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Evaluation of Variants and the Effect of Vaccine on Mortality in Pregnant and Postpartum Women Infected with COVID-19

COVID-19 ile Enfekte Gebe ve Lohusalarda Varyantların ve Aşının Mortalite Üzerindeki Etkisi

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ABSTRACT Objective: Due to the anatomical, physiological, and immunological changes associated with pregnancy, pregnant women are a population at risk of coronavirus disease-2019 (COVID-19) disease-related morbidity and mortality. There aren't enough studies on the conditions of pregnant and puerperal women who are being followed up in intensive care. The goal of this study was to determine if there was a link between variant status, vaccination status, and mortality in pregnant and puerperal women who were monitored in the intensive care unit during the transition from the alpha to the delta variation.

Materials and Methods: The study was designed as a 6-month prospective observational study that occurred between August 1, 2021, and February 1, 2022. Age, present comorbidities, vaccination status, gravida, parity, gestational age (for pregnant women), variant status, birth style (cesarean section or normal delivery), and COVID-19 medical therapies in the critical care unit were all recorded.

Results: During the observation period, forty patients were enrolled in the study. The patients average age was 30.9±5.2. The pregnant patients' median gestational week was 32 weeks and 2 days. While 30 of the patients had no concomitant conditions, two had gestational diabetes, four had hypothyroidism, three had chronic hypertension, and one had Wilson's disease. In 37.5% of the patients, intubation was required. During the follow-up in intensive care, ten individuals died. The patients in the intensive care unit spent an average of 12.1±11.8 days there. While 7 (19.4%) of the 36 patients with alpha variants died, 3 (75%) of the 4 patients with delta variants died, a statistically significant difference (p=0.042).

Conclusion: In the pregnant population admitted to the intensive care unit, the delta variant was associated with a greater mortality rate. In our research, we discovered that the vaccination rate among pregnant women admitted to the intensive care unit was quite low.

Keywords: COVID-19 vaccine, COVID-19 variants, mortality, pregnancy, SARS-CoV-2

ÖZ Amaç: Gebelikle ilişkili anatomik, fizyolojik ve immünolojik değişiklikler nedeniyle gebeler koronavirüs hastalığı-2019'a (COVID-19) bağlı morbidite ve mortalite açısından risk altındaki popülasyonlardan biridir. Yoğun bakımda takip edilen gebe ve lohusa kadınların durumları ile ilgili yeterli çalışma bulunmamaktadır. Bu çalışmanın amacı, toplumda alfa varyasyonundan delta varyasyonuna geçiş sırasında yoğun bakım ünitesinde izlenen hamile ve lohusa kadınlarda varyant durumu, aşı durumu ve mortalite arasında bir bağlantı olup olmadığını görmektir.

Gereç ve Yöntem: Çalışma 1 Ağustos 2021 ile 1 Şubat 2022 tarihleri arasında gerçekleştirilen 6 aylık prospektif gözlemsel bir çalışma olarak tasarlandı. Yaş, mevcut komorbiditeler, aşılanma durumu, gravida, parite, gebelik haftası (hamileler için), varyant durumu, doğum şekli (sezaryen veya normal doğum) ve yoğun bakım ünitesindeki COVID-19 tıbbi tedavilerinin tümü kaydedildi.

Bulgular: Gözlem süresi boyunca, çalışmaya kırk hasta alındı. Hastaların yaş ortalaması 30,9±5,2 idi. Gebe hastaların medyan gebelik haftası 32 hafta 2 gündü. Hastaların 30'unda eşlik eden hastalık bulunmazken, ikisinde gestasyonel diyabet, dördünde hipotiroidi, üçünde kronik hipertansiyon ve birinde Wilson hastalığı vardı. Hastaların %37,5'inde entübasyon gerekti. Yoğun bakımda yapılan takipte on hasta hayatını kaybetti. Yoğun bakım yatış süresi burada ortalama 12,1±11,8 gün olarak tespit edildi. Alfa varyantı olan 36 hastanın 7'si (%19,4), delta varyantı olan 4 hastanın 3'ü (%75) mortaliteyle sonuçlandı ve aradaki fark istatistiksel olarak anlamlıydı (p=0,042).

Sonuç: Yoğun bakım ünitesine kabul edilen gebe popülasyonda delta varyantı daha yüksek bir ölüm oranı ile ilişkilendirilmiştir. Araştırmamızda yoğun bakım ünitesine kabul edilen gebelerde aşılanma oranının oldukça düşük olduğunu tespit ettik.

