GYNECOLOGY

A prospective study of the association between SARS-CoV-2 infection and COVID-19 vaccination with changes in usual menstrual cycle characteristics

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BACKGROUND: Despite anecdotal reports, the impacts of SARS-CoV-2 infection or COVID-19 vaccination on menstrual health have not been systemically investigated.

OBJECTIVE: This study aimed to examine the associations of SARS-CoV-2 infection and COVID-19 vaccination with menstrual cycle characteristics.

STUDY DESIGN: This study prospectively observed 3858 premenopausal women in the Nurses' Health Study 3 living in the United States or Canada who received biannual follow-up questionnaires between January 2011 and December 2021 and completed additional monthly and quarterly surveys related to the COVID-19 pandemic between April 2020 and November 2021. History of positive SARS-CoV-2 test, COVID-19 vaccination status, and vaccine type were self-reported in surveys conducted in 2020 and 2021. Current menstrual cycle length and regularity "before COVID-19" were reported at baseline between 2011 and 2016, and current menstrual cycle length and regularity "after COVID-19" were reported in late 2021. Pre- to post-COVID change in menstrual cycle length and regularity was calculated between reports. Logistic or multinomial logistic regression models were used to assess the associations between SARS-CoV-2 infection and COVID-19 vaccination and change in menstrual cycle characteristics.

RESULTS: The median age at baseline and the median age at end of follow-up were 33 years (range, 21—51) and 42 years (range, 27—56), respectively, with a median follow-up time of 9.2 years. This study documented 421 SARS-CoV-2 infections (10.9%) and 3527 vaccinations (91.4%) during follow-up. Vaccinated women had a higher risk of increased cycle length than unvaccinated women (odds ratio, 1.48; 95% confidence interval, 1.00—2.19), after adjusting for sociodemographic and behavioral factors. These associations were similar after in addition accounting for pandemic-related stress. COVID-19 vaccination was only associated with change to longer cycles in the first 6 months after vaccination (0—6 months: odds ratio, 1.67 [95% confidence interval, 1.05—2.64]; 7—9 months: odds ratio, 1.43 [95% confidence interval, 0.96—2.14]; >9 months: odds ratio, 1.41 [95% confidence interval, 0.91—2.18]) and among women whose cycles were short, long, or irregular before vaccination (odds ratio, 2.82 [95% confidence interval, 1.51—5.27]; odds ratio, 1.10 [95% confidence interval, 0.68—1.77] for women with normal length, regular cycles before vaccination). Messenger RNA and adenovirus-vectored vaccines were both associated with this change. SARS-CoV-2 infection was not associated with changes in usual menstrual cycle characteristics.

CONCLUSION: COVID-19 vaccination may be associated with short-term changes in usual menstrual cycle length, particularly among women whose cycles were short, long, or irregular before vaccination. The results underscored the importance of monitoring menstrual health in vaccine clinical trials. Future work should examine the potential biological mechanisms.

Key words: COVID-19 vaccine, menstrual cycle change, menstrual cycle length, menstrual health, SARS-CoV-2 infection

Introduction

SARS-CoV-2 has infected more than 48 million people in the United States as of December 2021.[1] The Centers for Disease Control and Prevention recommends COVID-19 vaccination for all eligible persons, including those who have been previously infected.[2] As of December 2021, 71% of the US population has received at least 1 dose.[3] Vaccines approved in the United States have a profile for mild to moderate adverse events, most of which are injection site pain, headache, fatigue, and myalgia.[4–6] Anecdotal reports that emerged in 2021 suggested that SARS-CoV-2 infection or COVID-19 vaccination could result in changes in menstrual cycles, raising widespread media attention and public interest, including a rapid response from the US National Institutes of Health by funding a COVID-19 and menstrual health network.[7–9] In addition, concerns and unfounded information concerning COVID-19 vaccination impairing reproductive health have become a major reason for vaccine mistrust in the general population and vaccine hesitancy among children, adolescents, and women of reproductive age.[10–12] Therefore, the reproductive safety of COVID-19 vaccination is an emerging public health issue. Nevertheless, the impacts of SARS-CoV-2 infection and COVID-19 vaccination on menstrual health have not been systemically investigated.

Menstruation is tightly regulated by the hypothalamic-pituitary-ovarian (HPO) axis and can reflect women's overall health.[13] The menstrual cycle can be sensitive to a wide variety of inputs, including stress, weight change, diet, and

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AJOG at a Glance

Why was this study conducted?
Despite the increasing public questions and mistrust concerning the potential adverse reproductive impacts of COVID-19 infection and vaccination, there is still limited research investigating this topic.

Key findings
In this prospective study of 3858 premenopausal nurses, vaccination against COVID-19 was associated with a 1.7-fold increased risk of a short-term (<6 months) increase in usual menstrual cycle length, especially among women who had irregular, short, or long prevaccination menstrual cycles. These associations were observed for both messenger RNA and adenovirus-vectored vaccines and were not explained by pandemic-related behavioral changes and mental stress. SARS-CoV-2 infection was not related to changes in menstrual characteristics.

