Comparison of Maternal and Perinatal Outcomes Associated with Delta (B.1.617.2) and Other Variants of Severe Acute Respiratory Syndrome-Coronavirus 2

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ABSTRACT

Objective: To compare the frequency of adverse maternal and perinatal outcomes associated with delta (B.1.617.2) and other variants of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2).

Study Design: An observational study.

Place and Duration of the Study: Bursa City Hospital, Bursa, Turkey, from March 2020 to February 2022.

Methodology: The study included 423 pregnant women diagnosed with COVID-19 based on real-time reverse transcriptase-polymerase chain reaction (RT-PCR) testing. The patients were divided into the delta variant (n=135) and other variants (n=288) (alpha, beta, gamma) groups, and maternal and perinatal outcomes were compared between the groups. Data including symptoms, laboratory findings, radiological findings, hospital and intensive care unit (ICU) stay, delivery outcomes, and mortality rates were recorded.

Results: The delta variant group demonstrated higher rates of moderate and severe pneumonia than the other variant group (p=0.005). According to the World Health Organization (WHO) classification, 49.6% and 18.5% of patients experienced moderate and severe disease, respectively in the delta variant group, compared to 38.5% and 10.1%, respectively in the other variant group (p=0.001). A total of 20.0% of the patients in the delta variant group and 8.3% of the patients in the other variant group required ICU stay. The length of ICU stay was significantly longer in the delta variant group (p=0.001).

Conclusion: The rates of maternal morbidity and mortality increased in the pregnant population with low rates of vaccination in the period of the fourth wave which was associated with the delta variant. No significant difference was observed in perinatal morbidity between the delta and other variants.

Key Words: *COVID-19, Delta variant, Maternal morbidity, Perinatal outcomes, Adverse pregnancy outcomes.*

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INTRODUCTION

Similar to other ribonucleic acid (RNA) viruses, *SARS-CoV-2* is able to adapt to new human hosts and is prone to genetic evolution with the development of mutations over time, increasing mutant variants that may have different properties from their ancestral strains.[1,2] During the pandemic, several variants of *SARS-CoV-2* have been identified, of which only a few are considered variants of concern (VOCs) by the WHO given their impact on global public health.[3]

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Since the outbreak of the pandemic, five *SARS-CoV-2*VOCs have been identified, including alpha (B.1.1.7), beta (B.1.351), gamma (P.1), delta (B.1.617.2), and omicron (B.1.1.529).[4] The delta variant first appeared in India in late 2020 and has been recorded in 140 countries as of August 2021.[5] The first case of the delta variant in Turkiye was announced by the Republic of Turkiye, Ministry of Health on July 6th, 2021. According to the Global Initiative on Sharing All Influenza Data (GISAID) statistics, from June 28th to July 12th, 2021, the delta variant accounted for 76% of the sequences sent from Turkiye.[6]

The delta VOC has been reported to be more infectious and cause more severe COVID-19 than the conventional variant strains.[7] The *SARS-CoV-2* VOC studies carried out in the general population revealed an increase in the rates of hospital admission, severe illness, intensive care unit (ICU) admission, and mortality.[8,9] However, there is a limited number of studies reporting a similar increase in maternal morbidity and mortality in pregnant women.[10-12]

The aim of the present study was to compare adverse maternal and perinatal outcomes such as preeclampsia (PE), preterm labor, and gestational diabetes mellitus (GDM) in pregnant patients infected by the delta and other variants of *SARS-CoV-2*.

METHODOLOGY

This single-centre retrospective study included pregnant women diagnosed with COVID-19 in the Obstetrics and Gynaecology-Infectious Diseases Clinic of Bursa City Hospital, Bursa, Turkiye, between March 2020 and February 2022. The study included 423 pregnant women who were diagnosed with COVID-19 based on the real-time reverse transcriptase-polymerase chain reaction (RT-PCR) testing results. All reported variants were confirmed based on a review of the Republic of Turkiye, Ministry of Health, Laboratory Information System Management program. Viral RNA was extracted from the nasal/oropharyngeal swab fluids using the magnetic particle technic on the GeneRotex96 (Tianlong Science, Xi'an, China). The diagnosis of COVID-19 was made using dual gene target RT-qPCR (BioSpeedy, Istanbul, Turkiye). The N501Y/variant detection PCR kit (BioSpeedy, Istanbul, Turkiye), and N501Y, delHV69-70, and E484K multiple mutation detection PCR kits (RTA Laboratories, Istanbul, Turkiye) were used for mutation screening. Positive strains were prepared for sequencing. The delta variant (B.1.617.2) was found in 135 patients, and the rest of the variants (alpha (B.1.1.7), beta (B.1.351), and gamma (P.1)) were detected in 288 patients. The study protocol was approved by the Institutional Ethics Committee (No. 2022-3/8) and the study was conducted in accordance with the principles of the Declaration of Helsinki.