Anahtar Kelimeler: COVID-19 aşısı, COVID-19 varyantları, mortalite, gebelik, SARS-CoV-2

Introduction

Pregnant women are one of the populations at potential risk for coronavirus disease-2019 (COVID-19) disease-related morbidity and mortality due to the anatomical, physiological and immunological changes associated with pregnancy. Several studies have been published with the goal of providing evidence for treatment by describing the clinical features and outcomes of pregnant women infected with COVID-19. COVID-19 infection during pregnancy has been linked to an increased risk of preterm birth, fetal loss, and cesarean delivery, as well as a higher risk of mortality (1-3).

The need for intensive care in COVID-19 infection during pregnancy has been reported as 1% and the need for mechanical ventilation has been reported as 0.3% (4). Hantoushzadeh et al. (5) presented 7 maternal deaths and 9 critically ill cases. Among them, 6 patients began needing mechanical ventilation within 1 week of onset, highlighting the speed of COVID-19 infection in pregnancy. Based on the limited reports above, we learned that in some severe cases, the disease may progress to the point of requiring mechanical ventilation and intensive care after onset, even resulting in maternal death within a very short time (1 to 2 weeks).

It is well known that most pregnancy complications, such as hypertensive disorders of pregnancy, will resolve after termination of pregnancy. However, postpartum exacerbation for COVID-19 has been found to occur soon after birth due to short-term pathophysiological changes (6). Published articles arguing that cytokine storms may be exacerbated by birth (7,8).

As the evidence about the safety of vaccines produced for the prevention of COVID-19 in pregnant women became widespread, vaccines began to be applied in the pregnant population. It has been reported that the rates of admission to hospital, need for intensive care and perinatal death are higher in unvaccinated COVID-19 pregnant women compared to vaccinated women (9). In our country, it is recommended by the Ministry of Health to have the COVID-19 vaccine in every period of pregnancy and in the puerperium (10).

Studies on the effects of omicron and delta variants, which emerged towards the end of 2021, on pregnancy and puerperium are limited. In the study by Sahin et al. (11), when the pre- and post-variant periods were compared, it was reported that the need for maternal intensive care, pregnancy complications and mortality in the post-variant

period were higher in the post-variant period. It has also been reported that there was an increase in morbidity in pregnancy with COVID-19, especially in the pregnant population with low vaccine acceptance, during the period when the delta variant was observed (12,13). However, there are not enough studies on variant conditions in pregnant and puerperal women who are under intensive care follow-up.

In this study, we aimed to evaluate the relationship between variant status, vaccination status and mortality in pregnant and puerperal women who were followed in the intensive care unit (ICU) (during the period when the alpha variant changed to the delta variant).

Materials and Methods

The study was designed as a prospective observational study and was conducted after the approval of the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Ethics Committee (approval number: 2021.10.232) between August 1, 2021 and February 1, 2022, in a 6-month period in a 3rd step training and research hospital with intensive care and a separate pandemic service for pregnant women. In this process, our hospital was serving with 2 pandemic ICUs, each with 16 beds. The study included pregnant and postpartum patients who were over the age of 18 in the pandemic ICUs, whose COVID-19 disease was confirmed by polymerase chain reaction (PCR) positivity, and who were followed up due to COVID-19-related pneumonia during the specified period. Patients who were followed up, who had a negative PCR test but suspected COVID-19 according to clinical and imaging were excluded from the study. Patients were included in the study after their written consent was obtained.

Age, current comorbidities, vaccination status, gravida, parity, gestational week (for pregnant women), variant status, mode of delivery (cesarean section or normal delivery), medical treatments for COVID-19 in the ICU were recorded. Extracorporeal therapy (continuous renal replacement therapies and extracorporeal membrane oxygen administration) and pre-intubation oxygen support type (non-invasive mechanical ventilation, high-flow oxygen therapy or mask oxygen with a reservoir) were recorded. The date of symptom onset, the date of positive PCR test, the date of admission to the ICU, the date of intubation, the date of extubation, the date of discharge from the ICU, the date of birth and survival of the patients who gave birth

during or before the follow-up were recorded. According to the recorded dates, the length of stay in the ICU, the intubation time, the time between symptom onset and admission to the ICU, and the puerperium duration for those who were puerperant were calculated as days. Complete blood count, liver and kidney function tests (ure, cre, alt, ast, albumin), C-reactive protein, procalcitonin, ferritin, D-dimer, international normalized ratio values on the day of admission to the ICU and on the day of intubation were obtained retrospectively from the hospital computer system. The blood gas parameters on the day of admission to the ICU and on the day of intubation were recorded in the study data file on the same day.