What does this add to what is known?
Our findings have implications for vaccine developers, clinicians, and researchers to better understand the possible menstrual cycle changes after vaccination and to inform patient expectations.

medication use, all of which changed during the COVID-19 pandemic.[14] Acute viral infection has been associated with disturbances in menstruation (eg, dysmenorrhea or short or long cycles) through mechanisms involving immune dysregulation and direct inflammation of the ovaries.[15,16] Moreover, new-onset menstrual abnormalities have been reported after vaccination against typhoid and hepatitis B.[17,18] Previous studies have found an increase in changes in menstrual cycle characteristics during the COVID-19 pandemic or specifically after SARS-CoV-2 infection or COVID-19 vaccination, although findings are inconsistent.[19–28] However, this limited literature is severely hampered by cross-sectional designs that do not allow before and after comparisons and lack of comparison with uninfected or unvaccinated women and fails to account for pandemic-related stress and behavioral changes.[19–28]

Here, we prospectively examined the associations of SARS-CoV-2 infection and COVID-19 vaccination with changes in usual menstrual cycle characteristics, among premenopausal health professionals participating in an ongoing prospective cohort study. In addition, we examined the duration of such changes, potential differences by vaccine type, and whether pandemic-related stress (eg, distress, psychological well-being, or local COVID-19 burden) accounted for changes in usual menstrual cycle characteristics.

Materials and Methods

Study design and population

The Nurses' Health Study 3 is an ongoing Internet-based open cohort study established in 2010, which includes female and male nurses and nursing students from the United States and Canada.[29] As of December 2021, 48,907 female and 856 male participants born on or after January 1, 1965, and aged ≥18 years had enrolled. Follow-up questionnaires were sent to participants approximately every 6 months. The most recent questionnaire (MOD12) was launched in July 2021 and contained questions regarding SARS-CoV-2 infection and COVID-19 vaccination status. MOD2 (baseline, starting January 2011) and MOD12 (end of follow-up, December 2021) questionnaires collected information about current menstrual cycle characteristics. Moreover, we administered a series of supplementary questionnaires assessing health and well-being during the pandemic (COVID-19 substudy) beginning in April 2020. The 12,323 participants (40% of 30,643 invited) who completed the first supplementary COVID-19 questionnaire were asked to complete monthly and quarterly surveys until November 2021.

Women were eligible for this study if they completed the Module 2 (MOD2) and Module 12 (MOD12) questionnaires before December 8, 2021 (n=9345), and had participated in the COVID-19 substudy or completed COVID-19 questions in MOD12 (n=9167). Women were excluded if they reported the use of hormonal contraception in MOD12 (n=717), had reached menopause (n=2836), had missing menstrual cycle information on either MOD2 (n=1135) or MOD12 (n=13), were pregnant or had been pregnant in the 6 months preceding menstrual cycle assessment (n=607), or were unsure about vaccination status (blinded clinical trial participant, n=1), leaving 3858 participants in the analysis (Figure). The study was approved by the institutional review boards of Brigham and Women's Hospital and the Harvard School of Public Health. Return of the completed questionnaires implied consent.

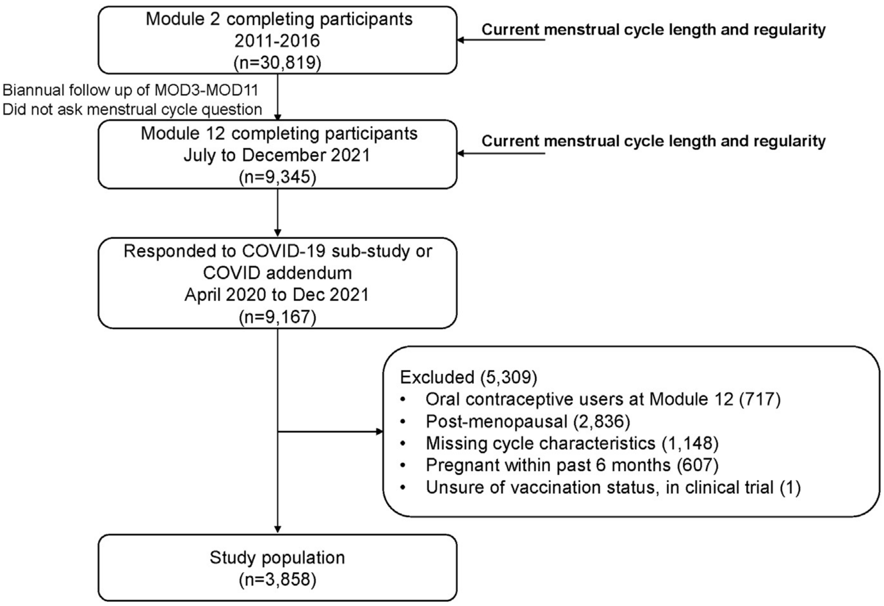
Menstrual cycle characteristics

Prepandemic and pandemic usual menstrual cycle length and regularity were measured on the MOD2 and MOD12 questionnaires, respectively, using the same set of questions. Participants were asked to report the usual length (<21 days, 21–25 days, 26–31 days, 32–39 days, 40–50 days, >50 days or too irregular to count, or no period or amenorrhea) and regularity (very regular [within 3 days], regular [within 5–7 days], usually irregular, always irregular, or no period or amenorrhea) of their menstrual cycles. Change in menstrual cycle length and regularity was derived by calculating the difference in length or regularity that was reported at 2 time points: a pre-COVID assessment (MOD2) and a post-COVID assessment (MOD12). Self-report of usual menstrual cycle characteristics has been previously validated.[30,31]

SARS-CoV-2 infection and COVID-19 vaccination status

The date of a positive SARS-CoV-2 diagnostic test since March 1, 2020, was

FIGURE
Flowchart of the study population selection, the Nurses' Health Study 3



Participants were asked to report the usual length (<21 days, 21—25 days, 26—31 days, 32—39 days, 40—50 days, >50 days or too irregular to count, or no period or amenorrhea) and regularity (very regular [within 3 days], regular [within 5—7 days], usually irregular, always irregular, or no period or amenorrhea) of their menstrual cycle.

