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Clinical Characteristics and Outcomes of Vaccinated and Unvaccinated Pregnant Women Hospitalized With COVID-19: An Observational Study by Vaccination Status

COVID-19 Nedeniyle Hastaneye Yatırılan Aşılı ve Aşısız Gebelerin Klinik Özellikleri ve Sonuçları: Aşılama Durumuna Göre Gözlemsel Bir Çalışma

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Abstract

Objective: To evaluate maternal and obstetric characteristics, presenting symptoms, and pregnancy outcomes in vaccinated versus unvaccinated groups of pregnant women hospitalized with a diagnosis of coronavirus disease-2019 (COVID-19).

Methods: A total of 190 pregnancies hospitalized with a diagnosis of COVID-19 were included in this observational study and divided into two groups: vaccinated (n=82) and unvaccinated (n=108). Data on maternal and obstetric characteristics, presenting symptoms, radiological involvement, laboratory findings, need for oxygen or stay in the intensive care unit, and length of hospital stay were recorded. Pregnancy outcomes were evaluated using gestational week at diagnosis, gestational week at delivery, delivery due to COVID-19, fetal birthweight, and Apgar score.

Results: When compared with the vaccinated group, unvaccinated pregnant women COVID-19 were younger and had significantly lower rates of use of assisted reproductive technology, hypertensive disease, diabetes, coronary artery disease, and asthma. Unvaccinated women were more likely to present with dyspnea, fever, and chest pain, as well as radiological involvement and need for the intensive care unit. Gestational week at delivery, fetal birthweight, and Apgar scores were significantly lower, length of hospital stay was significantly longer, and the rate of delivery due to COVID-19 was significantly higher in the unvaccinated group versus the vaccinated group.

Conclusion: Our findings indicate a milder course of disease and a lower risk of adverse pregnancy outcomes in vaccinated versus unvaccinated pregnant women diagnosed with COVID-19. Hence, our findings suggest that pregnant women should be counseled to receive the COVID-19 vaccine to prevent maternal and fetal risks related to severe acute respiratory syndrome coronavirus 2 infection.

Keywords: COVID-19, pregnancy, maternal characteristics, adverse pregnancy outcomes, vaccination status

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Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) tanısı ile hastaneye yatırılan aşılanmış ve aşılanmamış gebe gruplarında maternal ve obstetrik özellikler, başvuru semptomları ve gebelik sonuçlarını değerlendirmek.

Yöntem: Bu gözlemsel çalışmaya COVID-19 tanısı nedeniyle hastaneye yatırılan toplam 190 gebe dahil edildi ve aşılı (n=82) ve aşısız (n=108) olarak iki gruba ayrıldı. Maternal ve obstetrik özellikler, başvuru semptomları, radyolojik tutulum, laboratuvar bulguları, oksijen ihtiyacı veya yoğun bakım ve hastanede kalış süreleri kaydedildi. Tanı anındaki ve doğumdaki gebelik haftası, COVID-19 nedeniyle doğum, fetal doğum ağırlığı ve Apgar skoru kullanılarak gebelik sonuçları değerlendirildi.

Bulgular: Aşılanan grupla karşılaştırıldığında, aşılanmamış COVID-19'lu hamile kadınlar daha gençti ve yardımcı üreme teknolojisi ile gebelik, hipertansif hastalık, diyabet, koroner arter hastalığı ve astım oranları önemli ölçüde daha düşüktü. Aşılanmamış gebelerin nefes darlığı, ateş ve göğüs ağrısının yanı sıra radyolojik tutulum ve yoğun bakım ünitesi gereksinimi daha fazlaydı. Aşılanmamış grup aşılanmış gruba göre doğumdaki gebelik haftası, fetal doğum ağırlığı ve Apgar skorları anlamlı derecede düşük, hastanede kalış süresi önemli ölçüde daha uzun ve COVID-19 nedeniyle doğum oranı anlamlı derecede daha yüksek bulundu.

