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## Is the phase of the menstrual cycle relevant when getting the covid-19 vaccine?

**OBJECTIVE:** Stability of the menstrual cycle is a key indicator of health, and its alteration can affect the physical, emotional, sexual, and social aspects of menstruating individuals' lives.<sup>1</sup> A recently published study showed a statistically significant increase in cycle length after vaccination against COVID-19 and no significant changes in the menses length.<sup>2</sup> However, there is no information about the potential association between vaccination time and change in cycle length. This study aims at assessing the association between the phase of the menstrual cycle at vaccination time and change in cycle length.

**STUDY DESIGN:** We analyzed data collected by the menstrual cycle tracking smartphone application Lunar App.<sup>3</sup> This application allows users to track their menstrual cycle and menses, recording the beginning and end dates, pain intensity, blood loss quantity during menses (more, equal, or less than usual), and their COVID-19 vaccination status.

The database contained 28,876 users and 162,529 cycles. The distribution of the percentages of the users' age ranges (years) was as follows: 18 to 24, 11.85%; 25–34, 49.15%; 35 to 44, 28.56%; 45 to 54, 8.31%; other, 2.13%. We filtered the database, keeping only users who had reported their vaccination status and at least 5 consecutive cycles. We considered the first doses or monodoses of the vaccine for the analysis and removed incomplete and/or wrong data. After this filtering process, we ended up with 371 users and 1855 cycles registered between September 2020 and February 2022. The relatively small size of the final sample is caused by the imposed restrictive inclusion and exclusion criteria to ensure the maximum attainable data quality.

For analysis, we employed the self-controlled case series method.<sup>4</sup> Each participant in our cohort was a control and a case before and after getting the COVID-19 vaccine, respectively. Our primary outcome was menstrual cycle length change in days. The secondary outcomes were menses length change in days and variations in the usual blood quantity and pain intensity during the menses. We stratified the analysis of all outcomes by the phase of the menstrual cycle of the user at vaccination time. We considered the luteal phase, ie, the period between menstruation and the 14 days before it<sup>5</sup> owing to the relative robustness of this phase. We considered the rest of the cycle as the follicular phase. The distribution of the medians (over each user) of cycle lengths before the vaccine had a median value of 28 days, with a (5–95) interpercentile range of (22–34) days.

For calculating the menstrual cycle length change, we computed the difference between the median length of the 3

cycles before the vaccine and the length of the cycle in which the vaccine was given (4th cycle) for each user. We then computed the median over all the users and the 95% confidence intervals of the point estimate. We used medians, because the data was not normally distributed. We proceeded similarly for the menses length but employed data from the fifth cycle. For the blood loss quantity and pain intensity, we computed the differences in the percentages of cycles with abnormalities in each endpoint before and after the vaccine and the 95% confidence intervals of the point estimates. Users reported abnormalities when they had more or less blood loss quantity or pain intensity than usual during menses. We employed the Wilcoxon signed-rank and chi-square tests for statistical hypothesis testing of medians and proportions, respectively. Statistical significance was set at  $P < .005$ . The participants of this study provided their consent for the analysis of their data for menstrual or reproductive health research purposes on registration in the app, and the study obtained the approval of an ethics committee. The app does not gather information about the usage of contraception or cycle control methods, and this is a potential limitation of our study, as it could affect the outcomes.

**RESULTS:** We observed an increase in the median cycle length of 0.5 (0.0–1.0) days ( $P$  value  $< 0.005$ ) for all individuals, with 8.08% of the individuals having an increase of 8 or more days, which is considered clinically significant.<sup>6</sup> We observed no variation in menses length, which is in line with results previously reported in the literature.<sup>2</sup> In addition, we observed no significant variations in the percentages of cycles with abnormal blood loss or pain intensity.

Furthermore, the stratified analysis showed an association between the phase of the menstrual cycle of the individual at vaccination time and cycle length change. Thus, individuals vaccinated during the follicular phase showed a median cycle length increase of 1 (0.0–1.0) day ( $P$  value  $< .005$ ), with 11.82% of the users having an increase of 8 or more days. Individuals vaccinated during the luteal phase showed no change (Table).

**CONCLUSION:** Our results show an association between the phase of the menstrual cycle at vaccination time and change in cycle length. Thus, vaccination during the luteal phase would have a protective effect over Covid-19 vaccine-related menstrual cycle disorders, compared to vaccination during the follicular phase. The presented results suggest considering the phase of the menstrual cycle for the design of future COVID-19 vaccination policies and recommend vaccination during the luteal phase. ■

TABLE

**Menstrual cycle phase association with COVID-19 vaccine-related menstrual cycle disorders**

Outcome	All vaccinated individuals		Individuals vaccinated during follicular phase (186; 50.13%)		Individuals vaccinated during luteal phase (185; 49.87%)	
	Change	P value	Change	P value	Change	P value
Cycle length	0.5 (0.0–1.0)	<.005	1.0 (0.0–1.0)	<.005	0.0 (0.0–1.0)	.961
Menses length	0.0 (0.0–0.0)	.010	0.0 (0.0–0.0)	.101	0.0 (0.0–0.0)	.049
Percentage of cycles with abnormal blood loss during menses	–2.88 (–7.75 to 2.00)	.149	–3.76 (–10.90 to 3.37)	.202	–1.98 (–8.60 to 4.64)	.459
Percentage of cycles with abnormal pain intensity during menses	–0.45 (–5.70 to 4.80)	.827	–1.08 (–8.70 to 6.55)	.720	0.18 (–7.02 to 7.38)	.948

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