

Association Between Menstrual Cycle Length and Coronavirus Disease 2019 (COVID-19) Vaccination

A U.S. Cohort

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OBJECTIVE: To assess whether coronavirus disease 2019 (COVID-19) vaccination is associated with changes in cycle or menses length in those receiving vaccination as compared with an unvaccinated cohort.

METHODS: We analyzed prospectively tracked menstrual cycle data using the application “Natural Cycles.” We included U.S. residents aged 18–45 years with normal cycle lengths (24–38 days) for three consecutive cycles before the first vaccine dose followed by vaccine-dose cycles (cycles 4–6) or, if unvaccinated, six cycles over a similar time period. We calculated the mean within-individual change in cycle and menses length (three prevaccine cycles vs first- and second-dose cycles in the vaccinated cohort, and the first three cycles vs cycles four and five in the unvaccinated cohort). We used mixed-effects models to estimate the adjusted difference in change in cycle and menses

length between the vaccinated and unvaccinated cohorts.

RESULTS: We included 3,959 individuals (vaccinated 2,403; unvaccinated 1,556). Most of the vaccinated cohort received the Pfizer-BioNTech vaccine (55%) (Moderna 35%, Johnson & Johnson/Janssen 7%). Overall, COVID-19 vaccine was associated with a less than 1-day change in cycle length for both vaccine-dose cycles compared with prevaccine cycles (first dose 0.71 day-increase, 98.75% CI 0.47–0.94; second dose 0.91, 98.75% CI 0.63–1.19); unvaccinated individuals saw no significant change compared with three baseline cycles (cycle four 0.07, 98.75% CI –0.22 to 0.35; cycle five 0.12, 98.75% CI –0.15 to 0.39). In adjusted models, the difference in change in cycle length between the vaccinated and unvaccinated cohorts was less than 1 day for both doses (difference in change: first dose 0.64 days, 98.75%

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CI 0.27–1.01; second dose 0.79 days, 98.75% CI 0.40–1.18). Change in menses length was not associated with vaccination.

CONCLUSION: Coronavirus disease 2019 (COVID-19) vaccination is associated with a small change in cycle length but not menses length.

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Concerns about a possible association between coronavirus disease 2019 (COVID-19) vaccination and abnormal menstrual cycles may lead to vaccine hesitancy. Unfortunately, clinical trials of the current COVID-19 vaccines did not collect menstrual cycle outcomes postvaccine.^{1–4} VAERS (Vaccine Adverse Event Reporting System) does not actively collect information regarding menstrual cycles, and, by May 2021, only a small number of individuals (fewer than 200) had self-reported a menstrual-related issue to VAERS.⁵ Social media reports suggest menstrual disturbances are much more common but that these disturbances appear to be temporary.^{6,7} The lack of population-level, prospective evidence about the relationship of COVID-19 vaccination and menstrual cycles limits our ability to sufficiently address these concerns and to counsel individuals who menstruate about what to expect with vaccination.

Menstrual cyclicity is an overt sign of health and fertility. Menstrual characteristics are not static, and variability exists month to month across an individual's lifespan.^{8–10} The International Federation of Gynecology and Obstetrics classifies a variation in cycle length as normal if less than 8 days. Regularly menstruating individuals can also experience sporadic or stress-induced ovulation perturbances, which may result in a skipped cycle or a temporary change in cycle length.^{11–14} This normal variability may be perceived as concerning, especially in conjunction with a new exposure such as COVID-19 vaccination.

Here, we present an analysis of prospectively collected menstrual cycle tracking data from U.S. individuals using the U.S. Food and Drug Administration–cleared digital fertility-awareness application “Natural Cycles” to assess whether COVID-19 vaccination is associated with changes in cycle or menses length during the menstrual cycles when vaccine doses are received.

METHODS

We conducted a retrospective cohort analysis of menstrual cycle data that were collected prospectively. Cycle data ranged from October 2020 to September 2021, with initial COVID-19 vaccine

doses administered between December 2020 and July 2021. Individuals who use the digital fertility-awareness application Natural Cycles voluntarily choose to prospectively track physiologic data related to their menstrual cycles for purposes of nonhormonal pregnancy prevention or planning and consent to the use of their de-identified data for research (consent can be removed if desired). A detailed description of variables tracked by the application has been published elsewhere.¹⁰ We included U.S. residents aged 18–45 years who were at least three cycles postpregnancy or postuse of hormonal contraception. Included individuals had normal prevaccination menstrual cycle lengths (average 24–38 days).⁸ Each individual contributed six consecutive cycles of data. For those who received a COVID-19 vaccination, we included three prevaccine cycles and three post–first vaccine dose, inclusive of the vaccination cycle. We included six consecutive cycles for those who remained unvaccinated. Included vaccine types were Pfizer-BioNTech (Pfizer), Moderna, Johnson & Johnson/Janssen [J&J/Janssen], and unspecified. We excluded menopausal individuals and those who received the Oxford/AstraZeneca vaccine to focus on U.S. Food and Drug Administration–approved, U.S.-available vaccines.

