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Prevalence of menstrual irregularities after coronavirus disease 2019 vaccination: A cross-sectional study in the Eastern Province, Saudi Arabia

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Abstract:

BACKGROUND: Reports indicate that there are menstrual cycle disturbances following coronavirus disease 2019 (COVID-19) vaccination. The present study explored the prevalence of menstrual irregularities after COVID-19 vaccination and the association of menstrual irregularities with vaccine type, doses, immediate adverse effects, history of COVID-19 infection, and its severity.

MATERIALS AND METHODS: For this cross-sectional study, 406 women of reproductive age completed an online survey about the postvaccine changes in their menstruation (cycle duration, bleeding days, and bleeding amount), COVID-19 vaccine history (doses, type of vaccine, and immediate adverse effects), history of COVID-19 infection, and its severity. Data was analyzed using SPSS; descriptive statistics were computed and Chi-square test, and binary logistic regression analysis were performed.

RESULTS: Of the total 406 women, 45% reported postvaccine changes in their menstrual cycle. The most common menstrual change was increased dysmenorrhea (68%), followed by an increase in the length of the cycle (52%). There was a significant association between postvaccine menstrual changes and the age, marital status, and family history of menstrual irregularities. No association was observed between postvaccine menstrual changes and COVID-19 vaccine-and COVID-19 infection-related variables. As per the best-fit model of our predictors, the odds of having postvaccine menstrual changes were 0.41 times less in "single" women (confidence interval [CI] = 0.26–0.27; $P < 0.001$) and 1.714 times greater in women who had a "family history of menstrual irregularities" (CI = 1.092–2.690; $P = 0.02$), respectively.

CONCLUSION: A substantial number of women complained of postvaccine menstrual changes regardless of their age, type of COVID-19 vaccine, doses, immediate adverse effects, and COVID-19 infection history/severity. Being "single" decreased the probability, whereas having a family history of menstrual irregularities increased the probability significantly of having postvaccine menstrual changes.

Keywords:

Coronavirus disease 2019 vaccines, dysmenorrhea, menstrual cycle, menstruation disturbances, SARS-CoV-2

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Introduction

The menstrual cycle is regulated by the hypothalamo-pituitary-gonadal axis and can be disturbed by physical/emotional stress.[1] Vaccination could act as a physical stressor because it triggers an immune response.[2] Several studies have reported menstrual cycle irregularities following coronavirus disease 2019 (COVID-19)

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vaccination. In a UK-based survey involving 4989 participants, 20% of the study participants admitted having menstrual disturbances after the COVID-19 vaccine.[3] A USA-based study reported an increase of half a day or 2 days in the cycle length of women who had a single or double dose of vaccine.[4] Caspersen *et al*.,[5] reported increased risks of heavier or more prolonged bleeding in the first cycle after the COVID-19 vaccine in a sample of 12–15-year-old Norwegian girls.

In a study involving the MENA region (mainly Jordan, United Arab Emirates and Saudi Arabia), 66.3% of the study sample reported menstrual irregularities after receiving the COVID-19 vaccine, especially the first dose (46.7%).[6] A cross-sectional study involving 4942 women across six Arab countries concluded that the COVID-19 vaccination may have had an adverse effect on menstruation in terms of pain and heavy bleeding.[7] In another study involving 1254 Arab women, 83.5% of women reported menstrual changes post-COVID-19 vaccination.[8] Morsi *et al*.,[9] collected data from 731 women vaccinated with mRNA Vaccine (Pfizer-BioNTech), 50.9% of whom complained of postvaccine menstrual changes. The changes in the menstrual cycle correlated with their age. Qashqari *et al*.,[10] reported postvaccine menstrual changes in 46.7% of the study participants. In a study by Almousa[11] involving 343 women, 60.3% of participants reported menstrual irregularities postvaccination, namely disturbances in the duration of the cycle. For about 14% of the participants, the cycles ran longer than 35 days, and for about 10.2% of participants, they were shorter than 25 days. COVID-19 vaccination was associated with changes in the menstrual cycle length, painful menstruation, and heavy flow, especially in the 15–24 age group. On the other hand, Ljung *et al*., evaluated the risks of menstrual disturbances and bleeding after COVID-19 vaccination in 2,946,448 women aged 12–74 years from December 2020 to February 2022.[12] This large study showed no changes in the menstrual cycle after vaccinations.