Sonuç: Bulgularımız, COVID-19 tanılı gebe kadınların aşılananları aşılanmayanlara göre daha hafif bir hastalık seyri ve daha az olumsuz gebelik sonuçları gösterdi. Bu nedenle bulgularımız, şiddetli akut solunum sendromu koronavirüs 2 enfeksiyonu ile ilgili maternal ve fetal riskleri önlemek için hamile kadınlara COVID-19 aşısı yaptırmaları konusunda danışmanlık verilmesi gerektiğini gösterdi.

Anahtar Kelimeler: COVID-19, gebelik, maternal özellikler, olumsuz gebelik sonuçları, aşılama durumu

Introduction

The coronavirus disease-2019 (COVID-19), caused by a novel coronavirus identified as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), has led to substantial morbidity and mortality since the declaration of a global pandemic in March 2020[1]. Although it is considered probable that physiological, mechanical, and immunologic alterations in pregnancy affect susceptibility to COVID-19, limited data address this issue[2,3]. COVID-19 vaccination for pregnant and lactating women is the subject of ongoing global debate because of the lack of concrete data on the safety and efficacy of vaccination in these populations[4-6]. Nonetheless, accumulating evidence indicates that pregnant women are at an increased risk of severe disease and COVID-19-related complications, such as the need for invasive ventilation and intensive care unit (ICU) admission, compared with non-pregnant women[7-11]. Studies have also reported an association between COVID-19 and adverse pregnancy outcomes, such as increased risk of preeclampsia, gestational diabetes, hypertensive disorders of pregnancy, preterm birth, and low birthweight, particularly in cases of severe disease[10,12-14]. For these reasons, pregnant women have been classified as a high-risk population for COVID-19 infection. Given the reported efficacy and safety of COVID-19 vaccines in non-pregnant populations and promising emerging data on vaccination during pregnancy, COVID-19 vaccines are considered appropriate for pregnant women who prefer vaccination[15-17]. Research on COVID-19 pneumonia in relation to maternal and fetal adverse outcomes, as well as studies of COVID-19 vaccination in pregnant women, is needed to support high-quality obstetric care for pregnant women infected with COVID-19[3-5]. Therefore, this study was designed to evaluate maternal and obstetric characteristics, presenting symptoms of COVID-19, and pregnancy outcomes in unvaccinated and vaccinated pregnant women hospitalized with a diagnosis of COVID-19.

Materials and Methods

Study Population

A total of 190 pregnant women hospitalized at a tertiary care obstetric clinic between December 2021 and February 2022 with a diagnosis of COVID-19 were included in this observational study. Patients were divided into two groups according to COVID-19 vaccination status: vaccinated (n=82) and unvaccinated (n=108). COVID-19 was diagnosed based on SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) test positivity. Written informed consent was obtained from each subject. The study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and was approved by an institutional ethics committee.

The Ethical Committee of University of Health Sciences Turkey, Başaksehir Çam and Sakura City Hospital (decision no: KAEK/2021.11.268) approved this study.

Assessments

For all patients in the vaccinated and unvaccinated groups, data were recorded on maternal characteristics (age, weight, height) and obstetric characteristics (gravidity, parity,

hypertensive disease, gestational or pregestational diabetes, coronary artery disease, asthma), presenting symptoms, laboratory findings, and radiological involvement at the time of COVID-19 diagnosis, need for oxygen support or ICU admission, and length of hospital stay. Pregnancy outcomes were evaluated using gestational week at diagnosis, gestational week at delivery, delivery due to COVID-19, fetal birthweight, and Apgar score.

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY). The chi-square test was used for the analysis of categorical variables. Numerical variables were analyzed with Student's t-test and the Mann-Whitney U test. Data were expressed as mean ± standard deviation (SD), median (minimum-maximum), and percent (%), as appropriate. Statistical significance was set at $p<0.05$.