The primary exposure was COVID-19 vaccination status as reported by individuals using the Natural Cycles application. Prompted by in-application messages from Natural Cycles, individuals logged their vaccination date(s) or confirmed their unvaccinated status. Individuals without confirmed vaccination information were not included in the data set.

Our primary outcome was the within-individual change in cycle length (in days) from the three-cycle prevaccination average to the initial vaccination cycle. For vaccinated individuals, cycle four was the first vaccine-dose cycle; the cycle of the second dose varied based on when the second vaccine dose occurred (cycle four, five, or six). For the unvaccinated cohort, we designated cycle four as the artificial first vaccine-dose cycle and cycle five as the artificial second-dose cycle; cycles one, two, and three were considered the equivalent of prevaccination cycles. Secondary outcomes were the same within-individual change in cycle length for the second vaccination cycle and corresponding changes in menses length for the first and second vaccine-dose cycles. We also examined the proportion of participating individuals who experienced a clinically significant change in cycle length (8 days or more).

Additional sociodemographic information was collected to further characterize the cohort. Of note, individuals using the Natural Cycles application are required to log only their age; logging other sociodemographic information is voluntary. Missingness was nonignorable and was included as a category in analyses. We categorized age at the start of the first cycle as 18–24, 25–29, 30–34, 35–39, or 40–45 years. Race and ethnicity were reported as Asian, Black, Hispanic, Middle Eastern or North African, Native Hawaiian or Pacific Islander, or White, which we collapsed into a binary variable for modeling owing to small sample sizes for some groups. We classified state of residence into Census regions: Northeast, Midwest, South, or West. Additional characteristics included parity (nulliparous vs parous), body mass index (BMI [calculated as weight in kilograms divided by height in meters squared]: underweight or normal weight, overweight, or obese), education (at least a 4-year college degree or not), and relationship status (in a steady relationship or not).

We had more than 99% power to detect an unadjusted 1-day difference in cycle length change or 0.5-day difference in menses length change by vaccination status, at a significance level of 0.0125 (98.75% CIs), to account for multiple comparisons among the four main outcomes: cycle and menses length for the first and second vaccine-dose cycles.

The Oregon Health & Science University Institutional Review Board approved the protocol. De-identified data were used under a data-use agreement with Natural Cycles USA Corp (New York, New York) and from the Reading Independent Ethics Committee (Reading, United Kingdom).

We compared within-individual changes in cycle and menses length between the three prevaccination-cycle average and the first- and second-dose vaccination cycles, or with cycle four and five for the unvaccinated participants, using two-sided *t* tests. We created histograms overlaying vaccination status to compare the distributions of changes in cycle and menses length and compared the proportion of individuals who experienced a clinically significant change in cycle length (8 days or more) using Pearson's χ^2 tests. Longitudinal multivariable mixed-effects models were used for all outcomes and plotted the adjusted marginal means. Models contained random intercepts and slopes at the individual level and an interaction term between time (prevaccination and postvaccination) and vaccination status to determine the effect of vaccination, that is, the adjusted difference in the change in cycle and menses length between vaccination groups. All estimates were

adjusted for age, race and ethnicity, BMI, education, parity, and relationship status. Census region was not associated with any outcome, did not act as a confounder, and was excluded from models.

As a subanalysis, we separated individuals who received both vaccine doses in one cycle from those who received doses over two cycles. We compared unadjusted within-individual changes in cycle length between the three prevaccination cycles and the vaccine (both doses) cycle. We also compared changes between cycle six and the three prevaccine cycles by vaccination status to test whether any changes observed in the vaccination cycle persisted over time.

We conducted multiple sensitivity analyses to confirm the robustness of our results. First, we compared changes in cycle and menses length by vaccine brand. Second, we excluded individuals with any prevaccination cycle whose absolute cycle length was outside of the 24–38-day range (579 individuals). Third, we excluded any individuals who reported polycystic ovarian syndrome, thyroid disorder, or endometriosis (226 individuals). Fourth, we excluded any individuals who reported use of emergency contraception during at least one study cycle (157 individuals). Finally, although the data did not meet the missing at random assumption required for imputation techniques, we used imputation followed by weighting with covariate balancing propensity scores and bootstrapped SEs to confirm that our results were not biased by missing data.¹⁵

RESULTS

Of 10,179 eligible individuals, 3,959 representing 23,754 cycles met inclusion criteria (Fig. 1). The majority of excluded individuals had not tracked a sufficient number of cycles during the study period (4,744 individuals). We excluded 304 individuals with nonconsecutive cycles, 331 with an average prevaccination cycle length outside of the 24–38-day range, and individuals who were less than three cycles post-pregnancy ($n=109$) or post-hormonal contraception use ($n=713$). We also excluded a small number of individuals outside of the study age range ($n=3$), who received the Oxford/AstraZeneca vaccine ($n=14$), or who were menopausal ($n=2$).