In most studies that explored menstrual irregularities following COVID-19 vaccination, the participants had received a single dose of the vaccine or followed up for 1–3 months only. There was no concept of boosters or cross-vaccination (mix and match method) then.[13,14] As menstrual disturbances may have long-term effects on female fertility and vaccine acceptance,[15] it is imperative to explore the effects of booster doses, mixed vaccines, and any long-term links/associations between COVID-19 vaccination and menstrual cycle disturbances. This should help maintain the confidence of young women in vaccination programs.

The current study was designed to find the frequency of postvaccine menstrual changes in women and explore the association/link of menstrual changes with variables related to the COVID-19 vaccine (type, doses, and immediate adverse effects of vaccine), COVID-19 infection history and its severity, and prevaccine menstrual history (menarche, family history of menstrual irregularities, etc.).

Materials and Methods

The data for this cross-sectional study were collected from January 2023 to March 2023. The potential study participants were women in the reproductive age groups (15–49 years old), living in the Eastern Province, who had taken more than one dose of the COVID-19 vaccine and had had at least three menstrual cycles after the last dose of COVID-19 vaccine. Women with any one of the following conditions were excluded: irregular menstruation, pregnancy, lactation, menopause, pre-menopause, use of hormonal contraception before, during, or after the vaccination, hysterectomy, and pre-existing illnesses (premature ovarian failure, polycystic ovarian disease, thyroid imbalance disease, fibroids, endometriosis, adenomyosis, hypothalamic amenorrhea). Ethical approval was obtained from the Institutional Review Board vide Letter Number IRB-2023-01-017 dated 17/01/2023 and informed written consent was taken from all participants in the study.

A survey based on the studies of Muhaidat *et al*.,[6] and Alahmadi *et al*.,[16] was created in Google Forms, eliciting information on postvaccine menstrual cycle changes (i.e., changes in the duration of the cycle, bleeding days, bleeding amount, and side pains/dysmenorrhea), COVID-19 vaccine history (number of doses, type of vaccine, and any immediate adverse effects), history of COVID-19 infection and its severity, history of menstrual irregularities in the family, and age of menarche and demographic variables. Survey items were piloted on 18–20 women to remove any uncertainty. The reliability was checked through the test–retest technique. The validity was checked through face validity by four experts. The survey link was shared with participants through various social media platforms such as WhatsApp, telegram, and twitter.

A sample size of 384 was calculated using a free online sample calculator (https://www.openepi.com/SampleSize/SSPropor.htm) (accepted margins of error 5%, the confidence interval 95%, the approximation of population size 1,090,268.[17]).

Data were analyzed using the Statistical Package for the Social Sciences software (IBM SPSS Statistics for Windows, Version 27, IBM Corporation, Armonk, NY, USA). Frequencies were calculated through descriptive statistics. Chi-square test was used to find association

between menstrual cycle changes and study variables. A significant Chi-square association was followed by Phi and Crammer's V coefficients whose values were interpreted as described by Akoglu.[18] In binary logistic regression for univariate and multivariate analysis, the presence or absence of menstrual cycle changes was the dependent variable (DV), and the remaining variables were predictors/independent variables (IV). When IV had more than two categories, it was dichotomized (e.g., age, marital status, and age of menarche). To find the best-fit model for our proposed predictors, the selection method "Forward LR" was used. $P < 0.05$ was considered statistically significant.

Results

Of the 771 participants, 365 were excluded on account of one or more exclusion criteria, so 406 participants were included in the final analysis. The details about inclusion/exclusion are available in Figure 1. The characteristics of the study participants are shown in Table 1. Most of the study participants (≥70%) were 15–25 years old and "single." 53.6% of participants had a history of COVID-19 infection. Of the COVID-19 positive women, 73% of the women had mild symptoms (fever, cough, sore throat, malaise, headache, muscle ache, nausea, vomiting, diarrhea, and loss of taste and smell), and 2% had severe symptoms (use of an oxygen machine or admission to hospital). 83% of women had received three doses of the vaccine. Most women (64.8%) received Pfizer-BioNTech only, followed by 29.8% of women who received mixed (more than one type) vaccines. About half