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self-reported on MOD12 and each of the COVID-19 substudy questionnaires. COVID-19 vaccination status, vaccine type, and date of the first dose were self-reported on MOD12 and the second and third quarterly follow-up of the COVID-19 substudy.

Covariates

Demographic and socioeconomic characteristics, including age, race and ethnicity, height, weight, education, smoking status, and country or state of residence were self-reported at enrollment. History of gynecologic diseases was self-reported on MOD12. Current healthcare working status was reported on the COVID-19 substudy baseline survey. Depressive symptoms, anxiety symptoms, perceived stress, posttraumatic stress disorder symptoms, and worry about COVID-19 were measured repeatedly in the COVID-19 substudy (Table S1). County- and date-specific COVID-19 mortality data were used to derive a measure of time- and place-specific COVID-19 burden.[32]

Statistical analysis

We first compared sociodemographic, behavioral, and mental health characteristics according to SARS-CoV-2 infection and COVID-19 vaccination status at the end of follow-up. To examine the cross-sectional associations between SARS-CoV-2 infection and COVID-19 vaccination and cycle characteristics in 2021, we fitted logistic or multinomial logistic regression models with infection and vaccination each as the independent variable to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of categorized cycle characteristics in 2021, adjusting for demographic, behavioral, and socioeconomic factors; time of follow-up; and prepandemic cycle characteristics and mutually adjusting for infection and vaccination status. Among 3116 participants who were not using hormonal contraception at MOD2, we also examined changes in usual menstrual cycle length (no change, shorter, or longer) and regularity (no change, more regular, or less regular) during follow-up concerning infection and vaccination status. In a subgroup of participants (n=2209) with repeated measures of pandemic-related stress, we further adjusted for the most recently reported and the highest level of stress during follow-up, respectively. Missing categorical values for covariates were assigned to a missing indicator, and median values were assigned for continuous variables of covariates with missing values (<1%). In secondary analyses, we stratified analyses by the timing between vaccination and report of usual menstrual cycle characteristics (0—6, 7—9, or >9 months) and vaccination type (unvaccinated, messenger RNA [mRNA; Pfizer-Moderna], or adenovirus vectored [Janssen]) to examine whether the change in usual menstrual cycle characteristics was transient and if there were potential differences by vaccine type. In this analysis, we excluded participants who reported receiving the AstraZeneca vaccine (n=9) and participants who did not report vaccine type (n=6). Lastly, we performed 4 sensitivity analyses. First, we excluded 1354 women more than 45 years old at the end of follow-up to minimize the effect of menstrual changes during the menopausal transition. Second, to reduce outcome misclassification, we excluded 119 women reporting "no period or amenorrhea" at any time point. Third, we excluded 348 women with self-reported gynecologic conditions known to cause menstrual disorders, including polycystic ovary syndrome, uterine fibroids, and endometriosis. Fourth, to examine whether women with irregular or short or long cycles were more susceptible to menstrual cycle changes, we stratified analyses by prepandemic menstrual cycle characteristics. All analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC). All statistical tests were 2-sided, and statistical significance was defined as $P<.05$.

Results

The 3858 women were predominantly White (89.7%) and resided in the United States (97.7%). The median age at baseline and the median age at end of

TABLE 1
Demographic, socioeconomic, and health characteristics according to SARS-CoV-2 infection and COVID-19 vaccination status between January 2011 and December 2021, 2021, the Nurses' Health Study 3 (N=3858)