The final study sample included 2,403 vaccinated individuals and 1,556 unvaccinated individuals (Table 1). The vaccinated cohort was slightly older (34% 30–34 years of age vs 24% among unvaccinated) and more likely to be nulliparous (79% vs 69%) and college educated (77% vs 60%) as compared with the unvaccinated group. Vaccinated individuals were also

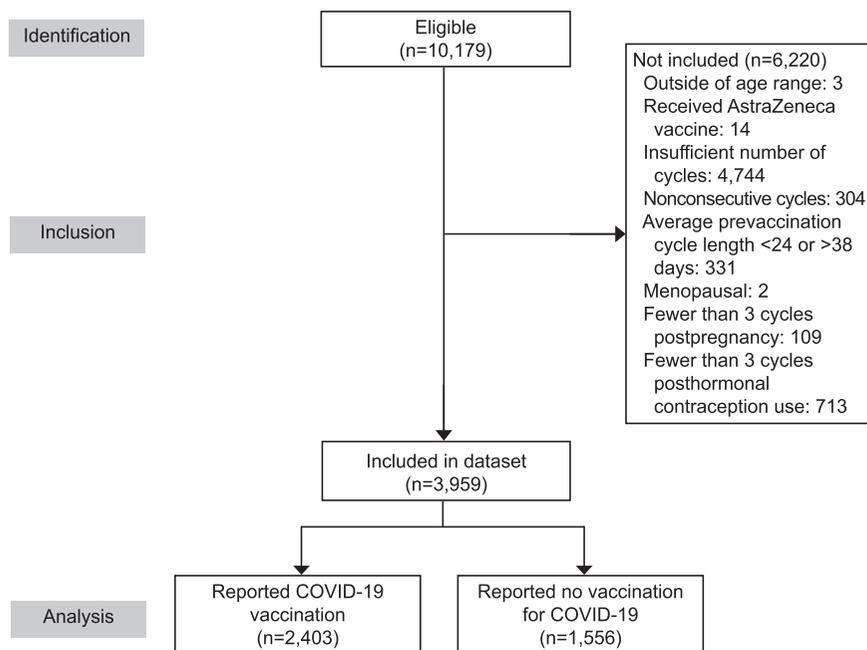


Fig. 1. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) flow diagram. COVID-19, coronavirus disease 2019.

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more likely to identify as White (54% vs 47%) and to live in the Northeast (20% vs 13%) or West (37% vs 34%) U.S. Census regions. More than half of the vaccinated cohort received the Pfizer Covid-19 vaccine (55%) (Moderna 35%, J&J/Janssen 7%).

Overall, the vaccinated cohort experienced a less than 1-day unadjusted increase in the length of their menstrual cycle during the first vaccine cycle compared with their three prevaccination cycles (Table 2, 0.71-day increase, 98.75% CI 0.47–0.94); the unvaccinated cohort had no significant change in cycle four compared with their first three cycles (0.07-day increase, 98.75% CI –0.22 to 0.35). Although statistically significant, the overlaid histograms show a cycle length change distribution in vaccinated individuals that is roughly equivalent to that in unvaccinated individuals (Fig. 2A, left), and the proportion of individuals who experienced a clinically significant change in cycle length of 8 days or more did not differ by vaccination status (4.3% for unvaccinated vs 5.2% for vaccinated, $P=.181$; data not shown). After adjusting for confounders, the difference in the change in cycle length by vaccination status was 0.64 days (Fig. 2B, left, Table 2, 98.75% CI 0.27–1.01) (see Appendix 1, available online at <http://links.lww.com/AOG/C572>, for the full model).

The majority of vaccinated individuals received a second vaccine dose: 15% in cycle four, 63% in cycle five, and 2% in cycle six (data not shown). This group, which excluded individuals who received the one-dose J&J/Janssen vaccine (7%) or who did not receive

a second dose of the Pfizer or Moderna vaccines (13%), experienced an unadjusted mean 0.91-day increase in cycle length during their second vaccine cycle (Fig. 2A, right, Table 2, 98.75% CI 0.63–1.19); unvaccinated individuals had no significant change (0.12 day-increase, 98.75% CI –0.15 to 0.39). During the second vaccine cycle, a slightly higher proportion of participants had a change in cycle length of 8 days or more (4.6% unvaccinated vs 6.5% vaccinated, $P=.017$), although this difference was not statistically significant at the 0.0125 significance level. After adjusting for confounders, the difference in the change in cycle length for the second vaccine cycle by vaccination status was 0.79 days (Fig. 2B, right, Table 2, 98.75% CI 0.40–1.18).