The study included pregnant women with a positive PCR test for COVID-19, while those with suspected COVID-19 based on clinical, laboratory and radiological tests and pregnant patients under the age of 18 years were excluded from the study. Demographic data of the patients, maternal age, gravidity/parity, body mass index (BMI), systemic diseases, smoking and regular medication status, gestational age at the time of admission, symptoms and vital signs at the time of admission, laboratory and radiological findings, treatments during hospitalisation, variant type, ICU admission, pregnancy complications after COVID-19, and delivery data were recorded. All clinical, laboratory, and radiological data were retrieved from the Hospital Management Information Systems (HBYS) and E-pulse system.

Pregnancy complications were defined as PE, threatened preterm labor (TPL), premature rupture of membranes (PROM), and GDM.[13,14] Radiological findings, thoracic computed tomography (CT) scans and chest radiographs were evaluated on the Picture Archiving and Communication System (PACS) and were reported by experienced radiologists. Pneumonia was classified as mild, moderate or severe, with a classification made based on the Radiographic Assessment of Lung Edema (RALE) scoring system from chest radiographs. Thoracic CT scans were classified based on the chest CT score.[15]

Patients were classified as mild, moderate, and severe based on clinical presentation.[16] All patients admitted to the ICU were assessed by an intensivist based on the duration of stay, need for high-flow nasal oxygen (HFNO), extracorporeal membrane oxygenation (ECMO), intubation, complications, treatments, and interventions.

Statistical analysis was performed using the SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were presented in mean ± standard deviation (SD), median (min--max) or number and frequency, where applicable. The normality of the quantitative data, the comparison of the normally distributed quantitative variables, and the comparison of non-normally distributed variables among the pregnant COVID-19 patients with and without the delta variant were analysed using the Shapiro-Wilk test, independent samples t-test, and Mann-Whitney U test, respectively. The relationship between the variant type and categorical variables was analysed using the Pearson chi-square test. Risk factors with a p-value less than 0.10 in Tables I and II were included in the multiple models, and the final multiple binary logistic regression model was established with the backward variable elimination method. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 423 pregnant women diagnosed with COVID-19 based on RT-PCR testing were included. The mean age and BMI were 29.79 ± 5.19 years and 28.20 ± 5.39 kg/m^2, respectively in the patients with the delta variant, and 29.21 ± 5.57 years and 29.79 ± 5.08 kg/m^2, respectively in the other variant group (p=0.308 and p=0.273, respectively). Gestational age at the time of admission in the delta variant group and in the other variant group was 32.46 ± 6.52 weeks and 28.97 ± 9.06 weeks, respectively, indicating a significantly higher gestational age in patients with the delta variant (p=0.001, Table I).

Regarding the clinical symptoms, pregnant women with the delta variant demonstrated significantly higher rates of fever and sore throat (p=0.006 and p=0.044, respectively). Based on radiological findings, the delta variant group had higher rates of moderate and severe pneumonia than the other variant group (p=0.005). According to the WHO classification, 49.6% of the patients had moderate and 18.5% had severe disease in the delta Variant group, compared to 38.5% and 10.1%, respectively, in the other variant group. The delta variant group had significantly higher rates of moderate and severe disease (p=0.001).

The mean length of hospital stay was 8.68 ± 11.16 days and 7.30 ± 5.44 days in the delta variant group and the other variant group, respectively, indicating no significant difference between the two groups (p=0.335). A total of 20.0% of the patients in the delta variant group and 8.3% of the patients in the other variant group required ICU stay. The length of ICU stay was significantly longer in the delta variant group (p=0.001).

