

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

Association Between Menstrual Cycle Length
and Coronavirus Disease 2019
(COVID-19) Vaccination
A U.S. Cohort

OBSTETRICS & GYNECOLOGY

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preface

- Concerns about a possible association between coronavirus disease 2019 (COVID-19) vaccination and abnormal menstrual cycles may lead to **vaccine hesitancy**.
- Social media reports suggest menstrual disturbances are much more common but that these disturbances appear to be temporary
- Menstrual cyclicity is an overt sign of **health and fertility**.

preface

- 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

- **retrospective cohort** analysis of menstrual cycle data
- We included U.S. residents aged 18–45 years who were at least three cycles post-pregnancy or post-use of hormonal contraception.
- Included individuals had normal pre-vaccination menstrual cycle lengths (average 24–38 days)

METHODS

- Our primary outcome was the within-individual change in cycle length (in days) from the three-cycle pre-vaccination average to the initial vaccination cycle.
- 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

METHODS

- We categorized
 - Age
 - Race and ethnicity
 - State of residence
 - Parity
 - Body mass index
 - Education

METHODS

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

Characteristic	Unvaccinated (n=1,556)	Vaccinated (n=2,403)	Overall (N=3,959)	<i>P</i>
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)	

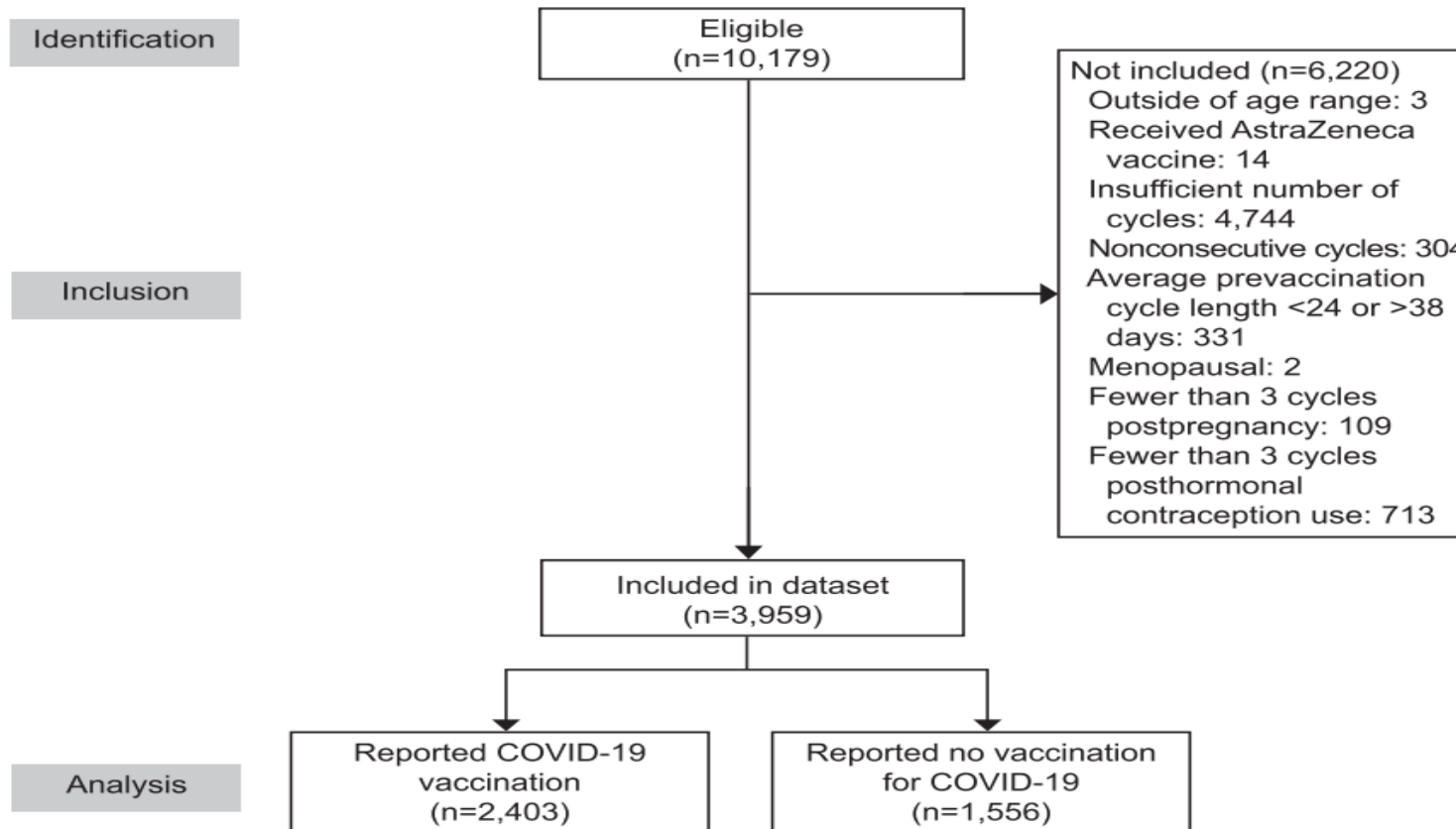
METHODS

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)	