The increase in cycle length for both the first and second vaccine cycles appears to be driven largely by the 358 individuals who received both vaccine doses within a single cycle (cycle four). This subgroup experienced a 2-day unadjusted mean cycle length increase (Table 3, 2.38 days, 98.75% CI 1.52–3.24), and 10.6% had an increase in cycle length of 8 days or more compared with 4.3% in the unvaccinated cohort ($P<.001$). When these individuals were removed from the analysis, the unadjusted increases in cycle length for first and second doses in separate cycles were smaller (Table 3) and there were no significant differences in the proportion of individuals with a change in cycle length of 8 days or more compared with unvaccinated individuals (data not shown). In adjusted models, individuals who received both vaccine doses within one cycle

Table 1. Characteristics of the Study Participants (N=3,959)

Characteristic	Unvaccinated (n=1,556)	Vaccinated (n=2,403)	Overall (N=3,959)	P
Age (y)*				<.001
18–24	376 (24.2)	239 (10.0)	615 (15.5)	
25–29	578 (37.2)	898 (37.4)	1,476 (37.3)	
30–34	374 (24.0)	817 (34.0)	1,191 (30.1)	
35–39	161 (10.4)	343 (14.3)	504 (12.7)	
40–45	67 (4.3)	106 (4.4)	173 (4.4)	
Race and ethnicity				<.001
Asian	6 (0.4)	42 (1.8)	48 (1.2)	
Black	70 (4.5)	100 (4.2)	170 (4.3)	
Hispanic	64 (4.1)	142 (5.9)	206 (5.2)	
Middle Eastern or North African	6 (0.4)	15 (0.6)	21 (0.5)	
Native Hawaiian or Pacific Islander	3 (0.2)	13 (0.5)	16 (0.4)	
No data	677 (43.5)	783 (32.6)	1,460 (36.9)	
White	730 (46.9)	1,308 (54.4)	2,038 (51.5)	
U.S. region				<.001
Northeast	207 (13.3)	481 (20.0)	688 (17.4)	
Midwest	302 (19.4)	372 (15.5)	674 (17.0)	
South	473 (30.4)	563 (23.4)	1,036 (26.2)	
West	521 (33.5)	899 (37.4)	1,420 (35.9)	
No data	53 (3.4)	88 (3.7)	141 (3.6)	
Parity				<.001
Nulliparous	1,080 (69.4)	1,903 (79.2)	2,983 (75.4)	
Parous	263 (16.9)	245 (10.2)	508 (12.8)	
No data	213 (13.7)	255 (10.6)	468 (11.8)	
BMI category [†]				.037
Underweight or normal weight	679 (43.6)	1,116 (46.4)	1,795 (45.3)	
Overweight	177 (11.4)	310 (12.9)	487 (12.3)	
Obese	101 (6.5)	157 (6.5)	258 (6.5)	
No data	599 (38.5)	820 (34.1)	1,419 (35.8)	
Education level				<.001
Less than 4-y college	351 (22.6)	201 (8.4)	552 (13.9)	
College degree or more	927 (59.6)	1,853 (77.1)	2,780 (70.2)	
No data	278 (17.9)	349 (14.5)	627 (15.8)	
Relationship status				.001
Not in relationship	168 (10.8)	294 (12.2)	462 (11.7)	
In relationship	1,120 (72.0)	1,798 (74.8)	2,918 (73.7)	
No data	268 (17.2)	311 (12.9)	579 (14.6)	
Vaccine type				N/A
Unvaccinated	1,556 (100.0)	0 (0.0)	1,556 (39.3)	
Pfizer	0 (0.0)	1,326 (55.2)	1,326 (33.5)	
Moderna	0 (0.0)	835 (34.8)	835 (21.1)	
J&J/Janssen	0 (0.0)	168 (7.0)	168 (4.2)	
Unspecified	0 (0.0)	74 (3.1)	74 (1.9)	

BMI, body mass index; N/A, no statistical test was performed; Pfizer, Pfizer-BioNTech; J&J/Janssen, Johnson & Johnson/Janssen. Data are n (%) unless otherwise specified.

* At cycle 1.

[†] At enrollment into the application.

experienced a 2-day increase in cycle length compared with unvaccinated individuals (Table 3, difference in change by vaccination status 2.32 days, 98.75% CI 1.59–3.04). The adjusted difference for individuals who received one dose in their first vaccine cycle was no longer significant compared with unvaccinated individuals (difference in change by vaccination status 0.34 days, 98.75% CI –0.01 to 0.70), and the adjusted differ-

ence for individuals who received one dose in their second vaccine cycle was also smaller (0.45 days, 98.75% CI 0.06–0.84). These differences do not appear to be driven by individuals with naturally longer cycle lengths; among the 358 individuals who received two doses in a single cycle, just 15 (4%) received their second dose outside of our defined normal cycle length range of 24–38 days (data not shown).