Characteristic	SARS-CoV-2 infection No (n=3437)	SARS-CoV-2 infection Yes (n=421)	COVID-19 vaccination No (n=331)	COVID-19 vaccination Yes (n=3527)
Age at baseline (y),[a] mean (SD)	33.4 (6.3)	33.4 (6.6)	32.5 (5.9)	33.4 (6.3)
Age at end of follow-up (y),[b] mean (SD)	42.4 (6.3)	42.4 (6.7)	41.8 (5.9)	42.5 (6.4)
Race and ethnicity, n (%)				
Hispanic	133 (3.9)	19 (4.5)	18 (5.4)	134 (3.8)
Non-Hispanic White	3082 (89.7)	378 (89.8)	283 (85.5)	3177 (90.1)
Others	205 (6.0)	18 (4.3)	27 (8.2)	196 (5.6)
Region, n (%)				
West	813 (23.7)	69 (16.4)	67 (20.2)	815 (23.1)
Midwest	941 (27.4)	146 (34.7)	120 (36.3)	967 (27.4)
South	714 (20.8)	107 (25.4)	83 (25.1)	738 (20.9)
Northeast	818 (23.8)	91 (21.6)	52 (15.7)	857 (24.3)
Military or outside of the United States	151 (4.4)	8 (1.9)	9 (2.7)	150 (4.3)
BMI at baseline (kg/m^2),[a] mean (SD)	25.5 (5.9)	27.2 (7.0)	25.8 (5.8)	25.7 (6.1)
BMI at end of follow-up (kg/m^2),[b] mean (SD)	27.4 (8.8)	29.2 (7.7)	27.4 (6.2)	27.6 (8.9)
Weight change (lb), mean (SD)	5.0 (17.7)	5.4 (11.2)	4.4 (9.2)	5.1 (17.7)
Smoking status, n (%)				
Never	3262 (95.0)	396 (94.1)	307 (92.8)	3351 (95.1)
Past	87 (2.5)	16 (3.8)	12 (3.6)	91 (2.6)
Current	85 (2.5)	9 (2.1)	12 (3.6)	82 (2.3)
Educational attainment, n (%)				
Nursing student, diploma in nursing, or associate's degree	198 (5.8)	27 (6.4)	49 (14.8)	176 (5.0)
Bachelor's degree	1372 (39.9)	171 (40.6)	160 (48.3)	1383 (39.2)
Master's degree	1478 (43.0)	183 (43.5)	97 (29.3)	1564 (44.4)
Doctorate degree	389 (11.3)	40 (9.5)	25 (7.6)	404 (11.4)
COVID-19 substudy participants only	No (n=2653)	Yes (n=338)	No (n=249)	Yes (n=2742)
Frontline healthcare worker, n (%)[c]	2001 (75.4)	279 (82.5)	176 (70.6)	2104 (76.7)
Depressive symptoms (PHQ-2),[d] mean (SD)	2.4 (1.7)	2.5 (1.7)	2.0 (1.6)	2.5 (1.7)
Anxiety symptoms (GAD-2),[d] mean (SD)	3.1 (1.7)	3.1 (1.6)	2.6 (1.7)	3.2 (1.7)
Posttraumatic stress symptoms (IES-6),[d] mean (SD)	1.8 (0.8)	1.7 (0.8)	1.4 (0.8)	1.8 (0.8)
Perceived stress (PSS-4),[d] mean (SD)	6.7 (3.0)	6.6 (3.0)	6.1 (2.9)	6.8 (3.0)
Worry about COVID-19,[d] n (%)				
Not at all	25 (1.0)	3 (0.9)	14 (5.6)	14 (0.5)
Not very worried	225 (8.5)	39 (11.6)	79 (31.7)	185 (6.8)
Somewhat worried	1492 (56.5)	199 (59.1)	129 (51.8)	1562 (57.2)
Very worried	901 (34.1)	96 (28.5)	27 (10.8)	970 (35.5)

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TABLE 1
Demographic, socioeconomic, and health characteristics according to SARS-CoV-2 infection and COVID-19 vaccination status between January 2011 and December 2021, 2021, the Nurses' Health Study 3 (N=3858) *(continued)*

Characteristic	SARS-CoV-2 infection No (n=3437)	SARS-CoV-2 infection Yes (n=421)	COVID-19 vaccination No (n=331)	COVID-19 vaccination Yes (n=3527)
Residential county COVID-19 mortality/10,000,[d,e] n (%)				
0.00	395 (15.7)	59 (18.0)	54 (22.5)	400 (15.4)
>0.00 to <0.25	763 (30.3)	83 (25.3)	53 (22.1)	793 (30.4)
0.25 to <0.75	621 (24.7)	91 (27.7)	74 (30.8)	638 (24.5)
0.75–7.37	739 (29.4)	95 (29.0)	59 (24.6)	775 (29.7)

Values of polytomous variables may not sum to 100% because of missing data. Missing data were 0.7% for BMI and 0.6% for race and ethnicity. The IES-6 was, adapted to be specific to COVID-19 trauma.

BMI, body mass index; *GAD-2*, 2-Item Generalized Anxiety Disorder; *IES-6*, 6-Item Impact of Events Scale; *MOD2*, Module 2; *MOD12*, Module 12; *PHQ-2*, 2-Item Patient Health Questionnaire; *PSS-4*, 4-Item Perceived Stress Scale; *SD*, standard deviation.

[a] MOD2 (2011–2016); [b] MOD12 (2021); [c] Physically working at a site providing clinical care; [d] The highest psychological distress level during follow-up; [e] County- and date-specific COVID-19 mortality data on the date of questionnaire return from the COVID-19 Data Repository by the Center for Systems Science and Engineering at Johns Hopkins University were used to derive a measure of local COVID-19 burden.