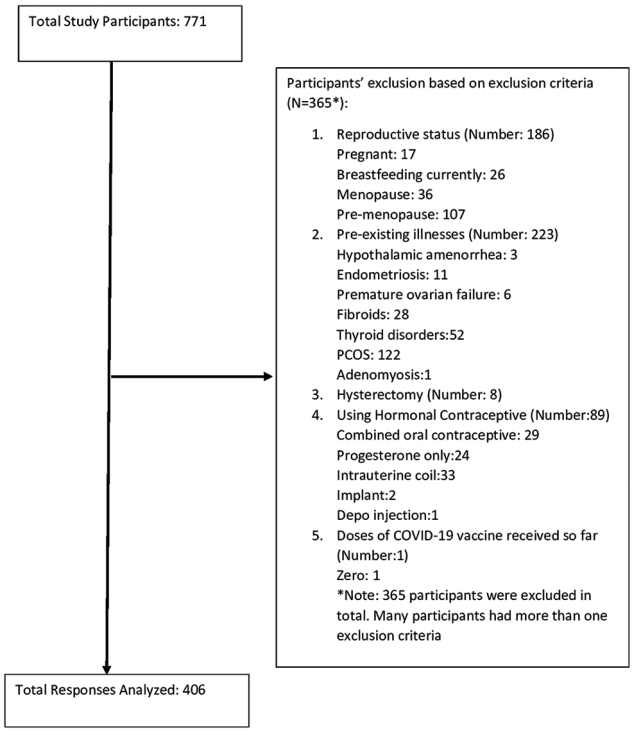

Figure 1: Flow chart for selection of study participants
PCOS = Polycystic ovary syndrome, COVID-19 = Coronavirus disease 2019

Table 1: Characteristics of study participants (*n*=406)

Variables	*N* (%)
Age (years)	
15–25	282 (69.5)
26–35	71 (17.5)
36–49	53 (13.1)
Social status	
Single	299 (73.6)
Married	98 (24.2)
Divorced	5 (1.2)
Widowed	4 (1.0)
Age of menarche (years)	
<9	5 (1.2)
9–10	64 (15.8)
11–12	184 (45.3)
13–14	119 (29.3)
15–16	30 (7.4)
>16	4 (1.0)
Family history of menstrual irregularities	
No	296 (72.9)
Yes	110 (27.1)
How many doses of COVID-19 vaccine have you received?	
Two	61 (15.0)
Three	337 (83.0)
Four	8 (2.0)
Which of the following vaccines have you received?	
mRNA vaccine (Pfizer-BioNTech)	263 (64.8)
Mix and match (>1 type)	121 (29.8)
Recombinant vaccine (Oxford/AstraZeneca)	20 (5.0)
mRNA vaccine (Moderna)	1 (0.2)
Adenovirus vaccine (Johnson and Johnson)	1 (0.2)
Number of months passed since the last dose?	
4–8	73 (17.9)
9–12	145 (35.7)
>12	188 (46.3)
Any immediate side-effects of COVID-19 vaccine?	
Yes	336 (83.0)
No	70 (17.0)
History of COVID-19 infection?	
Yes	218 (53.7)
No	188 (46.3)
If your answer to the previous question was "yes," what was the severity of your COVID-19 symptoms? (*n*=218)	
I did not have any symptoms	25 (12.0)
Mild symptoms (fever, cough, sore throat, malaise, headache, muscle ache, nausea, vomiting, diarrhea, loss of taste and smell)	161 (73.0)
Moderate symptoms (difficulty in breathing)	28 (13.0)
Severe symptoms (use of an oxygen machine or admission to hospital)	4 (2.0)
Postvaccine menstrual cycle changes	
Yes	198 (49.0)
No	208 (51.0)

COVID-19=Coronavirus disease 2019

of the participants (49%) admitted postvaccine changes in their menstrual cycle.

Characteristics of postvaccine menstrual changes in subjects are shown in Table 2. The most common menstrual change was increased dysmenorrhea (68%), followed by an increase in the length of the cycle (52%) and increased bleeding (45%). Forty-seven percent and 43% of the women noticed menstrual cycle changes after 3rd and 2nd doses, respectively. 59% of the participants are still experiencing menstrual disturbances.

The Chi-square test [Table 3] revealed a lack of association of menstrual cycle changes with vaccine-related variables (type, dosage, and immediate adverse effects), COVID-19 infection history, and severity. Menstrual cycle changes were associated with age, marital status, and a family history of menstrual irregularities.