Table 2. Within-Individual Unadjusted Change in Cycle Length and Menses Length From Three Prevacination–Cycle Average to First or Second Vaccination Cycle and Adjusted Difference in Change Compared With Unvaccinated Individuals

	n	Cycle Length		Menses Length	
		Change in Length (d)	Adjusted Difference in Change vs Unvaccinated Individuals (d)*	Change in Length (d)	Adjusted Difference in Change vs Unvaccinated Individuals (d)*
1st dose					
Unvaccinated	1,556	0.07 (−0.22 to 0.35)	—	−0.09 (−0.18 to 0.00)	—
Vaccinated	2,403	0.71 (0.47–0.94)	0.64 (0.27–1.01)	−0.01 (−0.09 to 0.06)	0.08 (−0.04 to 0.19)
2nd dose					
Unvaccinated	1,556	0.12 (−0.15 to 0.39)	—	−0.09 (−0.18 to −0.01)	—
Vaccinated	1,919	0.91 (0.63–1.19)	0.79 (0.40–1.18)	−0.01 (−0.09 to 0.07)	0.08 (−0.04 to 0.20)

Data are mean (98.75% CI) unless otherwise specified.

* Differences are from mixed-effects models with random intercepts and random slopes at the individual level, an interaction between vaccination status and prevaccination–postvaccination timing, and adjusted for age, race, body mass index, educational attainment, parity, and relationship status.

By cycle six, for those who received both vaccine doses in a single cycle (cycle four), the change in cycle length compared with their three prevaccination cycles was no longer different from the changes in the unvaccinated group. Unvaccinated individuals had a nonsignificant change in cycle length from the prevaccination average of 0.24 days (98.75% CI −0.04 to 0.51), and the 358 individuals who received two doses in their first vaccine cycle also had a nonsignificant change of 0.17 days (98.75% CI −0.33 to 0.67).

We found no changes in unadjusted menses length for either the first or second vaccination cycle (Table 2, Appendix 2 [Appendix 2 is available online at <http://links.lww.com/AOG/C572>]). There were no differences in adjusted menses length changes by vaccination status for either vaccine cycle: first dose 0.08-day difference (98.75% CI −0.04 to 0.19), second dose 0.08-day difference (98.75% CI −0.04 to 0.20) (see Appendix 3, available online at <http://links.lww.com/AOG/C572>, for full modeling results). Stratification by individuals who received both doses in one cycle did not change results for menses length (data not shown).

Sensitivity analyses comparing the changes in cycle and menses length by vaccine brand, excluding those with more variable prevaccination cycle lengths, gynecologic disorders, or emergency contraception use, and imputation and sample weighting did not alter our results in a clinically meaningful way (see Appendices 4 and 5, available online at <http://links.lww.com/AOG/C572>, for imputation and weighting results).

DISCUSSION

We evaluated 23,754 menstrual cycles prospectively reported by 3,959 U.S. individuals to evaluate whether COVID-19 vaccination is associated with menstrual cycle disturbances during cycles when vaccination occurs. After adjusting for confounders, we found that normally cycling individuals experienced small variations in cycle length regardless of vaccination status. Statistically significant differences existed between vaccination status groups, but the change in cycle length was less than 1 day, which is below the reportable difference in the menstrual cycle tracking application and is not clinically significant. A subset of individuals who received both vaccine doses in a single cycle had, on average, an adjusted 2-day increase in their vaccination cycle length compared with unvaccinated individuals. Although approximately 10% of these individuals experienced a clinically notable change in cycle length of 8 days or more, this change attenuated quickly within two postvaccine cycles. We found no change in menses length between or within vaccination cohorts.

Menstrual cycle timing is regulated by the hypothalamic-pituitary-ovarian axis, which can be affected by life, environment, and health stressors.^{11–13,16} Our results cannot be explained by generalized pandemic stress because our unvaccinated control group saw no changes over a similar time period. Our findings are consistent with a recent analysis of 18,076 Natural Cycles application users before and during the pandemic that also demonstrated no population-level cycle timing disruptions due to pandemic stress.¹⁷