Results

Maternal and Obstetric Characteristics by Vaccination Status

Compared with the vaccinated group, unvaccinated pregnant women with COVID-19 were younger (median 33.0 vs 38.0 years, p=0.001) and had significantly lower rates of assisted reproductive technology (ART) use (4.6 vs 9.8%, p<0.001), hypertensive disease (13.9 vs 22.0%, p<0.001), gestational or pregestational diabetes (7.4 vs 18.3%, p<0.001), coronary artery disease (6.5 vs 11.0%, p<0.001), and asthma (12.0 vs 19.5%, p<0.001) (Table 1).

COVID-19 Presentation Characteristics and Laboratory Findings by Vaccination Status

Unvaccinated women were more likely than vaccinated women to present with dyspnea (76.9 vs 65.9%, p<0.001), fever (78.7 vs 78.0%, p<0.001), sputum discharge (66.7 vs 59.8%, p<0.001), myalgia (44.4 vs 40.2%, p=0.02), and chest pain (34.3% vs 30.5%, p<0.001) (Table 2). Overall, 43.9% of vaccinated women and 48.1% of unvaccinated women experienced loss of taste and smell (p=0.247). Regaining taste and smell were more common for vaccinated women than unvaccinated women, although this difference was not statistically significant (75.0 vs 67.3%, p=0.439) (Table 2). Radiological involvement (67.6 vs 63.4%, p<0.001) and need for ICU stay (29.6 vs 17.1%, p<0.001) were significantly more common in the unvaccinated group than in the vaccinated group, and the length of hospital stay was significantly longer (median 5.0 vs. 4.0 days, p<0.001) (Table 2). Laboratory analysis revealed that unvaccinated women differed from vaccinated women in having significantly lower lymphocyte counts (p=0.013), hemoglobin levels (p<0.001), and hematocrit levels (p<0.001), and significantly higher serum levels of C-reactive protein (CRP) (p<0.001), aspartate transaminase (AST) (p<0.001), alanine transaminase (ALT) (p=0.002), and ferritin (p=0.036) (Table 2).

Pregnancy Outcomes in Vaccinated vs Unvaccinated Groups

Unvaccinated pregnant women were diagnosed with COVID-19 at an earlier gestational week than vaccinated pregnant women (median 30.0 vs 34.5 weeks, p=0.013; Table 3). Gestational week at delivery (median 34.0 vs 37.0 weeks, p<0.001), fetal birthweight (median 2,400 vs 2,500 g, p=0.01), and Apgar scores (median 7.0 vs 8.0, p=0.025) were significantly lower for unvaccinated versus vaccinated pregnant women. The rate of delivery due to COVID-19 was significantly higher in the unvaccinated group (32.4 vs 23.2%, p<0.001) (Table 3).

Discussion

Our findings revealed significant differences in the maternal and obstetric characteristics, presenting symptoms, and pregnancy outcomes of vaccinated and unvaccinated pregnant women with COVID-19. The unvaccinated group was younger, had less frequent use of ART, and had lower rates of hypertensive disease, gestational or chronic diabetes, coronary artery disease, and asthma. COVID-19 appeared at an earlier gestational week in unvaccinated pregnant women, and clinical and laboratory manifestations (dyspnea, chest pain, radiological involvement, ICU stay, lower lymphocyte count, and higher CRP and ferritin levels) indicated more advanced disease. COVID-19 in unvaccinated women was also associated with more adverse pregnancy outcomes than in vaccinated women, such as an earlier gestational week at delivery (median 34.0 vs 37.0 weeks), higher risk of delivery due to COVID-19 (32.4 vs 23.2%), lower fetal birthweight (median 2,400 vs 2,500 g) and Apgar scores (median 7.0 vs 8.0), and longer hospital stays (median 5.0 vs 4.0 days). It is hypothesized that the association between pregnancy and greater severity of COVID-19 is linked to mechanical changes (i.e., decreased lung volume as the fetus grows), immunological changes, and increased risk of thromboembolic disease during pregnancy[2]. These factors may account for reports that pregnant COVID-19 patients are at an increased risk of an ICU stay (three times the risk), invasive ventilation (2.9 times the risk), and mortality (1.7 times the risk) compared with non-pregnant COVID-19

