



Impact of Pfizer-BioNTech COVID-19 Vaccination on the Menstrual Cycle

Pfizer-BioNTech COVID-19 Aşısının Menstrüel Döngü Üzerindeki Etkisi

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Abstract

Objective: To evaluate the effect of Pfizer-BioNTech Coronavirus disease-2019 (COVID-19) vaccination on the menstrual cycle.

Method: This cross-sectional survey study investigated whether Pfizer-BioNTech COVID-19 vaccination affected the menstrual cycle of women who had regular cycles.

Results: One hundred and sixty two of 327 (49.5%) patients who had regular cycles expressed that their menstrual cycle had been affected after vaccination. Univariate analysis revealed a statistically significant relationship between age, body mass index (BMI), parity, smoking, pads per day, intrauterin device (IUD) and the incidence of menstrual change after vaccination. The factors identified by multivariate analysis as being independently related with the menstrual disorders following vaccination were BMI [odds ratio (OR) 1.09, 95% confidence interval (CI) 1.01-1.17, $p=0.023$], smoking (OR 2.19, 95% CI 1.28-3.78, $p=0.005$), pads per day (OR 1.42, 95% CI 1.14-1.75, $p=0.005$) and IUD (OR 5.1, 95% CI 1.99- 13.0, $p=0.001$).

Conclusion: Approximately half of the participants declared menstrual disorder after vaccination. BMI, smoking, number of pads per day, and IUD were found to be independent risk factors for menstrual changes.

Keywords: COVID-19, menstrual cycle, Pfizer-BioNTech, vaccination

Öz

Amaç: Pfizer-BioNTech Koronavirüs hastalığı-2019 (COVID-19) aşısının menstrüel döngü üzerindeki etkisini değerlendirmektir.

Yöntem: Bu anket çalışması ile, Pfizer-BioNTech COVID-19 aşısının düzenli menstrüel siklusu olan kadınların menstrüel döngüsünü etkileyip etkilemediğini araştırılmıştır.

Bulgular: Menstrüel siklusu düzenli olan 327 kadından 162'si (%49,5), menstrüel döngüsünün aşılamadan sonra etkilendiğini belirtmiştir. Univaryant analiz sonucunda aşılama sonrası adet değişim insidansı ile yaş, vücut kitle indeksi (VKİ), parite, sigara, günlük ped sayısı, rahim içi araç (RİA) arasında istatistiksel olarak anlamlı bir ilişki olduğu ortaya konulmuştur. Multivaryant sonucunda ise bağımsız olarak ilişkili olarak tanımlanan faktörler VKİ [olasılık oranı (OO) 1,09, %95 güven aralığı (GA) 1,01-1,17, $p=0,023$], sigara (OO 2,19, %95 GA 1,28-3,78, $p=0,005$), günlük ped sayısı (OO 1,42, %95 GA 1,14-1,75, $p=0,005$) ve RİA (OO 5,1, %95 GA 1,99-13,0, $p=0,001$) olarak bulunmuştur.

Sonuç: Çalışmaya katılan kadınların yaklaşık yarısı aşı sonrası adet düzensizliği bildirmiştir. VKİ, sigara, günlük ped sayısı ve RİA adet düzensizliği için bağımsız risk faktörü olarak bulunmuştur.

Anahtar kelimeler: Aşı, COVID-19, menstrüasyon, Pfizer-BioNTech

Introduction

In Turkey, the first Coronavirus disease-2019 (COVID-19) case was identified in March 2020, and the first doses of the Pfizer-BioNTech COVID-19 vaccine were administered in July 2021(1). Previously published studies reported that major and minor menstrual disorders were observed after administration of the Pfizer-BioNTech COVID-19

vaccine (2). Menstrual irregularities, such as heavy bleeding, and shorter or longer cycles have been described in numerous reports of recent research evaluating menstrual disorders connected to severe acute respiratory syndrome-coronavirus-2 immunization (3,4). In the same sense that irregular menstruation can raise concerns about fertility in women of childbearing age, postmenopausal bleeding



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can raise fears about endometrial cancer. For this purpose, we designed this study to determine whether the vaccine affected menstrual cycles.

Materials and Methods

This study was approved by Ethics Committee of University of Health Sciences Turkey, Derince Training and Research Hospital, Non-Invasive Clinic Ethics Committee (approval date 27.10.22, institution review board number: 2022-92), patients who received the Pfizer-BioNTech COVID-19 vaccine were informed and included in the study if they gave consent. They were asked to complete a survey form created via Google or face-to-face. Information was given about the study's voluntary nature, which stated that the findings would not be disclosed to any outside parties. The questionnaire asked about the individuals' demographics and menstrual patterns (period time, pads per day, pain) of premenopausal patients before and after vaccination (Supplementary File 1). The vaccination had been administered at least 3 months prior to the survey. Patients were asked to provide details about their menstrual cycle following any dose of the Pfizer-BioNTech COVID-19 vaccine. It was also questioned whether postmenopausal patients had bleeding.