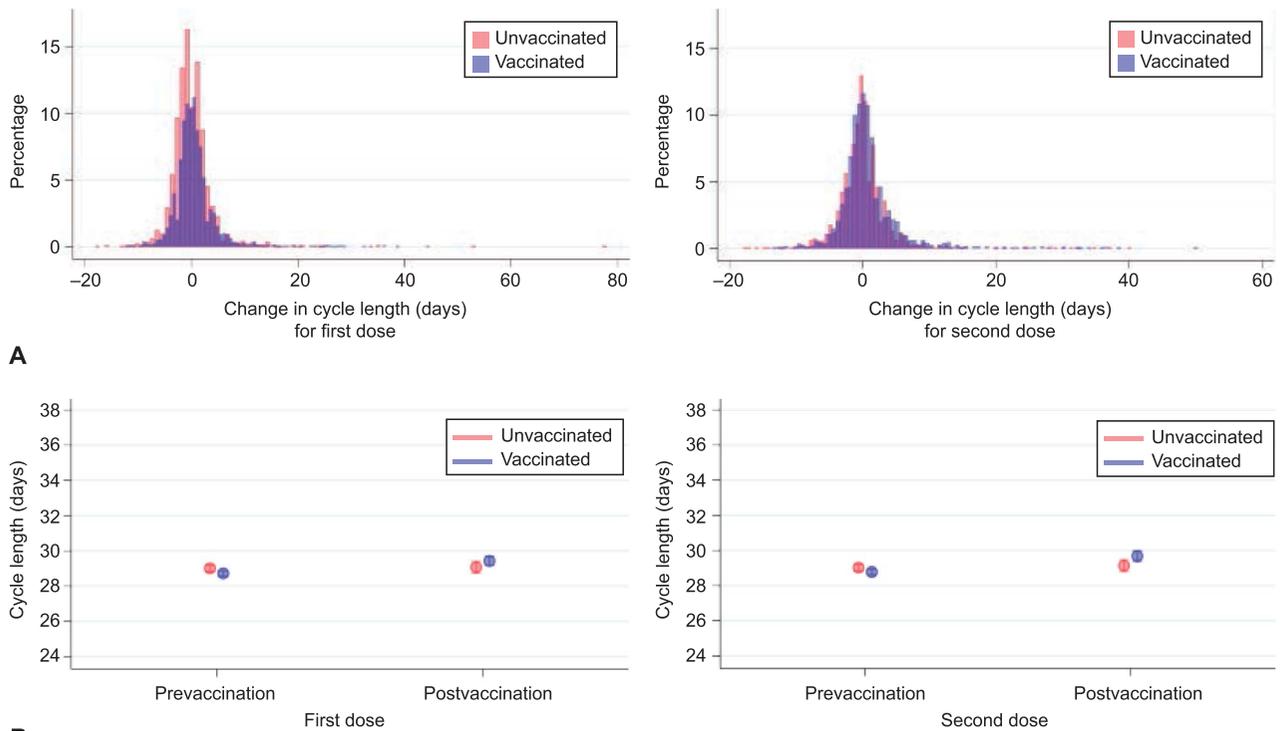


Fig. 2. A. Overlaid histograms of the change in cycle length (days) between the three prevaccination cycle average and the vaccination cycle for first dose (*left*) or second dose (*right*). Histograms for unvaccinated individuals are shown in *red*, vaccinated individuals are shown in *blue*, and overlapping distributions are shown in *purple*. **B.** Adjusted marginal means for cycle length (days) for the three prevaccination cycle average and the vaccination cycle first dose (*left*) or second dose (*right*). Estimates are from mixed-effects models with random intercepts and random slopes at the user level, an interaction between vaccination status and prevaccination and postvaccination timing, and adjusted for age, race, body mass index, educational attainment, parity, and relationship status. Unvaccinated individuals are shown in *blue*; error bars represent 98.75% CIs.

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mRNA vaccines create a robust immune response or stressor, which could temporarily affect the hypothalamic-pituitary-ovarian axis if timed correctly.^{18–20} Our findings for individuals who received two doses in a single cycle supports this hypothesis. Given the dosing schedule of the mRNA COVID-19 vaccines in the United States (21 days for Pfizer and 28 days for Moderna), an individual receiving two doses in a single cycle would have received the first dose in the early follicular phase. Cycle length variability results from events leading to the recruitment and maturation of the dominant follicle during the follicular phase, processes known to be affected by stress.^{12,21} In contrast, an acute severe illness with or without septicemia, such as COVID-19, could be catastrophic to hypothalamic-pituitary-ovarian axis function, sometimes permanently.^{18,22–24}

This research directly addresses concerns raised by self-reports through VAERS and public discourse.^{5–7,25} The types of concerns raised range from cycle and

menses length changes to differences in menstrual-associated symptoms, unscheduled bleeding, and changes in the quality and quantity of menstrual bleeding.⁶ Self-reports are useful for rapidly identifying potential signals or rare adverse events, but they are limited by significant confounding and reporting biases. Our study strengths include prospectively collected menstrual cycle data, which limits recall bias, a control group of unvaccinated individuals, and adjustment for sociodemographic factors associated with vaccination status and menstrual cycle changes (eg, age, BMI). Our sample size is also sufficiently large to identify small differences, even 1 day, in cycle and menses length that may be of interest to individuals but might not rise to the level of clinical concern (8 days or more) or trigger a medical evaluation for secondary amenorrhea (no menses for 3 months).^{8,26} However, for an individual, small cycle changes can cause concern or raise hopes, especially if avoiding or planning for pregnancy, and this level of detail will likely be valuable.