Table 2: Nature of postvaccine menstrual changes (*n*=198)

Menstrual cycle changes	*N* (%)
Cycle length	
Increase (delayed)	102 (52.0)
Decrease (early)	63 (31.0)
No change	33 (17.0)
Number of bleeding days	
Increase	65 (33.0)
Decrease	82 (41.0)
No change	51 (26.0)
Amount of bleeding	
Increase	88 (45.0)
Decrease	86 (43.0)
No change	24 (12.0)
Dysmenorrhea	
Increase	134 (68.0)
Decrease	22 (11.0)
No change	42 (21.0)
After which dose of COVID-19 vaccine did you first notice a change in menstrual cycle?	
One	17 (9.0)
Two	86 (43.0)
Three	92 (47.0)
Four	3 (1.0)
For how many cycles postvaccine have the menstrual changes persisted?	
One cycle	19 (9.5)
Two–four cycles	45 (23.0)
Five–ten cycles	8 (4.0)
>10 cycles	9 (4.5)
Still experiencing	117 (59.0)
Number of months since the last dose?	
4–8	37 (19.0)
9–12	66 (33.0)
>12	95 (48.0)

COVID-19=Coronavirus disease 2019

A binary logistic regression test (univariate and multivariate) was employed to explore the odds ratios (OR) between the DV (Menstrual cycle changes "Yes" and "No" category) and IV (age, marital status, age of menarche, family history of menstrual cycle irregularities, COVID-19 infection, and vaccine-related variables) [Table 4]. The odds of having postvaccine menstrual changes ("Yes" category) were 0.44 and 0.42 times less in young (15–25 years old) and "single" women ($P < 0.001$). On the other hand, the odds of having postvaccine menstrual changes were 1.68 times greater in women who had a "family history of menstrual irregularities" ($P = 0.02$). In multivariate regression analysis, "age" and the "family history of menstrual irregularities" were the only variables that maintained their significant predictive value ($P = 0.048$ and $P = 0.011$, respectively).

In binary logistic regression analysis, when all the predictors were entered simultaneously (Method used "Enter"), the model showed significant improvement ($P = 0.001$) in the fit as compared to the null model (Model 0). This confirmed that our proposed model was a good fit. The Hosmer and Lemeshow test also confirmed the good fit of our model ($P = 0.484$). Nagelkerke R^2 (Pseudo R^2) values of 0.084 indicated that 8.4% variation in the DV can be accounted to the predictors (IV). From the classification tables of regression analysis, the percentage accuracy in classification was found to be 58.6%. To find the best-fit model for our predictor, all the predictors were entered simultaneously again, but the selection method used was forward stepwise likelihood ratio "Forward LR" [Table 5]. The "marital status" of the women was found to be the strongest predictor (Model 1). Being "single" significantly decreased the probability/likelihood of having postvaccine menstrual cycle changes (OR = 0.418, $P < 0.001$). The next strongest predictor was "family history of menstrual irregularities," which increased the likelihood of menstrual changes 1.714 times ($P = 0.019$). Model 2 having both the predictors (marital status and family history of menstrual irregularities) was a better fit than Model 1 which contained marital status as the only predictor.

Discussion

In the current study, 49% of participants complained of menstrual changes after COVID-19 vaccine. The most common menstrual change was an increase in dysmenorrhea (68%), followed by longer cycle length (52%) and heavier bleeding (45%).

Our results are in accordance with an Italian study[19] in which 50%–60% of women reported vaccine-induced

Table 3: Association between menstrual cycle changes and coronavirus disease 2019 vaccine parameters, coronavirus disease 2019 infection history, and demographic characteristics