Healthy women over the age of 18 years with regular menstrual cycles and without a previous history of abnormal bleeding were included in the study. Patients who were of reproductive age were included if they had at least three cycles of post-pregnancy or post-hormonal contraceptive use.

Exclusion criteria included those with gynecological or hematological illnesses and those using oral contraceptives or the levonorgestrel-releasing intrauterine system (Mirena®).

At first, postmenopausal women were also asked to participate in the survey; however, as none of the participants reported breakthrough bleeding, this group was not included in the analysis of women of reproductive age to prevent misinterpretation.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 21.0 was used for all statistical analyses. Comparison of categorical variables was performed using exact Fisher's test, Pearson's chi-square test, and Yates continuity correction. After the normality of variables was examined by the Kolmogorov-Smirnov test, comparison of continuous variables was performed using an independent-

samples t-test or Mann-Whitney U test. P-values <0.05 were considered statistically significant. Data are expressed as mean \pm standard deviation or median and interquartile range for continuous variables, and absolute numbers and percentages for categorical values. Multivariate logistic regression was performed for variables that were significant in the univariate analysis. The odds ratio (OR) was supported by confidence intervals and p-values.

Results

Throughout the study, 392 questionnaires were completed. Four were excluded because of incomplete answers, 13 of them used oral contraceptive drugs, and 6 of them stated that they did not have regular periods. Twenty-three responders in all were excluded from the research, and with 369 participants overall, the study was finished. Forty-two of them were in the postmenopausal period. None of the postmenopausal women had postmenopausal bleeding following vaccination. The mean age of postmenopausal women was 56.3 ± 7.2 years (range 45-68).

Excluding the postmenopausal group, 327 women of reproductive age were evaluated for statistical analysis. The mean age was 36.3 ± 7.8 years (range 18-49). One hundred sixty-five of 327 women (51.5%) reported no change after being vaccinated. One hundred sixty-two (49.5%) women who had regular cycles stated that their menstrual cycle had been affected after vaccination. Sixty-nine women had unusually heavy flows after vaccination, and 75 had longer bleeding. Forty-eight of these group of women both experienced heavy and longer bleeding. Eighteen women experienced breakthrough bleeding. Fifty-seven women had decreased menstrual bleeding, 33 had a shorter menstrual bleeding, and 21 of these experienced both decreased and shortened bleeding. Eighteen (5.5%) women expressed that they had menstrual cycles in longer time intervals, while 6 (1.8%) women had menstrual cycles more often. Dysmenorrhea developed in 15 of 178 patients (8.4%) who had not previously complained of dysmenorrhea.

There were no differences in the reported onset of new menstrual-related symptoms among patients who received one, two, three, or four vaccination doses ($p=0.096$). It was not associated with previous COVID-19 disease ($p=0.493$).

Univariate analysis revealed a statistically significant relationship between age, body mass index (BMI), parity, smoking, pads per day, intrauterine device use, and the incidence of menstrual change after vaccination (Table 1). It was found that the age of those who had menstrual

changes was older than that of those who did not (37.8 ± 7.4 vs. 34.7 ± 7.9 , $p < 0.001$) but it was not found statistically significantly by multivariate analysis ($p = 0.187$). The factors identified by multivariate analysis as being independently related with the menstrual disorders following vaccination were BMI [OR 1.09, 95% confidence interval (CI) 1.01-1.17, $p = 0.023$], smoking (OR 2.19, 95% CI 1.28-3.78, $p = 0.005$), pads per day (OR 1.42, 95% CI 1.14-1.75, $p = 0.005$) and intrauterin device (OR 5.1, 95% CI 1.99-13.0, $p = 0.001$) (Table 2).

There was no statistically significant difference in age between the group that experienced an increase in bleeding and the group that experienced a decrease (39.2 ± 5.6 vs. 37.5 ± 8.6 , $p = 0.217$).

Of the 162 patients with menstrual disorders, 45 (27.8%) contacted a doctor, no issues found in 36 of them. Ovarian cysts were detected in 3 patients and premenopausal signs were found in 6 patients.