Table 3. Unadjusted Change in Cycle Length From Three Prevacination–Cycle Average to Coronavirus Disease 2019 (COVID-19) Vaccination Cycle and Adjusted Difference in Change Compared With Unvaccinated Individuals for First and Second Doses and for Both Doses Received in the Same Cycle

	n	Change in Cycle Length (d)	Adjusted Difference in Change vs Unvaccinated Individuals (d)*
1st dose (1 dose/cycle)			
Unvaccinated	1,556	0.07 (−0.22 to 0.35)	—
Vaccinated	2,045	0.41 (0.19–0.64)	0.34 (−0.01 to 0.70)
2nd dose (1 dose/cycle)			
Unvaccinated	1,556	0.12 (−0.15 to 0.39)	—
Vaccinated	1,561	0.57 (0.29–0.85)	0.45 (0.06–0.84)
1st and 2nd dose in same cycle			
Unvaccinated	1,556	0.07 (−0.22 to 0.35)	—
Vaccinated	358	2.38 (1.52–3.24)	2.32 (1.59–3.04)

Data are mean (98.75% CI) unless otherwise specified.

* Differences are from mixed-effects models with random intercepts and random slopes at the individual level, an interaction between vaccination status and prevaccination–postvaccination timing, and adjusted for age, race, body mass index, educational attainment, parity, and relationship status.

Our study also has limitations. First, it may not be generalizable to the U.S. population given the selection of Natural Cycles users (more likely to be White, college educated, and have lower BMIs than national distributions and not using hormonal contraception). Second, we also chose to analyze a cohort with consistent normal cycle lengths to clearly identify any associations between cycle and menses length and COVID-19 vaccination. We recognize that many individuals who menstruate do not fit into this normal category.^{8,10} Other subpopulations are known to have greater baseline variations in menstrual cyclicity, such as individuals with BMIs higher than 35. We do not yet know whether these populations experience greater changes in cycle and menses length in association with COVID-19 vaccination. Third, although our results suggest that individuals receiving two doses in a single cycle return to baseline cycle length quickly, our data do not yet include enough subsequent cycles without vaccine to investigate this fully for the entire vaccinated cohort. Finally, we do not have data on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in either our vaccinated or unvaccinated groups.

Our findings are reassuring; we find no population-level clinically meaningful change in menstrual cycle length associated with COVID-19 vaccination. Our findings support and help explain the self-reports of changes in cycle length. Individuals receiving two COVID-19 vaccine doses in a single cycle do appear to experience a longer but temporary cycle length change. Coronavirus disease 2019 (COVID-19) vaccination is not associated with changes in menses length. Questions remain about other possible

changes in menstrual cycles, such as menstrual symptoms, unscheduled bleeding, and changes in the quality and quantity of menstrual bleeding.

REFERENCES

1. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *New Engl J Med* 2020;383:2603–15. doi: 10.1056/NEJMoa2034577
2. Oliver SE, Gargano JW, Marin M, Wallace M, Curran KG, Chamberland M, et al. The Advisory Committee on Immunization Practices' interim recommendation for use of Moderna COVID-19 vaccine – United States, December 2020. *MMWR Morb Mortal Wkly Rep* 2021;69:1653–6. doi: 10.15585/mmwr.mm695152e1
3. Sadoff J, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against covid-19. *New Engl J Med* 2021;384:2187–201. doi: 10.1056/NEJMoa2101544
4. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *New Engl J Med* 2021;384:403–16. doi: 10.1056/NEJMoa2035389
5. NOT-HD-21-035: notice of special interest (NOSI) to encourage administrative supplement applications to investigate COVID-19 vaccination and menstruation (admin supp clinical trial optional). Accessed June 12, 2021. <https://grants.nih.gov/grants/guide/notice-files/NOT-HD-21-035.html>
6. Brumfiel G. Why reports of menstrual changes after COVID vaccine are tough to study. *NPR* August 9, 2021.
7. Lee KMN, Junkins EJ, Fatima UA, Cox ML, Clancy KBH. Characterizing menstrual bleeding changes occurring after SARS-CoV-2 vaccination. Accessed November 12, 2021. <https://www.medrxiv.org/content/10.1101/2021.10.11.21264863v1>
8. Munro MG, Critchley HOD, Fraser IS; FIGO Menstrual Disorders Committee. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions [published erratum appears in *In J Gynaecol*