patients after adjusting for age and comorbidities[18-21]. Additional risk factors, such as obesity, hypertension, and gestational diabetes, are thought to exacerbate COVID-19 during pregnancy, leading to higher rates of ICU admission, mechanical ventilation, and death[7,18,21-24]. There is also mounting evidence of an association between COVID-19 and adverse pregnancy outcomes (e.g., preeclampsia, gestational diabetes, hypertensive disorders of pregnancy, preterm delivery, low birthweight), particularly in those with severe disease[10,12-14]. Moreover, the stress and anxiety experienced by pregnant women because of the COVID-19 pandemic are associated with an increased risk of poor pregnancy outcomes, including preeclampsia, premature birth, low birth weight, and low Apgar score[25-28]. Complicated pregnancies are therefore thought to be more probable during the pandemic, even among women who avoid infection with SARS-CoV-2[28]. However, data on vaccine coverage suggest that pregnant women are less likely to receive the COVID-19 vaccine despite the increased risk of severe disease and the potential for adverse pregnancy and neonatal outcomes if infected[2]. Interestingly, our findings indicate that younger pregnant women and those without comorbidities or use of ART are less likely to get vaccinated against COVID-19. Nevertheless, unvaccinated pregnant women presented with more advanced COVID-19 symptoms, were less likely to regain their sense of taste and smell, and were at an increased risk of adverse pregnancy outcomes and delivery due to COVID-19. The higher rate of COVID-19 vaccination among older pregnant women with comorbidities or use of ART in this study is notable given that older maternal age and preexisting comorbidities (e.g., obesity, chronic obstructive pulmonary disease, asthma, chronic hypertension, and pregestational or gestational diabetes) have been identified as risk factors for hospitalization and greater severity of COVID-19 during pregnancy[2,7,14,18]. Our findings support the theory that pregnant persons, particularly younger women, are less likely to be vaccinated than non-pregnant women of reproductive age[29], and that the perceived danger of contracting COVID-19 is strongly associated with the probability of vaccination[5,30,31]. In addition to the direct impact of COVID-19 on pregnancy outcomes, there is evidence that the pandemic and its effects on healthcare systems resulted in the deterioration of pregnancy outcomes compared with the pre-pandemic period, even among those not infected with SARS-CoV-2[2,32].

Table 1. Maternal and obstetric characteristics in pregnant women with COVID-19 by vaccination status

		Pregnant women with COVID-19		
		Vaccinated (n=82)	**Unvaccinated (n=108)**	**p-value**
Maternal and obstetric characteristics				
Age (year)	Mean ± SD	36.2±5.2	32.4±7.3	**0.001**
	Median (min-max)	38.0 (23.0-45.0)	33.0 (18.0-42.0)	-
Height (cm), median (min-max)		159.0 (145.0-175.0)	158.0 (145.0-165.0)	**0.013**
Weight (kg), median (min-max)		68.5 (48.0-110.0)	65.0 (50.0-105.0)	0.497
Gravida, median (min-max)		2.0 (1.0-5.0)	2.0 (1.0-7.0)	0.054
Parity, median (min-max)		0.0 (0.0-4.0)	1.0 (0.0-5.0)	**0.001**
Assisted reproductive technique, %	No	90.2	95.4	**<0.001**
	Yes	9.8	4.6	
Hypertensive disease, %	No	78.0	86.1	**<0.001**
	Yes	22.0	13.9	
Pregestational or gestational diabetes, %	No	81.7	92.6	**<0.001**
	Yes	18.3	7.4	
Coronary artery disease, %	No	89.0	93.5	**<0.001**
	Yes	11.0	6.5	
Asthma, %	No	80.5	88.0	**<0.001**
	Yes	19.5	12.0	

SD: Standard deviation, COVID-19: Coronavirus disease-2019, min-max: Minimum-maximum