Statistical Analysis

In our study, according to the distribution of quantitative variables, mean and standard deviation or median (minimum-maximum) expressed as. Student t-test or Mann-Whitney U test was used to compare two groups. Qualitative data were expressed as the number and percentage of cases. Chi-square and Fisher's exact tests were used in the comparison of categorical variables between two groups.

Results

Forty patients were included in the study during the observation period. The mean age of the patients was 30.9 ± 5.2 . The median gestational week of the pregnant patients was 32 weeks and 2 days. While 30 patients had no comorbid disease, 2 patients had gestational diabetes mellitus (GDM), 4 patients had hypothyroidism, 3 patients had chronic hypertension and 1 patient had Wilson's disease. During the follow-up, 32 patients were delivered. Eight of these patients gave birth before their admission to the ICU, 11 of them gave birth on the day they were admitted to the ICU, and 13 of them gave birth after they were admitted to the ICU. All patients gave birth by cesarean section. Six of the 32 patients who gave birth gave birth at term (37 weeks and later), 18 patients had premature preterm births under 34 weeks, 8 patients had late preterm births between 34-37 weeks.

During the intensive care follow-up, 10 patients died. The medical treatments and oxygen support treatments given for COVID-19 during the ICU are presented in Table 1. The average length of stay of the patients in the ICU was 12.1 ± 11.8 days. The mean time between PCR positivity and admission to the ICU is 6.7 ± 5.1 days, and there is no

statistically significant difference between vaccinated and unvaccinated patients (6.1 ± 3.2 vs. 12.5 ± 13.3 ; $p=0.821$). Intubation was required in 37.5% of the patients. While 36 patients were never vaccinated, 1 of the remaining 4 patients was vaccinated with a single dose of inactivated vaccine, 1 with two doses of inactivated vaccine, and 2 with a single dose of mRNA vaccine. While 9 (25%) of the unvaccinated patients died, 1 (25%) of the patients who had any vaccine died. No statistically significant difference was found between the vaccinated and unvaccinated patients in terms of mortality ($p=1.000$) (Table 2).

Of the 10 patients with exitus, 7 were alpha variant and 3 were delta variant. No Omicron variant was found during the follow-up. While 7 (19.4%) of 36 patients with alpha variants died, 3 (75%) of 4 patients with delta variants died, and this was statistically significant ($p=0.042$).

Discussion

In our study, we found that mortality was higher in pregnant and puerperal women with delta variant compared to alpha variant. Due to the fact that it was conducted in a population with a low vaccination rate, we could not obtain sufficient information about the vaccine from our study. However, we can conclude that the very low rate of vaccination in pregnant women admitted to the ICU reduces the rate of need for intensive care in the pregnant population.

According to surveillance data published by the Centers for Disease Control and Prevention, among pregnant women hospitalized with symptomatic COVID-19, COVID-19-related hospitalization (41%), ICU admission (16.2%), and mechanical ventilation It was emphasized that (8.5%) (14).

In the study of 252 COVID-19 positive pregnant patients, thirteen women (5%) presented with or developed either severe or critical (moderate and severe) COVID-19 pneumonia. Respiratory support methods included low-flow nasal cannula for 7 women (54%), non-breathing mask for 2 women (15%), high-flow nasal cannula for 2 women (15%), and mechanical ventilation for 2 women (15%). Pregnancy loss or preterm delivery (iatrogenic or spontaneous) occurred in 6 (60%) of 10 severe or critically ill pregnancies diagnosed before 37 weeks of gestation. Intravenous remdesivir was administered to 5 women (38%), dexamethasone to 5 women (38%), convalescent plasma to 2 women (15%), and an interleukin-6 inhibitor to 1 woman (8%). Other non-obstetric bacterial infections were treated in 3 women (23%).

Table 1. Descriptive characteristics study population		
Variable	Mean ± SD	Min-max
Age	30.9±5.2	18-42
Gravidity	2.7±1.3	1-7
Parity	1.4±1.1	0-6
Gestational age (days)	225±27.1	168-266
PCR to Admission	6.7±5.1	0-24
LOS	12.1±11.8	1-61
Admission to Intubation	3.2±2.9	0-11
Variable	n	%
Comorbidities		
None	30	75%
GDM	2	5%
Hypothyroidis	4	10%
Chronic hypertension	3	7.5%
Wilson disease	1	2.5%
Vaccination status		
Non-vaccinated	36	90%
Single dose Sinovac	1	2.5%
Two doses Sinovac	1	2.5%
Single dose Biontech	2	5%
Variant status		
Alpha	36	90%
Delta	4	10%
Delivery type		
Cesarean	32	80%
Vaginal delivery	0	0%
Medical treatment		
Kaletra	29	72.5%
Favipravir	20	50%
Remdesivir	3	7.5%
IVIG	0	0%
Plazmaferez	0	0%
Actemra	4	10%
Anakinra	6	15%
Prednol	40	100%
Pulse prednol	17	42.5%
Continious renal replacement	2	5%
ECMO	3	7.5%
HFNO	25	62.5%
NIMV	9	22.5%
Reservoir mask	34	85%
Intubation	15	37.5%
Exitus	10	25%
LOS: Lenght of stay, GDM: gestational diabetes mellitus, IVIG: intravenous immunoglobuline, ECMO: extracorporeal membrane oxygenation, HFNO: high flow nasal cannula oxygen, NIMV: non invasive mechanical ventilation, min-max: minimum-maximum, SD: standard deviation		