METHODS

- 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 pre-vaccination cycle whose absolute cycle length was **outside of the 24–38-day range**
- Third, we excluded any individuals who reported **polycystic ovarian syndrome**, thyroid disorder, or endometriosis (226 individuals)

METHODS



RESULTS

- Of 10,179 eligible individuals, 3,959 representing 23,754 cycles met inclusion criteria
- The final study sample included 2,403 vaccinated individuals and 1,556 unvaccinated individuals

RESULTS

- The vaccinated cohort
 - was slightly **older**
 - more likely to be **nulliparous** (79% vs 69%) and **college educated** (77% vs 60%)
 - more likely to identify as **White** (54% vs 47%)

RESULTS

- 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 pre-vaccination cycles.

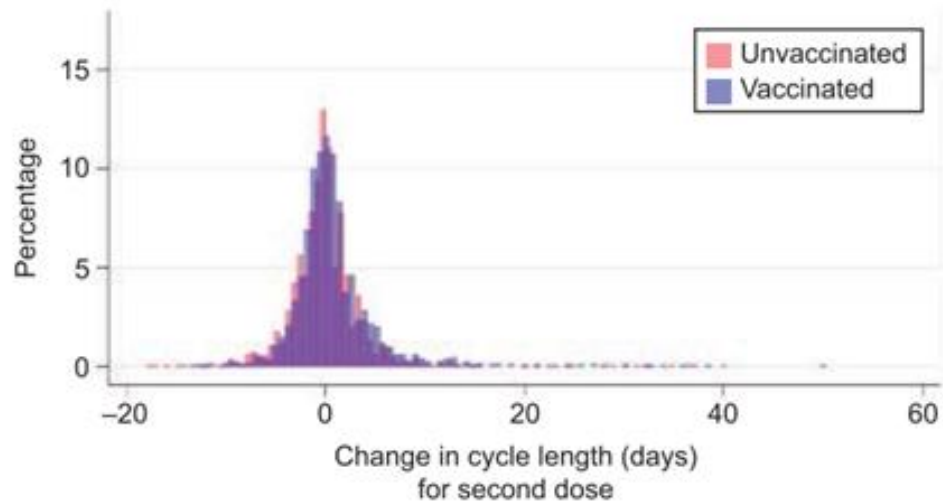
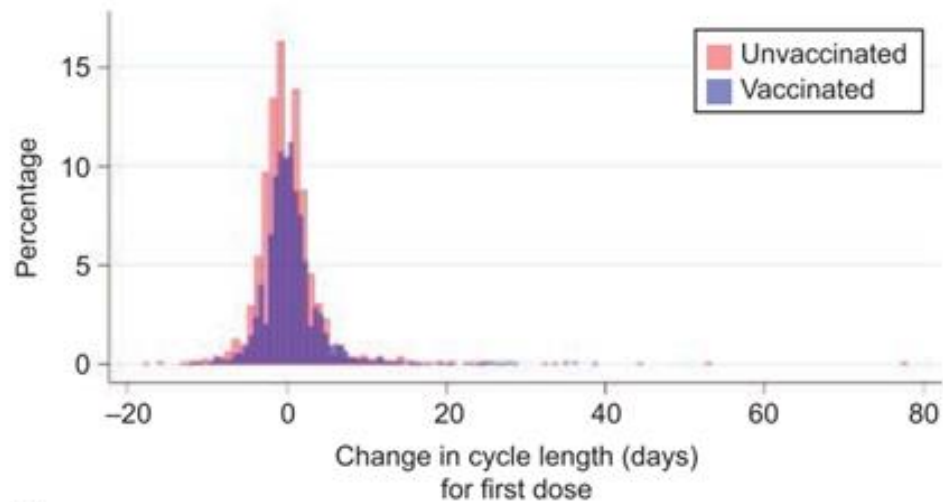
	n	Cycle Length		Menses Length	
		Change in Length (d)	Adjusted Difference in Change vs Unvaccinated Individuals (d)*	Change in Length (d)	Adjusted Difference in Change vs Unvaccinated Individuals (d)*
1st dose					
Unvaccinated	1,556	0.07 (−0.22 to 0.35)	—	−0.09 (−0.18 to 0.00)	—
Vaccinated	2,403	0.71 (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.

RESULTS

- Although statistically significant, the overlaid histograms show a cycle length change distribution in vaccinated individuals that is roughly equivalent to that in unvaccinated individuals



A

RESULTS

- After adjusting for confounders, the difference in the change in cycle length by vaccination status was 0.64 days (98.75% CI 0.27–1.01)

	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.