Table 2. COVID-19 presenting symptoms and laboratory findings by vaccination status					
	Pregnant women with COVID-19				
Presenting symptoms, %	**Vaccinated (n=82)**		**Unvaccinated (n=108)**		**p-value**
	No	**Yes**	**No**	**Yes**	
Cough	32.9	67.1	33.3	66.7	**<0.001**
Dyspnea	34.1	65.9	23.1	76.9	**<0.001**
Fever	22.0	78.0	21.3	78.7	**<0.001**
Sputum discharge	40.2	59.8	33.3	66.7	**<0.001**
Headache	57.3	42.7	61.1	38.9	**0.001**
Loss of taste and smell	56.1	43.9	51.9	48.1	0.247
Regains of taste and smell	25.0	75.0	32.7	67.3	0.439
Myalgia	59.8	40.2	55.6	44.4	**0.02**
Chest pain	69.5	30.5	65.7	34.3	**<0.001**
Nasal discharge	76.8	23.2	76.9	23.1	**<0.001**
Need for an ICU stay	82.9	17.1	70.4	29.6	**<0.001**
Oxygen need	53.7	46.3	50.9	49.1	0.562
Radiological involvement	36.6	63.4	32.4	67.6	**<0.001**
Laboratory findings, mean ± SD	**Vaccinated (n=82)**		**Unvaccinated (n=108)**		**p-value**
WBC (x10^3/mL)	5632.9±1125.7		6876.9±4088.8		0.12
Neutrophil (x10^3/mL)	3992.7±1563.5		4337.0±2189.4		0.597
Lymphocyte (x10^3/mL)	1669.4±1064.6		1236.6±919.2		**0.013**
Hemoglobin (g/dL)	11.6±1.2		10.9±1.4		**<0.001**
Hematocrit (%)	34.5±3.3		32.4±3.5		**<0.001**
Platelet (x10^3/mL)	238.2±96.0		227.3±89.0		0.452
MPV (fL)	11.0±1.3		10.6±1.3		0.098
RDW (%)	12.1±1.4		12.3±1.3		0.266
PDW (fL)	12.4±1.3		12.3±1.4		0.491
CRP (mg/dL)	9.1±7.4		27.8±32.8		**<0.001**
D dimer (ng/mL)	503.2±270.0		567.3±276.8		0.072
INR	1.0±0.2		0.9±0.1		0.498
PT (sn)	11.3±1.5		11.6±1.6		0.171
Urea (mg/dL)	26.1±6.8		30.7±14.3		0.179
Creatine (mg/dL)	0.8±0.2		0.9±0.2		0.054
Na (mg/dL)	138.7±3.0		138.2±3.0		0.216
K (mg/dL)	3.8±0.3		3.8±0.5		0.695
AST (U/dL)	30.6±5.5		39.8±11.2		**<0.001**
ALT (U/dL)	29.4±4.3		32.7±6.9		**0.002**
Albumin (g/dL)	3.53±0.7		3.4±0.6		0.284
Bilirubin (mg/dL)	0.4±0.1		0.4±0.1		0.061
Ferritin (ng/mL)	185.8±130.2		224.6±126.5		**0.036**
LDH (U/L)	202.4±29.7		207.0±27.7		0.217
Total cholesterol (mg/dL)	137.3±15.1		142.7±12.0		**0.013**
Triglycerides (mg/dL)	135.6±18.7		137.7±17.9		0.564

Table 2. Continued

	Pregnant women with COVID-19				
Presenting symptoms, %	**Vaccinated (n=82)**		**Unvaccinated (n=108)**		**p-value**
	No	**Yes**	**No**	**Yes**	
HDL (mg/dL)	35.8±9.7		35.5±11.0		0.733
LDL (mg/dL)	135.5±13.4		132.2±10.7		0.043
LOS (day), median (min-max)	4.0 (3.0-12)		5.0 (3.0-14.0)		<0.001

ICU: Intensive care unit, WBC: White blood cell, MPV: Mean platelet volume, RDW: Red cell distribution width, PDW: Platelet distribution width, CRP: C-reactive protein, INR: International Normalized Ratio, PT: Prothrombin time, AST: Aspartate transaminase, ALT: Alanine transaminase, LDH: Lactate dehydrogenase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, LOS: Length of hospital stay, COVID-19: Coronavirus disease-2019, min-max: Minimum-maximum