Table 2. Vaccinated vs unvaccinated patient's characteristics

	Vaccinated n=4	Unvaccinated n=36	p-value
Age	34.7±4.2	30.4±5.2	0.124
Gestational age (days)	215.2±18.1	226.7±27.8	0.332
FiO ₂ admission	30.3±34.2	89.5±15.8	0.003
Hb admission	11.9±0.5	10.5±1.3	0.040
PLT admission	157.5±10.3	253.7±98.9	0.042
Lymp admission	0.6±0.1	2.5±8.1	0.024
P50 admission	23.2±2.8	26.5±2.5	0.040
CRP admission	37.7±30	91.5±60	0.047
Procalcitonin admission	0.08±0.03	2.8±13.9	0.026
Symtom to admission	13.7±13	7.6±4.0	0.700
PCR to admission	12.5±13.3	6.1±3.2	0.821
LOS	7.7±8.3	12.6±12.1	0.309
Mortality	1 (25%)	9 (25%)	1.000

FiO₂: Fractional inspired oxygen, Hb: hemoglobin, Lymp: lymphocyte, P50: partial pressure of arterial oxygen when hemoglobin is fifty percent saturated, CRP: C-reactive protein, PCR: polymerase chain reaction, LOS: lenght of stay

Of 13 women presenting or developing severe or critical COVID-19 pneumonia, 2 (15%) were diagnosed at less than 24 weeks, 1 experienced second trimester pregnancy loss during prolonged intubation, and 1 was discharged for spontaneous delivery at 39 weeks (15).

As in our study, it was reported that increased morbidity in pregnancy with COVID-19 was observed during the delta variant-related fluctuation in a population with low vaccine acceptance. However, the vaccination rate in this population was higher than in our study (21.4% vs. 10%). In this study, 82 (5.4%) of 1515 pregnant COVID-19 cases required intensive care, mechanical ventilation was required in 11, and maternal death was observed in 2 patients (12).

In a prospective observational cohort study in the United Kingdom, pregnant women with GDM had delta infection (n=171, 11.1%) to wild-type variant (n=1,435, 10.2%) and Alpha variant (n=1,765, 10%) showed that he was more vulnerable than regardless of the variant, GDM was found to be significantly higher in pregnant women infected with symptomatic COVID-19 than in non-symptomatic women (16,17).

In the literature, the destructive effect of delta variant in pregnant women is explained as follows; delta variant itself is more contagious and effective in infecting host cells, delta variant causes a viral infection that accumulates more rapidly in the respiratory system, pregnant women

are more susceptible to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, lower vaccination rates in pregnant women compared to the general population (18).

It concluded that, as reported by the World Health Organization, COVID-19 is associated with an increased risk of admission to intensive care for pregnant women and an increased risk of preterm birth and admission to neonatal care for the baby (19).

We showed that ICU stay with SARS-CoV-2 is associated with an increased risk of cesarean section. This situation has been reported similarly in the literature (20).

The limitation of our study is the small number of vaccinated patients to compare with the unvaccinated. However, this is explained by the fact that vaccinated patients need less intensive care.

Conclusion

As a result, delta variant progressed with higher mortality in the pregnant population admitted to the ICU. Again, in our study, it was seen that the vaccination rate was very low in pregnant women who were taken to the ICU. Although the COVID-19 pandemic has lost its effect, it is a fact that vaccination in pregnant women will reduce maternal deaths for future outbreaks.

Ethics

Ethics Committee Approval: The study was designed as a prospective observational study and was conducted after the approval of the Başakşehir Çam and Sakura City Hospital Ethics Committee (approval number: 2021.10.232).

Informed Consent: Patients were included in the study after their written consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.H.A., D.G., A.Ö., Concept: G.H.A., G.T., Design: G.H.A., G.T., Data Collection and Process: G.H.A., D.G., A.Ö., Analysis or Interpretation: G.H.A., G.T., Literature Search: G.H.A., Writing: G.H.A.

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