Tabe I: Data of COVID-19 pregnants with delta variant and other variants.

Demographics	Delta No		Delta Yes		p-value*
	n	Median (IQR)	n	Median (IQR)	
Body mass index, kg/m^2	277	28.23(25.61-31.63	134	26.98(24.48-31.2)	0.273
Gravidity	287	2(1-3)	131	2(1-3)	0.512
Parity	287	1(.00-2)	131	1(.00-2)	0.627
Laboratory findings					
White blood cell, mm^{3}x10^3	285	7.54(6.02-9.36)	135	7.23(6.04-9.7)	0.937
Hemoglobin, g/dL	285	11.3(10.5-12.23)	134	11.4(10.5-12.23)	0.943
Platelet, mm^{3}x10^3	284	208(171.2-245.5)	135	209(172-244)	0.856
Lymphocyte(L), 10^3/uL	287	1.21(0.89-1.66)	135	1.13(0.93-1.71)	0.598
Neutrophil(N), x10^3/uL	287	5.6(4.23-7.19)	135	5.75(4.58-7.34)	0.435
NLR	287	4.48(3.07-6.41)	135	4.71(3.64-6.63)	0.296
Aspartate aminotransferase, U/L	279	19(16-28)	134	25(16-41.25)	<0.001
Alanine transaminase, U/L	280	14(10-23)	134	16.5(11-31.25)	0.011
Lactate dehydrogenase, U/L	170	191.5(159-240)	90	231(180.2-301.7)	<0.001
C-reactive protein, mg/dL	267	16(7-37.7)	131	22.7(10.9-57)	0.003
Ferritin, ng/dL	260	34.9(18-80.95)	125	53.2(24.64-96.85)	0.012
Procalcitonin, ng/dL	196	0.07(0.05-0.11)	97	0.1(0.06-0.23)	<0.001
D-dimer, ng/mL	268	1.02(0.66-1.65)	127	1.07(0.77-1.6)	0.418
Prothrombin time, seconds	244	8.02(7.68-8.3)	120	7.95(7.55-8.24)	0.073
International normalized ratio	243	0.9(0.86-0.93)	120	0.89(0.85-0.93)	0.237
Fibrinogen, mg/dL	80	505(440.2-589.7)	39	473(387-559)	0.084
Clinical data					
Gestational age, weeks	287	31(24-36)	135	34(28-38)	<0.001
Birth weight, g	265	3260(2990-3600)	122	3132(2800-3410)	<0.001
Hospital stay, days	288	6(3-10)	135	7(3-11)	0.259
Gestational age at birth, weeks	287	39(38-40)	123	38(37-39)	0.027

**Mann-Whitney u test and independent samples t-test. Date are given in number (percentile) or median (IQR): (25th-75th percentile).; NLR: neutrophil/lymphocyte ratio.*

Table II: Comparison of categorical variables between pregnant COVID-19 patients with the delta variant and other variants.

	Delta No			Delta Yes			p-value*
	No (%)	Yes (%)	Total	No (%)	Yes (%)	Total	
Pregnancy complications	229(98.3)	52(18.5)	281	109(82)	24(18)	133	0.910
Preeclampsia	253(90)	28(10)	281	125(94)	8(6)	133	0.183
Premature labor	258(91.8)	23(8.2)	281	122(91.7)	11(8.3)	133	0.976
GDM	275(97.9)	6(2.1)	281	126(94.7)	7(5.3)	133	0.088
Intensive care unit	264(91.7)	24(8.3)	288	108(80)	27(20)	135	0.001
Invasive ventilation	14(60.9)	9(39.1)	23	16(59.3)	11(40.7)	27	0.908
HFNO	8(34.8)	15(65.2)	23	12(44.4)	15(55.6)	27	0.487
Mortality	283(98.3)	5(1.7)	288	128(94.8)	7(5.2)	135	0.046
NSD		107(40.5)	107		39(31.7)	39	0.095
Cesarean section		157(59.5)	157		84(68.3)	84	

**Pearson's Chi-square test. GDM: gestational diabetes mellitus, HFNO: high-flow nasal oxygen, NSD: normal spontaneous delivery.*

No significant difference was observed between the groups with regard to invasive ventilation (p=0.908) and HFNO (p=0.487). The mortality rate was 5.2% in the delta variant group and 1.7% in the other variant group, indicating a significantly higher mortality rate in pregnant women infected with the delta variant (p=0.046, Table II). In addition, the delta variant group had significantly higher rates of favipiravir 200 mg (p=0.005), corticosteroids (at various doses, p=0.001), and low-molecular-weight heparin (LMWH, p=0.003).