Table 3. Pregnancy outcomes in pregnant women with COVID-19 by vaccination status

	Pregnant women with COVID-19		
	Vaccinated (n=82)	**Unvaccinated (n=108)**	**p-value**
Pregnancy outcome			
Gestational week at diagnosis, median (min-max)	34.5 (6.0-38.0)	30.0 (8.0-38.0)	**0.013**
Gestational week at delivery, median (min-max)	33.4±3.0	34.0 (23.0-38.0)	**<0.001**
Delivery due to COVID-19, %	23.2	32.4	**<0.001**
Fetal birthweight (g), median (min-max)	2500.0 (600.0-3700.0)	2400.0 (550.0-3870.0)	**0.01**
Apgar score, median (min-max)	8.0 (5.0-8.0)	7.0 (6.0-8.0)	**0.025**

COVID-19: Coronavirus disease-2019, min-max: Minimum-maximum

Previous studies showed similar clinical characteristics in pregnant women and non-pregnant adult patients with COVID-19 pneumonia (i.e., fever and cough as the main symptoms along with lymphopenia and elevated ALT or AST), but found that the need for hospitalization and mechanical ventilation and the length of hospital stay was higher among pregnant patients[3,33]. A systematic review of 37 studies involving 364 pregnant women with COVID-19 and 302 neonates reported that a majority of women were in the third trimester of pregnancy at the time of diagnosis[28]. The authors also noted mild-to-moderate symptoms (with fever and cough being the most common) and a favorable course of disease[28]. There were few maternal (n=2) or neonatal (n=3) deaths, but a notably high rate of preterm delivery (23.6%)[28]. However, given that nearly all pregnant patients in their study were healthy women without comorbidities, the authors emphasized a need for further research to examine the impact of maternal comorbidities and pregnancy stage on adverse pregnancy outcomes and the course of COVID-19 during pregnancy[28]. Risk factors in pregnancy, including pregestational and gestational diabetes, cardiovascular disease, and obesity, are thought to make pregnant women susceptible to severe complications of COVID-19[6,17]. In our cohort of pregnant women with COVID-19, the vaccinated group presented with milder symptoms than the unvaccinated group (lower rates of dyspnea, chest pain, radiological involvement, and ICU stay; higher lymphocyte count and lower CRP and ferritin levels) and had a much lower rate of adverse pregnancy outcomes, despite older age and a higher rate of comorbidities. Consequently, our findings indicate that pregnant women should be advised to receive the COVID-19 vaccine to reduce maternal and fetal risks associated with SARS-CoV-2 infection[6,17,34].

Study Limitations

A small sample size is the major limitation of this study. A lack of data on temporal changes in laboratory findings during the hospitalization period, which would add to the knowledge generated by the current study, is another limitation. Nevertheless, our findings on presenting symptoms and pregnancy outcomes related to COVID-19 in vaccinated and unvaccinated pregnant women are a valuable contribution to the literature.

Conclusion

Our findings indicate milder presenting symptoms and course of disease, along with a lower risk of adverse pregnancy outcomes, in vaccinated versus unvaccinated pregnant women diagnosed with COVID-19. These differences were found despite older maternal age and more frequent comorbidities in the vaccinated group. Hence, our findings

strongly suggest that pregnant women should be counseled to receive the COVID-19 vaccine to prevent maternal and fetal risks related to SARS-CoV-2 infection.

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Ethics

Ethics Committee Approval: The Ethical Committee of University of Health Sciences Turkey, Başaksehir Çam and Sakura City Hospital (decision no: KAEK/2021.11.268) approved this study.

Informed Consent: Written informed consent was obtained from each subject.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.Ö., G.B., Concept: Ö.Ö., G.B., U.Ç., Desing: Ö.Ö., Data Collection or Processing: Ö.Ö., G.B., Analysis or Interpretation: Ö.Ö., U.Ç., Literature Search: Ö.Ö., U.Ç., Writing: Ö.Ö., G.B.

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