Characteristics	Menstrual changes		*P*-value
	Yes (*n*=198) *N* (%)	No (*n*=208) *N* (%)	
Age (years)			
15–25	120 (61.0)	162 (78.0)	0.001[a]
26–35	46 (23.0)	25 (12.0)	
36–49	32 (16.0)	21 (10.0)	
Marital status			
Single	129 (65.2)	170 (82.0)	0.002[b]
Married	62 (31.3)	36 (17.0)	
Divorced	4 (2.0)	1 (0.5)	
Widowed	3 (1.5)	1 (0.5)	
Age of menarche (years)			
<9	3 (1.5)	2 (1.0)	0.76
9–10	33 (17.0)	31 (15.0)	
11–12	84 (42.0)	100 (48.0)	
13–14	61 (31.0)	58 (28.0)	
15–16	16 (8.0)	14 (7.0)	
>16	1 (0.5)	3 (1.0)	
Family history of menstrual irregularities			
No	134 (68.0)	162 (78.0)	0.02[c]
Yes	64 (32.0)	46 (22.0)	
Type of COVID-19 vaccine received?			
mRNA vaccine (Pfizer-BioNTech)	128 (65)	135 (65.0)	0.67
mRNA vaccine (Moderna)	1 (0.5)	0	
Recombinant vaccine (Oxford-AstraZeneca)	11 (5.5)	9 (4.3)	
Adenovirus vaccine (Johnson and Johnson)	0	1 (0.5)	
Mix and match (>1 type)	58 (29.0)	63 (30.2)	
Number of COVID-19 vaccine doses received?			
Two	33 (17.0)	28 (13.5)	0.20
Three	159 (80.0)	178 (85.5)	
Four	6 (3.0)	2 (1.0)	
Any immediate side-effects of COVID-19 vaccine			
No	29 (15.0)	41 (20.0)	0.18
Yes	169 (85.0)	167 (80.0)	
History of COVID-19 infection?			
No	88 (44.0)	100 (48.0)	0.49
Yes	110 (56.0)	108 (52.0)	
If your answer to the previous question was "yes," what was the severity of your COVID-19 symptoms?			
I did not have any symptoms	17 (15.0)	8 (7.0)	0.36
Mild symptoms (fever, cough, sore throat, etc.)	79 (72.0)	82 (76.0)	
Moderate symptoms (difficulty in breathing)	12 (11.0)	16 (15.0)	
Severe symptoms (use of an oxygen machine or admission to hospital)	2 (2.0)	2 (2.0)	

[a]0.18 (strong association), [b]0.19 (strong association), [c]0.12 (moderate association). Phi Crammer's V coefficients. COVID-19=Coronavirus disease 2019

changes in menstruation, regardless of the vaccine type. The menstrual irregularities increased after the second dose. In a study done in the US,[20] 42% of women in a large sample of 39,129 women complained of heavier menstrual bleeding after COVID-19 vaccination. In a Norwegian study, 25.1% of girls reported at least one menstrual change after receiving the first dose of the vaccine. In a study conducted in Spain involving 14,153 fully vaccinated women, 78% of the respondents reported postvaccine menstrual changes.[21] We noticed wide variations in the pattern of vaccine-induced menstrual changes. The cause of variation could be the time interval between the two vaccines, the type of vaccine, and the menstrual cycle phase in which participants got vaccinated.[22] For example, the gap between the first two doses of the vaccine is 3–4 weeks in US and Norway. However, this gap is 8 weeks in UK vaccination schedule. Women in US and Norway could, therefore, receive both doses in the same cycle, whereas this was not possible with the women in the UK.

Table 4: Univariate and multivariate logistic regression analysis for association between menstrual cycle changes and sociodemographic characteristics and coronavirus disease 2019 vaccine parameter (*n*=406)

Variables	Univariate analysis			
	Crude OR (95% CI OR)	*P*-value	Adjusted OR (95% CI OR)	*P*-value
Age (years)				
15–25	0.437 (0.28–0.67)	<0.001	0.524 (0.28–1.00)	0.048
26–49	Reference		Reference	
Marital status				
Single	0.418 (0.27–0.66)	<0.001	0.661 (0.34–1.27)	0.216
Married/divorced/widowed	Reference		Reference	
Age of menarche (years)				
≤12	0.868 (0.58–1.30)	0.488	1.020 (0.67–1.56)	0.926
≥13	Reference		Reference	
Family history of menstrual irregularities				
Yes	1.682 (1.08–2.62)	0.021	1.831 (1.15–2.92)	0.011
No	Reference		Reference	
Type of COVID-19 vaccine received?				
mRNA vaccine (Pfizer-BioNTech)	0.989 (0.66–1.47)	0.957	1.070 (0.70–1.64)	0.756
Mix and match Moderna/Oxford AstraZeneca	Reference		Reference	
Number of COVID-19 vaccine doses received?				
Two	1.234 (0.72–2.12)	0.446	1.125 (0.64–1.99)	0.685
Three–four	Reference		Reference	
Any immediate side-effects of COVID-19 vaccine				
Yes	1.431 (0.85–2.41)	0.178	1.551 (0.90–2.67)	0.113
No	Reference		Reference	
History of COVID-19 infection?				
Yes	1.157 (0.78–1.71)	0.463	1.037 (0.69–1.56)	0.860
No	Reference		Reference	