RESULTS

- The majority of vaccinated individuals received a second vaccine dose
- experienced an unadjusted mean **0.91- day increase** in cycle length during their second vaccine cycle (98.75% CI 0.63– 1.19);
- unvaccinated individuals had no significant change

2nd dose

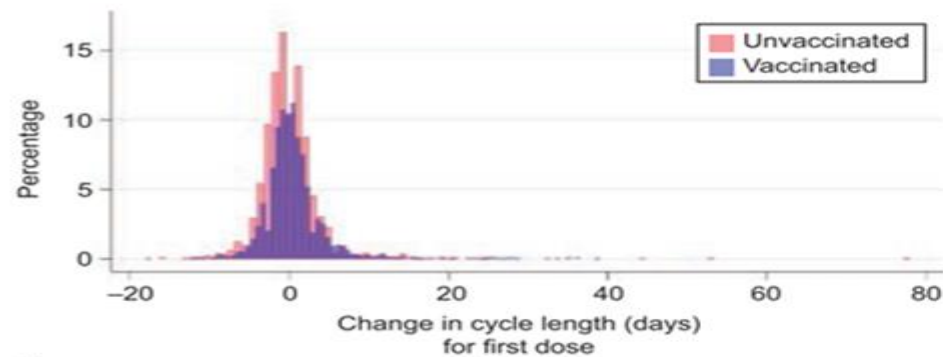
Unvaccinated	1,556	0.12 (-0.15 to 0.39)	=	-0.09 (-0.18 to -0.01)	=
Vaccinated	1,919	0.91 (0.63-1.19)	0.79 (0.40-1.18)	-0.01 (-0.09 to 0.07)	0.08 (-0.04 to 0.20)

RESULTS

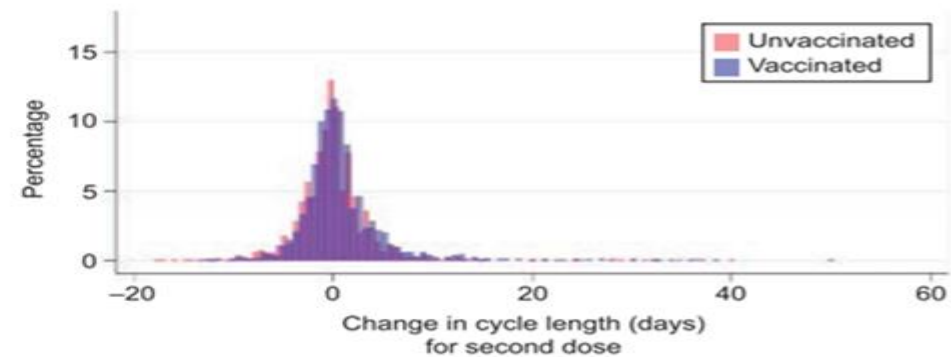
- after **adjusting for confounders**, the difference in the change in cycle length for the second vaccine cycle by vaccination status was **0.79 days** (98.75% CI 0.40–1.18).

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)



A



RESULTS

- 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
- This subgroup experienced a 2-day unadjusted mean cycle length increase (, 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)

RESULTS

- 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. Unadjusted Change in Cycle Length From Three Prevaccination–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.

RESULTS

- 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 pre-vaccination cycles was no longer different from the changes in the unvaccinated group.
- the 358 individuals who received two doses in their first vaccine cycle also had a nonsignificant change of 0.17 days (98.75% CI 20.33 to 0.67)

RESULTS

- 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 20.04 to 0.19), second dose 0.08-day difference (98.75% CI 20.04 to 0.20)

	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.

DISCUSSION

- 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
- We found no change in menses length between or within vaccination cohorts.

DISCUSSION

- Menstrual cycle timing is regulated by the hypothalamic-pituitary-ovarian axis, which can be affected by life, environment, and health stressors.
- Our results cannot be explained by generalized pandemic stress because our unvaccinated control group saw no changes over a similar time period.

DISCUSSION

- mRNA vaccines create a robust immune response or stressor, which could temporarily affect the hypothalamic-pituitary-ovarian axis if timed correctly
- Our findings for individuals who received two doses in a single cycle supports this hypothesis.

DISCUSSION

- 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.
- 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

DISCUSSION

- 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
- Self-reports are useful for rapidly identifying potential signals or rare adverse events, but they are limited by significant confounding and reporting biases

DISCUSSION

- 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.**

DISCUSSION

- Our study also has limitations
 - Other subpopulations are known to have greater baseline variations in menstrual cyclicity, such as individuals with BMIs higher than 35.
 - Finally, we do not have data on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in either our vaccinated or unvaccinated groups

DISCUSSION

- Our findings are reassuring; we find no population-level clinically meaningful change in menstrual cycle length associated with COVID19 vaccination
- 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