- Obstet 2019;144:237]. *Int J Gynaecol Obstet* 2018;143:393–408. doi: 10.1002/ijgo.12666
9. Harlow SD, Ephross SA. Epidemiology of menstruation and its relevance to women's health. *Epidemiol Rev* 1995;17:265–86. doi: 10.1093/oxfordjournals.epirev.a036193
 10. Bull JR, Rowland SP, Scherwitzl EB, Scherwitzl R, Danielsson KG, Harper J. Real-world menstrual cycle characteristics of more than 600,000 menstrual cycles. *NPJ Digit Med* 2019;2:83. doi: 10.1038/s41746-019-0152-7
 11. Nagma S, Kapoor G, Bharti R, Batra A, Aggarwal A, et al. To evaluate the effect of perceived stress on menstrual function. *J Clin Diagn Res* 2015;9:QC01–3. doi: 10.7860/JCDR/2015/6906.5611
 12. Williams NI, Berga SL, Cameron JL. Synergism between psychosocial and metabolic stressors: impact on reproductive function in cynomolgus monkeys. *Am J Physiol Endocrinol Metab* 2007;293:E270–6. doi: 10.1152/ajpendo.00108.2007
 13. Fenster L, Waller K, Chen J, Hubbard AE, Windham GC, Elkin E, et al. Psychological stress in the workplace and menstrual function. *Am J Epidemiol* 1999;149:127–34. doi: 10.1093/oxfordjournals.aje.a009777
 14. Lynch KE, Mumford SL, Schliep KC, Whitcomb BW, Zarek SM, Pollack AZ, et al. Assessment of anovulation in eumenorrheic women: comparison of ovulation detection algorithms. *Fertil Steril* 2014;102:511–18.e2. doi: 10.1016/j.fertnstert.2014.04.035
 15. Imai K, Ratkovic M. Covariate balancing propensity score. *J R Stat Soc B* 2014;76:243–63. doi: 10.1111/rssb.12027
 16. Valsamakis G, Chrousos G, Mastorakos G. Stress, female reproduction and pregnancy. *Psychoneuroendocrinology* 2019;100:48–57. doi: 10.1016/j.psyneuen.2018.09.031
 17. Nguyen BT, Pang RD, Nelson AL, Pearson JT, Nocchioli EB, Reissner HR, et al. Detecting variations in ovulation and menstruation during the COVID-19 pandemic, using real-world mobile app data. *PLoS One* 2021;16:e0258314. doi: 10.1371/journal.pone.0258314
 18. Girardi G, Bremer AA. Scientific evidence supporting coronavirus disease 2019 (COVID-19) vaccine efficacy and safety in people planning to conceive or who are pregnant or lactating. *Obstet Gynecol* 2022;139:3–8. doi: 10.1097/AOG.0000000000004636
 19. Skelly DT, Harding AC, Gilbert-Jaramillo J, Knight ML, Longest S, Brown A, et al. Two doses of SARS-CoV-2 vaccination induce robust immune responses to emerging SARS-CoV-2 variants of concern. *Nat Commun* 2021;12:5061. doi: 10.1038/s41467-021-25167-5
 20. Turnbull AV, Rivier CL. Regulation of the hypothalamic-pituitary-adrenal axis by cytokines: actions and mechanisms of action. *Physiol Rev* 1999;79:1–71. doi: 10.1152/physrev.1999.79.1.1
 21. Barbarino A, De Marinis L, Folli G, Tofani A, Casa SD, D'Amico C, et al. Corticotropin-releasing hormone inhibition of gonadotropin secretion during the menstrual cycle. *Metabolism* 1989;38:504–6. doi: 10.1016/0026-0495(89)90208-4
 22. Chrousos GP, Torpy DJ, Gold PW. Interactions between the hypothalamic-pituitary-adrenal axis and the female reproductive system: clinical implications. *Ann Intern Med* 1998;129:229–40. doi: 10.7326/0003-4819-129-3-199808010-00012
 23. Centers for Disease Control and Prevention, National Center for Health Statistics. COVID-19 mortality overview: provisional death counts for coronavirus disease 2019 (COVID-19). Accessed November 5, 2021. <https://www.cdc.gov/nchs/covid19/mortality-overview.htm>
 24. Annane D, Pastores SM, Arlt W, Balk RA, Beishuizen A, Briegel J, et al. Critical illness-related corticosteroid insufficiency (CIRCI): a narrative review from a multispecialty task force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). *Intensive Care Med* 2017;43:1781–92. doi: 10.1007/s00134-017-4914-x
 25. Male V. Menstrual changes after covid-19 vaccination. *BMJ* 2021;374:n2211. doi: 10.1136/bmj.n2211
 26. Practice Committee of American Society for Reproductive Medicine. Current evaluation of amenorrhea. *Fertil Steril* 2008;90:S219–25. doi: 10.1016/j.fertnstert.2008.08.038

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