L) (mean ± SD) (min–max)	16.68 ± 8.13 (9–75)	17.28 ± 14.59 (8–74)	0.38
Creatinine (mg/dl) (mean ± SD) (min–max)	0.57 ± 2.44 (0.30–4.85)	0.51 ± 0.34 (0.40–6.81)	0.54
ALT (IU/L) (mean ± SD) (min–max)	26.12 ± 41.73 (8–884)	43.21 ± 104.42 (10–1761)	< 0.001
AST (IU/L) (mean ± SD) (min–max)	28.10 ± 45.80 (9–1065)	51.59 ± 138.22 (6–1783)	< 0.001
Elevated liver enzymes (n, %) (ALT and AST ≥ twice the upper limit)	66 (4.6%)	126 (24.2%)	< 0.001
LDH (IU/L) (mean ± SD) (min–max)	220.66 ± 138.98 (125–3780)	291.41 ± 285.28 (120–5730)	< 0.001
D-Dimer (mcg/mL) (min–max)	2.08 ± 3.26 (0.01–67.25)	2.61 ± 4.33 (0.20–35.21)	0.01
CK-MB (ng/ml) (mean ± SD) (min–max)	1.10 ± 2.32 (0–45.6)	1.13 ± 2.06 (0–19.4)	0.78
Troponin (ng/ml) (mean ± SD) (min–max)	5.30 ± 77.85 (0–654)	18.17 ± 137.69 (0–2024)	0.03
Hypokalemia (K < 2.5 mmol/L) (n, %)	41 (2.9%)	35 (6.7%)	0.06
Radiologic imaging (n, %)	167 (11.8%)	76 (14.6%)	0.52
Chest X-ray (n, %)	103 (7.3%)	68 (13.1%)	0.24
Chest CT (n, %)	80 (5.6%)	26 (5%)	0.72
Pulmoner CT angiography (n, %)	6 (0.4%)	8 (1.5%)	0.003
Radiologic imaging findings suspicious for COVID-19 (n,%)	111 (7.8%)	85 (16.4%)	0.42

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; COVID-19, Coronavirus disease 19; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; Hct, hematocrit; IL-6, Interleukin 6; IQR, ınter-quartile range; LDH, lactate dehydrogenase; SD, standard deviation

knowledge, the present study was the most comprehensive study from a tertiary reference center dealing with pregnant women with COVID-19. In our opinion, the experience of Ankara City Hospital may guide health care systems to establish more effective clinical management protocols.

Pregnancy is a unique period accompanied by many physiological, endocrine, and immunological events [34,

Table 3 Comparison of obstetric and neonatal outcomes between the pre-variant and post-variant groups