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follow-up were 33 years (range, 21–51) and 42 years (range, 27–56), respectively. The median follow-up time was 9.2 years. Approximately 1 in 10 participants (421 [10.9%]) reported a positive COVID-19 test between March 2020 and October 2021. Among these participants, 223 tested positive after the first dose of the vaccine. Most participants (3527 [91.4%]) were vaccinated by December 2021. Among women infected with SARS-CoV-2, the median time from infection to end of follow-up was 8.7 months (range, 0.2–20.1). Among vaccinated participants, the median time from vaccination to end of follow-up was 8.5 months (range, 1.0–13.4). Most women who were vaccinated during follow-up received an mRNA vaccine; women vaccinated with adenovirus-vectored vaccines were vaccinated later in follow-up (Table S2). Participants who were infected were more likely to be Hispanic, reside in the Midwest and Southern United States, have a higher body mass index, and be frontline healthcare workers, and less likely to be very worried about COVID-19 (Table 1) than participants who never reported SARS-CoV-2 infection during follow-up. Vaccinated participants were more likely to reside in the West and Northeastern United States or outside of the United States, have gained more weight during follow-up, have higher educational attainment, be frontline healthcare workers, have higher levels of pandemic-related mental health distress, and reside in an area with greater COVID-19 mortality rate than women who had not received the first dose of a COVID-19 vaccine.

Before the pandemic, among nonoral contraceptive users, 18.6% of women reported cycles of ≥32 days, and 15.0% of women reported irregular cycles. The corresponding figures were 17.6% and 22.7% in 2021. SARS-CoV-2 infection and vaccination status were not associated with cycle length or regularity in 2021 after adjusting for age, baseline cycle characteristics, and other factors (Table S3).

Overall, 2227 women reported a change in either cycle length (n=1408) or regularity (n=1735) during follow-up. COVID-19 vaccination was associated with a 48% higher risk of change to longer cycles in multivariable-adjusted models (OR, 1.48; 95% CI, 1.00–2.19) (Table S4; Table 2). SARS-CoV-2 infection was not associated with changes in cycle length or regularity. The results were similar after adjusting for cycle characteristics at baseline (Table S5), healthcare worker status, mental health status, and local COVID-19 burden (Table S6).

COVID-19 vaccination was associated with a change in cycle length only in the first 6 months after vaccination (0–6 months: OR, 1.67 [95% CI, 1.05–2.64]; 7–9 months: OR, 1.43 [95% CI, 0.96–2.14]; >9 months: OR, 1.41 [95% CI, 0.91–2.18]) (Table 3). The association of vaccination status with change in cycle length was similar for mRNA and adenovirus-vectored vaccines (Table 4). There was a suggestion that adenovirus-vectored vaccines were related to a higher likelihood of change in cycle regularity, but there were few women in this group (n=75), with a shorter duration of postvaccination follow-up. We did not detect a difference in the observed associations between brands of mRNA vaccines (Table S7).

The results were similar in analyses restricted to participants <45 years old (Table S8), excluding participants reporting "no period" at any time points (Table S9) and participants with gynecologic conditions known to affect menstrual patterns (Table S10). Nevertheless, the association between COVID-19 vaccination and increased menstrual cycle length seemed to be driven by women reporting irregular or short or long (<26 or ≥32 days) cycles at baseline (Table 5; Tables S11 and S12).

Comment

Principal findings

In this prospective study of 3858 premenopausal women, COVID-19

TABLE 2

ORs and 95% CIs of change in menstrual cycle characteristics concerning SARS-CoV-2 infection and COVID-19 vaccination status, the Nurses' Health Study 3 (N=3116)

Change in usual menstrual characteristics	SARS-CoV-2 infection[a] n=349 OR (95% CI)	COVID-19 vaccination[b] n=2835 OR (95% CI)
Change in cycle length or regularity		
Any change (n=2227)	0.84 (0.66–1.08)	1.10 (0.84–1.45)
Change in cycle length		
Any change (n=1408)	0.89 (0.71–1.12)	1.27 (0.98–1.65)
Change in cycle length[c]		
Shorter (n=858)	0.89 (0.68–1.16)	1.17 (0.88–1.57)
Longer (n=550)	0.89 (0.64–1.22)	1.48 (1.00–2.19)
Change in cycle regularity		
Any change (n=1735)	0.90 (0.72–1.14)	0.86 (0.67–1.12)
Change in cycle regularity[c]		
More regular (n=709)	0.81 (0.60–1.10)	0.89 (0.65–1.22)
Less regular (n=1026)	0.97 (0.74–1.27)	0.83 (0.61–1.12)

Change in cycle characteristics was defined by change in 3 categories: cycle regularity ([1] very regular [±3 days], [2] regular [within 5–7 days], or [3] usually irregular or always irregular or no period) and cycle length ([1] <26 days, [2] 26–31 days, or [3] ≥32 days). Models were adjusted for age at baseline, follow-up time, body mass index at end of follow-up, weight change, race and ethnicity, educational attainment, region, and mutually adjusting for SARS-CoV-2 infection and vaccination. Of note, 742 hormonal contraception users at MOD2 were excluded from the analysis.

CI, confidence interval; *OR*, odds ratio.

[a] Reference: uninfected; [b] Reference: unvaccinated; [c] Multinomial logistic model.

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vaccination was associated with an increase in usual menstrual cycle length, after adjusting for potential confounders, including local COVID-19 burden and pandemic-related stressors. This change seemed to be limited to the 6 months after vaccination and was the strongest among women whose cycles were irregular, short, or long before the pandemic. This association was similar for adenovirus-vectored and mRNA vaccines. SARS-CoV-2 infection was not associated with changes in usual menstrual characteristics.