Discussion

Menstruation is an inflammatory process. Natural killer cells, macrophages, mast cells, neutrophils, dendritic cells, and T-cells are all drawn in throughout the menstrual cycle and contribute to the destruction and regeneration of the functional endometrium. The vaccination-induced systemic immune response may affect this inflammation (5). In addition, immune thrombocytopenia, in which both thrombotic and hemorrhagic events are observed following vaccination, is thought to occur via a heparin-induced thrombocytopenia-like mechanism (6,7). Menstrual alterations may be explained by immune-related procoagulative and pro-inflammatory states. Consistent with this, the recent research involving healthy participants found a link between receiving the COVID-19 vaccination and alterations in menstrual flow (3,8,9).

According to a web-based survey, 42% of people with regular menstrual cycles bled more heavily than usual, while 44% reported no change after being vaccinated. In addition,

Table 1. Characteristics of patients

	No change (n=165)	Change (n=162)	p
Age, y	34.7±7.9	37.8±7.4	<0.001
Parity	1 (0-2)	2 (0-2)	0.004
BMI, kg/m ²	23.3±3.7	24.7±3.6	<0.001
Smoking, n (%)	36 (21.8)	66 (40.7)	<0.001
Period time, day	5.8±1.4	6±1.3	0.084
Pads per day	2.6±1.0	3±1.1	0.001
Intrauterin device, n (%)	6 (3.6)	33 (20.4)	<0.001
COVID-19 disease history	36 (21.8)	30 (18.5)	0.493
Hypertension, n (%)	3 (1.8)	0 (0)	0.248
Diabetes mellitus, n (%)	3 (1.8)	6 (3.7)	0.333
Hypothyroidism, n (%)	6 (3.6)	3 (1.9)	0.502
Number of dosage, n (%)			0.096
One	24 (14.5)	33 (20.4)	
Two	75 (45.5)	81 (50)	
Three	60 (36.4)	39 (24.1)	
Four	6 (3.6)	9 (5.6)	

BMI: Body mass index, COVID-19: Coronavirus disease-2019

Table 2. Characteristic features of participants associated with post-vaccination menstrual irregularities

	OR	95% CI	p
Age	1.03	0.99-1.07	0.187
BMI	1.09	1.01-1.17	0.023
Parity	1.03	0.83-1.28	0.813
Smoking	2.19	1.28-3.78	0.005
Pre-vaccination used pads per day	1.38	1.10-1.72	0.005
Intrauterin device	5.1	1.99-13.0	0.001

Multivariate analysis was performed, OR: Odds ratio, CI: Confidence interval, BMI: Body mass index

66% of postmenopausal people reported breakthrough bleeding. They discovered a strong correlation between age and increased/breakthrough bleeding (3).

Up to 66% of the participants in another study reported experiencing new or worsening menstrual-related symptoms in the first cycle following vaccination; these changes were noted to be temporary after 2 months (10).

In the current study, various menstrual changes were observed. In addition to the observation of heavy and prolonged bleeding, the number of people reporting decreased and infrequent menstrual patterns was also significant. However, no patient experienced postmenopausal bleeding.

COVID-19-infected women experienced temporary menstrual abnormalities, primarily longer periods and decreased volume, as well as shortened or disordered menstrual cycles and increased volume, in line with vaccinated women (11,12). It was not the purpose of our study to investigate menstrual changes following COVID-19 disease. However, no relationship was found between history of COVID-19 disease and menstrual irregularities observed among vaccinated women.

In the current study, although the high ratio of being affected by the vaccine (n=162, 49.5%), the low rate (n=45, 27.8%) of consulting a doctor actually suggests that the complaints were either vague or temporary.

Study Limitations

The study's limitations include its small sample size, the subjectivity of the responses because there is variation in women's normal periods, and the possibility that participants' preconceived notions about the vaccine due to misinformation and anti-vaccine activists' discourse may influence the answers. Myths of vaccines regarding fertility and reproduction are especially powerful because they afflict a huge portion of the population.

It is important to show whether these changes can be linked to vaccination itself, clarify the duration of such changes, and begin to understand the mechanism of these vaccine-related menstrual changes. Therefore, it is necessary to quantify the prevalence of menstrual changes after vaccination in comparison with women vaccinated against other COVID-19 vaccines or unvaccinated control groups. By providing a more comprehensive understanding and open communication about potential menstrual changes related to vaccines, this research can help decrease vaccine hesitancy among menstruating individuals.

To assess the association between vaccination and menstrual alterations more precisely, a prospective evaluation before and after vaccination was required. Considering the chaos and anxiety that the COVID-19 era brought forth, this could not be planned. This study design can be conducted more systematically and prospectively in case similar situations occur in the future.

Conclusion

The following vaccination, approximately 50% of individuals reported having menstrual problems. It was found that BMI, smoking, IUDs, and pre-vaccination quantity number of pads used daily were independent risk factors for disordered menstruation.