Variables	Pre-variant group ($n=1416$)	Post-variant group ($n=519$)	p value
Pregnancy complications (*n*, %)	267 (18.8%)	237 (45.6%)	0.007
Threatened abortion (*n*, %)	10 (0.7%)	8 (1.5%)	0.23
Miscarriage (*n*, %)	34 (2.4%)	20 (3.8%)	0.02
Hiperemezis Gravidarum (*n*, %)	10 (0.7%)	5 (0.9%)	0.54
Cholestasis of pregnancy (*n*, %)	15 (1%)	11 (2.1%)	0.03
Fetal anomaly (*n*, %)*	17 (1.2%)	2 (0.3%)	0.12
Intrauterine fetal demise (*n*, %)	24 (1.7%)	11 (2.1%)	0.53
Fetal growth restriction (*n*, %)	18 (1.2%)	6 (1.2%)	0.62
Gestational diabetes (*n*, %)	24 (1.7%)	13 (2.5%)	0.09
Gestational hypertension (*n*, %)	13 (0.9%)	7 (1.3%)	0.13
Preterm labor (*n*, %)	62 (4.4%)	137 (26.4%)	< 0.001
Preterm premature rupture of the membranes (*n*, %)	16 (1.1%)	8 (1.5%)	0.24
Preeclampsia (*n*, %)	13 (0.9%)	6 (1.1%)	0.32
Eclampsia (*n*, %)	2 (0.1%)	1 (0.1%)	0.89
Placental abruption (*n*, %)	3 (0.2%)	8 (1.5%)	< 0.001
Deep vein thrombosis (*n*, %)	3 (0.2%)	1 (0.1%)	0.75
Clavicle fracture (*n*, %)	3 (0.2%)	1 (0.1%)	0.83
Delivery status			
Pregnancy loss (*n*, %)	58 (4.1%)	33 (6.4%)	< 0.001
Ongoing pregnancy (*n*, %)	154 (10.9%)	291 (56.1%)	
Delivered (*n*, %)	1204 (85%)	195 (37.5%)	
The time interval between diagnosis and delivery (days) (mean ± SD) (min–max)	7.82 ± 9.12 (1–34)	11.49 ± 10.54 (1–60)	0.23
Route of delivery			
Normal spontaneous vaginal delivery (*n*,%)	509 (42.3%)	77 (39.5%)	0.64
Cesarean section (*n*, %)	692 (57.4%)	117 (60%)	
Vaginal birth after cesarean section (*n*,%)	3 (0.3%)	1 (0.5%)	
Cesarean indications			
Previous cesarean section (*n*, %)	276 (39.8%)	37 (31.6%)	0.08
Fetal distress (*n*, %)	198 (28.6%)	31 (26.5%)	0.63
Cefalopelvic dysproportion (*n*, %)	124 (17.9%)	8 (6.8%)	0.02
Maternal health condition (*n*, %)	36 (5.2%)	28 (23.9%)	< 0.001
Malpresentation (*n*, %)	30 (4.3%)	9 (7.7%)	0.11
Multiple pregnancy (*n*, %)	16 (2.3%)	2 (1.7%)	0.68
Macrosomia (*n*, %)	12 (1.7%)	2 (1.7%)	0.98
Labor anesthesia			
None (*n*, %)	506 (42.1%)	75 (38.4%)	< 0.001
General (*n*, %)	36 (2.9%)	20 (10.2%)	
Regional (*n*, %)	662 (54.9.9%)	100 (51.3%)	
Spontaneous labor (*n*, %)	1021 (84.8%)	153 (78.4%)	0.02
Preterm delivery (n, %)	228 (18.9%)	87 (44.6%)	< 0.001
Gestational age at delivery (weeks) (mean ± SD) (min–max)	37.63 ± 2.43 (26–42)	35.53 ± 4.70 (25–41)	0.03
Birth weight (g) (mean ± SD) (min–max)	3141.15 ± 617.42 (540–4550)	2671 ± 920.52 (560–4195)	< 0.001
Apgar 1st minute (median) (IQR, min–max)	8 (1, 6–9)	7 (2, 6–9)	0.01
Apgar 5th minute (median) (IQR, min–max)	9 (1, 8–10)	9 (1, 8–10)	0.23
NICU admission (*n*, %)	230 (18.8%)	67 (34%)	< 0.001
Neonatal SARS-CoV-2 positivity (*n*, %)	1 (0.2%)	0 (0%)	0.76
SARS-CoV-2 positivity in the breastmilk	1 (0.2%)	0 (0%)	0.85

BMI, body-mass index. COVID-19, Coronavirus disease 19. IQR, ınter-quartile range; NICU, neonatal intensive care unit; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation

Table 4 Correlation of the post-variant period with disease severity and maternal mortality

	Disease severity		Maternal mortality	
	r	*p*	*r*	*p*
The post-variant period	0.19	< 0.001	0.12	< 0.001

35]. The aforementioned changes make the pregnant population vulnerable to some infectious agents [36–38]. Therefore, physicians dealing with pregnant women should be cautious in the management of infectious diseases in this specific population. As SARS-CoV-2 was also reported to have a more severe course in pregnant patients, follow-up and treatment of these cases should be performed by an experienced multidisciplinary team [23]. The most important reason for planning the current study was the significant increase observed in intensive care unit admission, obstetric complications, and maternal mortality in pregnant patients with COVID-19 after the variant period. Although the experience on COVID-19 has increased significantly, it is, unfortunately, difficult to prevent the negative effects of the disease on pregnant women. Thus, encouraging pregnant women for COVID-19 vaccination, early diagnosis of disease, meticulous follow-up, multidisciplinary approach, and administration of appropriate medications seem to be the main strategies for preventing adverse outcomes [23, 39, 40].

Readers may be concerned about a selection bias due to the design of the current study. As our experience and knowledge have increased on SARS-CoV-2, management protocols have been updated regularly. Moreover, attitudes of patients have been deeply affected from the cumulative knowledge. Thus, comparing two different periods based on parameters like hospitalization, treatment choices and delivery characteristics may be misguiding. However, the significantly increasing rates of ICU admission, maternal mortality and pregnancy complications in the post-variant period are indicative for a worse course of SARS-CoV-2 after the variants in pregnant population.

The main strengths of the present study were prospective design, the inclusion of comprehensive study parameters, and large number of cases. On the other hand, single-center experience and lack of information related to the long-term outcomes were the main limitations.

In conclusion, the post-variant COVID-19 period was associated with a severe course of the disease and increased rates of adverse obstetric outcomes in pregnant patients.

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Declarations

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