Results in the context of what is known

Menstrual health is known to change when challenged by psychosocial, interpersonal, or environmental stressors,[14,33] all of which occurred during the COVID-19 pandemic. Existing literature has generated conflicting results characterizing menstrual cycle profiles during the pandemic. Of note, 3 previous studies observed a higher prevalence of menstrual cycle disruptions (eg, irregularity, decreased duration of periods, and more severe menstrual symptoms) during the pandemic than before the pandemic,[21,23,25] whereas data of another 2 studies found no change or a decreased incidence of menstrual disorders (eg, anovulatory cycles, abnormal cycle lengths, and prolonged menses).[19,26] However, these studies examined neither infection nor vaccination. SARS-CoV-2 infection has been associated with menstrual irregularity or abnormal bleeding in 3 retrospective studies.[24,34,35] In contrast, Ding et al[36] found no change in menstrual characteristics but a significant decline in ovarian reserve (serum AMH [β, −0.162; 95% CI, −1.161 to −0.121]) when comparing patients with COVID-19 to age-matched uninfected women. However, these previous studies were cross-sectional and provided limited information about changes from prepandemic cycle characteristics or the temporality of change relative to infection or vaccination.

Our results suggested that COVID-19 vaccination results in short-term increased risk of change in cycle length (longer cycles), independent of infection status. Menstrual disruptions have been reported shortly after typhoid and hepatitis B virus vaccination, although mechanisms explaining these changes remain unexplored.[17,18] The UK Medicine and Healthcare products Regulatory Agency has documented more than 40,000 suspected menstrual disorder cases after 50 million COVID-19 vaccine doses were administered to women.[37] Of note, 3 retrospective studies revealed that 20% to 50% of vaccinated women reported changes in cycle length or flow, with longer cycle length and heavier flows more commonly reported in all 3 studies.[20,27,38] To date, most of the reported menstrual cycle changes were short lived.[27,37] Previous studies have yielded mixed results in investigating the associations between COVID-19 vaccine and menstrual cycle change. A retrospective study of 1273 vaccinated women in the United Kingdom did not find associations between COVID-19 vaccination and changes in menstruation.[22] Another retrospective study of 5000 premenopausal vaccinated women in the United Kingdom found that a history of positive COVID-19 test was associated with a 49% (95% CI, 20%–84%) increased risk of any cycle change after vaccination.[20] However, these studies lacked comparison with unvaccinated women and did not exclude women who were using hormonal contraception. Similar to our findings, a prospective cohort study of 3959 US women who had normal prevaccination menstrual cycle length (24–38 days) found that COVID-19 vaccination was associated with a small (<1 day) increase in usual cycle length compared with unvaccinated women, and such changes attenuated after 2 cycles.[28] However, this study did not account for SARS-CoV-2

TABLE 3

ORs and 95% CIs of change in menstrual cycle characteristics concerning SARS-CoV-2 infection and COVID-19 vaccination status, stratifying by the timing between infection or vaccination and end of follow-up assessment of cycle characteristics, the Nurses' Health Study 3 (N=3116)

	SARS-CoV-2 infection				COVID-19 vaccination			
Change in menstrual characteristics	Uninfected OR (95% CI) n=2767	0–6 mo from infection OR (95% CI) n=56	7–9 mo from infection OR (95% CI) n=130	>9 mo from infection OR (95% CI) n=159	Unvaccinated OR (95% CI) n=281	0–6 mo from vaccination OR (95% CI) n=392	7–9 mo from vaccination OR (95% CI) n=1541	>9 mo from vaccination OR (95% CI) n=641
Change in cycle length or regularity								
Any change	Ref (1.0)	0.52 (0.30–0.90)	1.06 (0.71–1.60)	0.88 (0.62–1.24)	Ref (1.0)	1.32 (0.93–1.87)	1.06 (0.80–1.42)	1.01 (0.74–1.39)
Change in cycle length								
Any change	Ref (1.0)	0.75 (0.43–1.31)	0.93 (0.65–1.34)	0.92 (0.66–1.27)	Ref (1.0)	1.40 (1.02–1.92)	1.30 (0.99–1.69)	1.20 (0.89–1.61)
Change in cycle length[a]								
Shorter	Ref (1.0)	0.56 (0.28–1.15)	0.91 (0.59–1.40)	1.03 (0.71–1.48)	Ref (1.0)	1.26 (0.87–1.80)	1.23 (0.91–1.66)	1.10 (0.79–1.54)
Longer	Ref (1.0)	1.13 (0.56–2.29)	0.94 (0.58–1.54)	0.72 (0.44–1.18)	Ref (1.0)	1.67 (1.05–2.64)	1.43 (0.96–2.14)	1.41 (0.91–2.18)
Change in cycle regularity								
Any change	Ref (1.0)	0.70 (0.41–1.21)	0.97 (0.67–1.39)	0.94 (0.68–1.31)	Ref (1.0)	0.88 (0.64–1.20)	0.84 (0.65–1.10)	0.85 (0.64–1.14)
Change in cycle regularity[a]								
More regular	Ref (1.0)	0.61 (0.29–1.26)	0.97 (0.60–1.54)	0.81 (0.52–1.24)	Ref (1.0)	0.89 (0.60–1.33)	0.89 (0.64–1.24)	0.81 (0.56–1.16)
Less regular	Ref (1.0)	0.81 (0.43–1.52)	0.96 (0.63–1.47)	1.04 (0.71–1.53)	Ref (1.0)	0.83 (0.57–1.21)	0.78 (0.57–1.07)	0.88 (0.62–1.24)