According to laboratory findings, significantly higher levels of aspartate aminotransferase (AST, p=0.001), alanine aminotransferase (ALT, p=0.011), lactate dehydrogenase (LDH, p=0.001), C-reactive protein (CRP, p=0.003), ferritin (p=0.012), procalcitonin (p=0.001), prothrombin time (PT, p=0.073), and activated partial thromboplastin time (aPTT, p=0.002)were found in the delta variant group, while the patients infected with other variants had significantly higher levels of fibrinogen (p=0.084, Table I).

Considering the pregnancy complications after COVID-19, no significant difference in GDM (p=0.088), PE (p=0.183), and TPL (p=0.976) was observed between the two groups (Table II). The gestational ages at the time of delivery in the delta variant and the other variant groups were 37.76 ± 3.01 weeks and 38.29 ± 2.84 weeks, respectively, indicating a statistically significant difference between the groups (p=0.027). The other variant group had a significantly higher birth weight (p=0.001). When the normal spontaneous delivery and cesarean delivery rates were compared considering the type of delivery, a statistically significant increase was identified in favour of cesarean delivery in the delta variant group (p=0.095, Table II).

DISCUSSION

In the present study, the authors compared adverse maternal and perinatal outcomes of the period of the fourth wave in which the *SARS-CoV-2* delta variant was prominent and the pre-delta periods. The finding revealed significantly increased rates of emergency admission, hospitalisation, ICU admission, cesarean delivery due to worsening COVID-19, and mortality rates in the patients infected with delta variant. In addition, the authors found lower gestational age at the time of delivery and birth weight, while there was no significant difference in the rate of GDM, PE, and TPL between the groups.

Given particularly the predominance of the delta variant, significant increases were recorded in the number of cases and hospitalisations both in the general population and in the pregnant population.[17] Previous studies have shown the delta variant to cause more severe disease and be more contagious.[18] Several meta-analyses have demonstrated adverse maternal outcomes in pregnant women with COVID-19, such as increasing preterm birth, PE, and stillbirth.[19] Some evidence suggests that the delta variant, compared to the wild-type strain and the alpha variant, causes more severe disease in pregnancy and an increased risk of stillbirth.[20] Pregnant women are more susceptible to *SARS-CoV-2* infection, have lower vaccination rates compared to the general population, and the delta variant is more contagious and the viral load accumulates more rapidly in the respiratory system, resulting in an increased need for hospital admissions and increased morbidity among pregnant patients.[21]

A prospective study by Adhikari *et al*. showed that both the number of cases and the rate of severe or critical illness (5.4%) increased significantly as a consequence of the locally predominant delta (B.1.617.2) variant, and the highest morbidity rate was identified in the underserved populations with the lowest vaccination rates.[22] The study by Zayet *et al*. included patients hospitalised between March 2020 and November 2021 (224 pre-delta cases, 69 delta cases) and defined severe disease as cases requiring ICU admission.[12] They divided the cases into three periods, based on the predominant variant (alpha, beta, and delta) and found the rates of severe and critical illness to be <2.33%, 6.25%, and 33.33%, respectively. In the present study, the authors made an assessment based on the WHO classification and found that the rate of severe disease was 10.1% in the non-delta group and significantly higher at 18.5% in the delta group. Similar to the aforementioned study, this study also reported a significantly higher need for ICU admission (27%) in the delta variant group.