CI=Confidence interval, OR=Odds ratio, SE=Standard error, COVID-19=Coronavirus disease 2019

Table 5: Final logistic regression model: Factors associated with menstrual cycle changes after receiving corona virus disease 2019 vaccine (*n*=406)

Correlates	Model 1				Model 2			
	OR	CI	SE	*P*-value	OR	CI	SE	*P*-value
Results of correlates								
Constant	1.816	-	0.202	0.003	1.583		0.210	0.029
Marital status	0.418	0.265–0.660	0.233	<0.001	0.413	0.261–0.265	0.235	<0.001
Family history of menstrual irregularities	-	-	-	-	1.714	1.092–2.690	0.230	0.019
Results of the overall model								
χ^2	14.505 (df=1, *P*<0.001)				20.063 (df=2, *P*<0.001)			
R^2 (Cox and Snell)	0.035				0.048			
R^2 (Nagelkerke)	0.047				0.064			
ΔR^2	-				0.17			

CI=Confidence interval, OR=Odds ratio, SE=Standard error

Menstruation is a localized inflammatory and hemorrhagic event regulated by the hypothalamo-pituitary-ovarian axis.[23] Lee *et al*.,[20] suggested that COVID-19 vaccination probably affected the inflammatory pathways and not hormonal pathways. They did not find a difference in vaccine-induced menstrual changes between the participants with and without hormonal contraceptives. If menstrual changes were due to vaccine-induced hormonal disruption, women taking exogenous hormones in the form of contraception would not exhibit menstrual changes. Nazir *et al*.,[24] suggested that the higher and faster immune response generated by the COVID-19 mRNA vaccines might be responsible for the abnormal activation of the innate immune cells of the endometrium, resulting in menstrual irregularities. Human papilloma virus vaccine (HPV) was also reported to cause menstrual disturbances.[25,26] However, studies reporting HPV-induced menstrual changes are few compared with the innumerable studies on COVID-19 vaccine-induced menstrual changes. COVID-19 vaccination has been on a larger scale and mandatory for traveling, attending workplaces, and commercial sites. This massive vaccination may have highlighted a previously underrecognized side effect of immunogenic vaccines administered in adulthood.

The current study did not find any association between menstrual cycle changes and COVID-19 vaccine characteristics (type, doses, and immediate adverse effects), and COVID-19 infection history and its severity. Our results agree with the European Medicines Agency which reported a lack of association between the COVID-19 vaccines and menstrual disorders.[27] Laganà *et al*.,[19] also reported that vaccine-induced menstrual changes were independent of COVID-19 vaccine type. Contrary to our results, Edelman *et al*.,[4] reported an association between COVID-19 vaccine and menstrual changes. This variance could be due to the difference in the study designs. Participants in Edelman's study were vaccinated and nonvaccinated women, whereas our study was of vaccinated women only. Additionally, they excluded the mRNA Oxford/AstraZeneca vaccine from their analysis whereas 5% of our participants had received mRNA Oxford/AstraZeneca. Our best-fit model showed significantly decreased chances of postvaccine menstrual changes in "single" women and significantly increased chances in women who had a "positive family history of menstrual irregularities" (ORs = 0.41 and ORs = 1.714; $P < 0.001$ and $P = 0.02$, respectively).

Our study is limited by recall bias, small sample size, and a wide age range (15–49 years old). Usually, menstrual irregularities start from ≥40 years of age. Furthermore, we did not ask the respondents about the phase of the menstrual cycle in which they received the vaccine doses. Finally, the mental status of the respondents was not assessed. In sensitive, anxious, and nervous women, any stress of unknown cause can lead to menstrual irregularities.[28]

Conclusion

Many women experienced menstrual changes after COVID-19 vaccination regardless of their age, vaccine type, doses, immediate adverse effects, and COVID-19 infection history/severity. Being single decreased the probability, whereas having a family history of menstrual irregularities increased the probability of having postvaccine menstrual changes.

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Conflicts of interest
There are no conflicts of interest.

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