Change in cycle characteristics was defined by change in 3 categories: cycle regularity ([i] very regular [±3 days], [2] regular [within 5–7 days], or [3] usually irregular or always irregular or no period) and cycle length ([1] <26 days, [2] 26–31 days, or [3] ≥32 days). Models were adjusted for age at baseline, follow-up time, body mass index at end of follow-up, weight change, race and ethnicity, educational attainment, region, and mutually adjusting for SARS-CoV-2 infection and vaccination. Of note, 742 hormonal contraception users at MOD2 were excluded from analysis; 4 participants were missing date of infection; and 261 participants were missing date of vaccination.

CI, confidence interval; *OR*, odds ratio; *Ref*, reference.

[a] Multinomial logistic model.

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TABLE 4

ORs and 95% CIs of change in menstrual cycle characteristics concerning COVID-19 vaccination status according to vaccine type, the Nurses' Health Study 3 (N=3102)

Change in menstrual characteristics	COVID-19 vaccination Unvaccinated OR (95% CI) n=281	mRNA vaccine[a] OR (95% CI) n=2746	Adenovirus-vectored vaccine[b] OR (95% CI) n=75
Change in cycle length or regularity			
Any change	Ref (1.0)	1.08 (0.82—1.42)	2.00 (1.04—3.85)
Change in cycle length			
Any change	Ref (1.0)	1.26 (0.97—1.63)	1.42 (0.85—2.39)
Change in cycle length[c]			
Shorter	Ref (1.0)	1.16 (0.86—1.55)	1.25 (0.69—2.28)
Longer	Ref (1.0)	1.47 (1.00—2.17)	1.78 (0.88—3.60)
Change in cycle regularity			
Any change	Ref (1.0)	0.84 (0.65—1.09)	1.97 (1.11—3.51)
Change in cycle regularity[c]			
More regular	Ref (1.0)	0.86 (0.63—1.18)	2.20 (1.12—4.33)
Less regular	Ref (1.0)	0.81 (0.60—1.10)	1.80 (0.94—3.44)

Change in cycle characteristics was defined by change in 3 categories: cycle regularity([1] very regular [±3 days], [2] regular [within 5—7 days], or [3] usually irregular or always irregular or no period) and cycle length ([1] <26 days, [2] 26—31 days, or [3] ≥32 days). Models were adjusted for age at baseline, follow-up time, body mass index at end of follow-up, weight change, race and ethnicity, educational attainment, region, and SARS-CoV-2 infection. Of note, 742 hormonal contraception users at MOD2, 9 participants who reported AstraZeneca vaccine, and 6 participants with unknown vaccine type were excluded from the analysis.

CI, confidence interval; *mRNA*, messenger RNA; *OR*, odds ratio.

[a] Pfizer or Moderna; [b] Johnson & Johnson (Jansen); [c] Multinomial logistic model.

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infection or mental health or pandemic-related stressors. Moreover, none of these studies had measures of prepandemic menstrual cycle characteristics.

Clinical implications

We observed increases in usual cycle length after vaccination with both mRNA and adenovirus-vectored COVID-19 vaccines, suggesting shared mechanisms. There are multiple plausible mechanisms to explain the observed association, including immunologic influences on sex hormones and systemic inflammatory responses that may invoke downstream responses in target organs.[39—41] A normal menstrual cycle is characterized by tightly regulated inflammatory and immune mediators, particularly matrix metalloproteinases, that facilitate the endometrial tissue breakdown and degradation needed for menstruation.[42—44] Furthermore, immune cell activation may contribute to heavy menstrual bleeding.[45] The immune response induced by both mRNA and adenovirus-vectored vaccines may temporarily affect the HPO axis, which could lead to menstrual disturbances.[46,47] More needs to be determined regarding the mechanisms by which inflammatory response to a vaccine affects the ovaries and uterus. We did not find evidence linking SARS-CoV-2 infection with subsequent menstrual changes, suggesting the short-term effect of vaccines might differ from the immune response to SARS-CoV-2 infection, which seems to be more extensive and tissue specific than that elicited by vaccines.[48,49] However, because of the small number of infected participants in this study, this finding needs to be interpreted with caution.

Although not statistically significant, changes in cycle length after the adenovirus-vectored vaccine seemed to be slightly stronger than those observed with mRNA vaccines. Given that the menstrual changes observed in our study were short term, this apparent difference could be the result of earlier access to mRNA vaccines in this study population rather than by a true difference in biological effects of different vaccine vectors. The difference in vaccination timing between mRNA and adenovirus-vectored vaccines in our study and the small number of women vaccinated with the latter (n=75) precluded us from evaluating whether the changes associated with the adenovirus-vectored vaccine were short term as was the case in the aggregate data.