In another study, Fisman *et al*. carried out a retrospective cohort review of 212,326 patients between February and June 2021 and found that the delta variant accounted for 2.8% of all cases, while in July 2021, 60% of cases had the delta variant, and patients of a younger age were less likely to have comorbidities.[9] The authors reported a significant increase in favour of the delta variant in the rates of hospital admission (108%), ICU admission (234%), and mortality (132%). Ilter *et al*. compared the delta variant with the prior period in unvaccinated pregnant women infected with COVID-19 and found increased oxygen support including ECMO and higher maternal morbidity rates.[23] In the current study, only hospitalised pregnant patients were included, and no comparison could be made with the general population. A significantly higher rates of ICU admission (27%) and mortality (5.2%) among the inpatients with the delta variant was found, but no significant difference in the need for invasive ventilation and HFNO. In a retrospective study by Seasely *et al*.[8] including all pregnant women with COVID-19 between March 2020 and August 2021, the patients were divided into pre-delta (n=224) and post-delta (n=69) groups. The authors found increased screen-positive rates (3% *vs.*15%), severe-critical illness rates (13% *vs.*36%), and ICU admission rates (8% *vs.*29%) in the delta group. The authors also reported a significant increase in the need for respiratory support, intubation, and pharmacological treatment in this group and that the rates of cesarean delivery, preterm delivery, and neonatal ICU admission were increased in the delta group. Similarly, in this study, a significant increase was observed in the rates of hospital admission and hospitalisation, cesarean delivery, ICU admission, and mortality in the delta variant group, while the preterm delivery rates of the two groups were not found to be significantly different.

A retrospective cohort study conducted by Wang *et al*. in December 2021 classified the delta period patients as follows: asymptomatic, symptomatic not requiring oxygen support, and symptomatic requiring oxygen support.[11] Symptomatic patients were in significantly lower gestational age than those with previous variants at the time of diagnosis, and the rate of symptomatic infection was higher. The most common laboratory abnormality was lymphopenia. The rates of antibiotic, antiviral, and corticosteroid drug use were higher in patients requiring oxygen support. One-third of deliveries were due to worsening COVID-19, while preterm delivery rates and neonatal outcomes were similar in the groups. Compared to the alpha variant, the delta variant is 60% more contagious and is associated more with hospital

admission and mortality.[14] In the present study, the gestational age at the time of diagnosis was higher in the delta variant group (32.46 ± 6.52 weeks). The rate of lymphopenia did not significantly differ between the groups, while the levels of AST, ALT, LDH, CRP, procalcitonin, ferritin, PT, and aPTT were found to be significantly higher in the delta variant group. Patients with the delta variant had significantly lower gestational age at the time of delivery and birth weight, and the rate of antibiotic, antiviral, corticosteroid drug and LMWH use was also higher in this group. While the cesarean delivery rate was higher in the delta variant group, 8.8% of these cases occurred due to a worsening of COVID-19 symptoms. In this study, there was no increase in perinatal morbidity, such as preterm delivery, PE, or GDM.

Nonetheless, there are some limitations to this study. Only inpatients were included in the study, while patients who were treated in the outpatient setting, those who did not accept hospitalisation, and those who were referred to external centres after diagnosis were excluded. Another limitation is the exclusion of COVID-19 vaccinated patients. This was due primarily to the fact that vaccination programmes started relatively late in the authors' country compared to the rest of the world, and full optimisation could not be achieved due to the use of inactive vaccines first and mRNA vaccines later, and vaccination rates were very low among pregnant women compared to the general population.

CONCLUSION

The rates of maternal morbidity and mortality were higher in the pregnant population with low rates of vaccination during the fourth wave of COVID-19 associated with the delta variant, while no significant difference was identified in perinatal morbidity among the variants. Pregnant women are one of the groups most susceptible to viral variants as with the delta variant, further data on mutations would shed light on new pandemics in the future. Currently, to achieve better management of COVID-19, the information on the clinical features of COVID-19 in pregnant women should continue to be updated for any new VOC emerging in the future.

ETHICAL APPROVAL:
The study was approved by the Institutional Ethics Committee of Bursa City Hospital (No. 2022-3/8).

PATIENTS' CONSENT:
Since it was designed as a retrospective study, the data were obtained from the electronic medical record system after approval of the Ethics Committee.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
SU, IK, HGTO: Conception, design, data acquisition, data analysis, manuscript drafting, interpretation, and statistical analysis.

GAA: Critical revision of the manuscript and supervision.
All the authors have approved the final version of the manuscript to be published.

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