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Ethics

Ethics Committee Approval: This study was approved by Ethics Committee of University of Health Sciences Turkey, Derince Training and Research Hospital, Non-Invasive Clinic Ethics Committee (approval date 27.10.22, institution review board number: 2022-92).

Informed Consent: Informed consent was obtained.

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Supplementary File 1.

Sizi bir formu doldurmaya davet ettim:

COVID-19 BIONTECH AŞISI SONRASI ADET DÜZENİNİ DEĞERLENDİRME

Merhaba, bu anketi 18 yaş üstü kadınlarda Covid-19 Biontech aşısının adet düzenine etkisini değerlendirmek üzere oluşturduk. Size özel bilgileriniz kimseyle paylaşılmayacak olup, tüm sonuçların genel bir istatistiği yapılarak elde edilen sonuçlar yayınlanacaktır. Teşekkürler.

YAŞINIZ *

KİLONUZ (KG) *

BOYUNUZ (CM) *

SİĞARA KULLANIYOR MUSUNUZ? *

- EVET
- HAYIR

COVID-19 HASTALIĞI GEÇİRDİNİZ Mİ?

- EVET- BİONTECH İLE HİÇ AŞILANMAMIŞ İKEN
- EVET- BİONTECH AŞISI OLDUKTAN SONRAKİ SÜREÇTE
- HAYIR

EK HASTALIĞINIZ VAR MI? VARSA NEDİR *

KAN SULANDIRICI İLAÇ KULLANIYOR MUSUNUZ? *

- EVET
- HAYIR

NORMAL VEYA SEZARYEN TOPLAM KAÇ DOĞUM YAPTINIZ? *

HER AY DÜZENLİ ADET GÖRÜR MÜSÜNÜZ? *

- EVET
- HAYIR-SEYREK OLUR
- HAYIR- SIK SIK OLURUM
- HAYIR- HİÇ BELLİ OLMAZ
- MENOPOZDAYIM

ADETİNİZ ORTALAMA KAÇ GÜN SÜRER?

ADET MİKTARINIZ NASIL, GÜNDE EN FAZLA KAÇ PED KULLANIRSINIZ BELİRTİNİZ ?

- NORMAL (EN YOĞUN OLDUĞU GÜN EN ÇOK 2-3PED)
- AZ (EN YOĞUN OLDUĞU GÜN 1 PEDİ DOLDURMAZ)
- YOĞUN (GÜNDE 2-3PEDDEN FAZLA VEYA PIHTI HALİNDE KANAMA)

ADETLERİNİZDE AĞRINIZ OLUR MU?

- EVET
- HAYIR

GEBELİKTE KORUNMAK İÇİN BİR ŞEY KULLANIYOR MUSUNUZ? *

- HAYIR
- DOĞUM KONTROL HAPI
- SİRİRAL
- İLAÇLI SİRİRAL (MIRENA)
- Diğer:

KAÇ DOZ BİONTECH COVID AŞISI OLDUNUZ? *

AŞI SONRASI ADET DÜZENİNİZDE BOZUKLUK-ARA KANAMA, LEKELENMENİZ OLDU MU? MENOPOZDAYSANIZ KANAMANIZ OLDU MU? *

- EVET
- HAYIR

Supplementary File 1. Continued

ADET KANAMA MİKTARINIZDA DEĞİŞİKLİK OLDU MU ?

- HAYIR
- EVET YOĞUNLAŞTI
- EVET AZALDI
- TAMAMEN KESİLDİ

ADET OLDUĞUNUZ GÜN SAYISI DEĞİŞTİ Mİ?

- HAYIR
- EVET UZADI VEYA ÖNCESİ-SONRASI LEKELENMELER OLUŞTU
- ARA KANAMALARIM OLDU
- EVET KISALDI
- TAMAMEN KESİLDİ

KAÇINCI DOZDAN SONRA DEĞİŞİKLİK OLDU? *

- OLMADI
- İLK
- 2.DOZDAN SONRA
- 3.
- BİRDEN FAZLA KEZ

AŞI SONRASI ADETLERİNİZDE AĞRI OLDU MU

- EVET
- HAYIR

EK YAN ETKİ OLDU MU? VARSA BELİRTİNİZ *

AŞI SONRASI DEĞİŞİKLİK NEDENİYLE KADIN-DOĞUM DOKTORUNA BAŞVURDUNUZ MU? *

- EVET
- HAYIR

BAŞVURDUYSANIZ BİR PROBLEM TESPİT EDİLDİ Mİ? *

- BAŞVURMADIM
- EVET SORUN SAPTANDI
- HAYIR BİR SORUN SAPTANMADI

SORUN SAPTANDIYSA NEDİR?

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