Strengths and limitations

Our study has limitations. Menstrual cycle characteristics and SARS-CoV-2 infection and vaccination were self-reported, although the validity of self-reported health information that is high in cohorts of health professionals

TABLE 5
ORs and 95% CIs of change in menstrual cycle characteristics concerning SARS-CoV-2 infection and COVID-19 vaccination status, stratified by menstrual cycle characteristics at baseline (participants who had regular [within 7 days] and normal [26–31 days] cycle length [n=1976] vs participants who had irregular [>7 days] or short or long [<26 or ≥32 days] [n=1140] cycle length), the Nurses' Health Study 3

	SARS-CoV-2 infection[a]		COVID-19 vaccination[b]	
	Baseline menstrual cycle characteristics		Baseline menstrual cycle characteristics	
Change in usual menstrual characteristics	Regular and normal length OR (95% CI)	Irregular or short or long cycle OR (95% CI)	Regular and normal length OR (95% CI)	Irregular or short or long cycle OR (95% CI)
Change in cycle length or regularity				
Any change	0.82 (0.61–1.11)	0.90 (0.56–1.46)	0.94 (0.66–1.32)	1.83 (1.12–3.00)
Change in cycle length				
Any change	0.80 (0.58–1.10)	1.02 (0.70–1.50)	1.19 (0.83–1.71)	1.69 (1.12–2.54)
Change in cycle length[c]				
Shorter	0.85 (0.58–1.22)	0.97 (0.62–1.50)	1.33 (0.87–2.05)	1.32 (0.85–2.06)
Longer	0.68 (0.42–1.11)	1.10 (0.68–1.77)	0.95 (0.56–1.60)	2.82 (1.51–5.27)
Change in cycle regularity				
Any change	0.89 (0.66–1.20)	0.97 (0.66–1.42)	0.77 (0.55–1.08)	1.05 (0.69–1.59)
Change in cycle regularity[c]				
More regular	0.82 (0.52–1.30)	0.83 (0.54–1.29)	0.82 (0.51–1.34)	1.05 (0.66–1.66)
Less regular	0.90 (0.64–1.25)	1.22 (0.76–1.97)	0.74 (0.51–1.08)	1.01 (0.59–1.74)

Change in cycle characteristics was defined by change in 3 categories: cycle regularity ([1] very regular [±3 days], [2] regular [within 5–7 days], [3] usually irregular or always irregular or no period) or cycle length ([1] <26 days, [2] 26–31 days, or [3] ≥32 days). Multivariable models were adjusted for age at baseline, follow-up time, body mass index at end of follow-up, weight change, race and ethnicity, educational attainment, and region and mutually adjusted for SARS-CoV-2 infection and COVID-19 vaccination with each other. Of note, 742 hormonal contraception users at MOD2 were excluded from analysis.

CI, confidence interval; *OR*, odds ratio.

[a] Reference: uninfected; [b] Reference: unvaccinated; [c] Multinomial logistic model.

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and menstrual characteristics have been demonstrated to be reported with strong accuracy.[50,51] That our study population was mainly healthcare workers with a high vaccination rate may have limited the generalizability to populations with a different pandemic experience, including those with access to vaccinations later in the course of the pandemic. In addition, for many participants, our primary exposure and outcome were collected on the same questionnaire, so the report of vaccination could have influenced the report of menstrual cycle characteristics. However, this bias should be absent from the change in menstrual characteristic analyses that used prepandemic and postexposure reports.

There were weaknesses in the precision of our data. First, although access to menstrual cycle data that were reported prospectively before the pandemic is a strength for unbiased evaluation of change, these prepandemic cycle characteristics were reported 5 to 10 years before the pandemic and may not be representative of participants' menstrual cycles immediately before COVID-19 vaccination or infection. Second, we did not have information about the date of vaccination relative to ovulation. Because the uterine immune system changes with the menstrual cycle, the date of inoculation relative to the date of last menstrual period may be relevant.[22,40,44] Third, we only collected menstrual cycle length in categories, which improved validity but may have precluded us from detecting more subtle changes in cycle characteristics if they exist. Furthermore, we collected information about "usual" cycle length. Thus, we may not have detected changes that were too mild or transient for participants to perceive and report them as newly "usual" cycle length or regularity. Any change not interpreted as "usual" would have biased our results toward an erroneous null association.

Our study has several strengths. Periodic surveys were administered over a 1-year period during the COVID-19 pandemic, rigorously measuring incident SARS-CoV-2 infection and COVID-19 vaccination, allowing comparison with those uninfected and unvaccinated. We were able to control for the impacts of the pandemic on an individual's social functioning, mental health, and behavioral practices using validated measures. Menstrual cycle characteristics were collected prospectively throughout women's reproductive years before and during the COVID-19 pandemic, which allowed us to compare menstrual cycle characteristics before and after COVID-19 infection and vaccination.

Conclusions

We found that COVID-19 vaccination may be associated with a short-term change toward longer menstrual cycles. These changes were not explained by differences in health-related behavioral factors or pandemic-related stress. In addition, these menstrual disturbances did not seem to be related to vaccine type. Our findings suggested the need to monitor menstrual cycle health in vaccine clinical trials and increased attention to sex-based differences in vaccine response, especially in the setting of the rollout of COVID-19 boosters, which provides another opportunity to study this important issue. Future research will be needed to understand the underlying mechanisms for these associations. ■

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