

1 Title:

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

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19 Conflicts of interest:

20 A.F. is the founder and product owner of LunarApp, the smartphone application used
21 for data collection for the present study. The remaining authors report no conflict of
22 interest.

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24 Sources of funding:

25 B.V. received funding from Agència de Gestió d'Ajuts Universitaris i de Recerca (Award
26 Number: 2020-18). This funding source had no direct role in this manuscript.

27 J.L.F. received funding from H2020 Science with and for Society
28 (Award Number: 872944). This funding source had no direct role in this manuscript.

29 Keywords:

30 COVID-19 vaccination, COVID-19 vaccine, follicular phase, luteal phase, menstruation,
31 menstrual cycle, menstrual cycle disorder, menstrual health, ovarian cycle, ovulation

32 Main text:

33 Objective

34 The menstrual cycle's stability is a key indicator of health, and its alteration can affect
35 physical, emotional, sexual, and social aspects of menstruating individuals' lives.¹ A
36 recently published study showed a statistically significant increase in cycle length after
37 vaccination against Covid-19 and no significant changes in menses length.² However,
38 there is no information about the potential association between vaccination time and
39 the change in cycle length. This study aims at assessing the association between the
40 phase of the menstrual cycle at vaccination time and the change in cycle length.

41 Study Design

42 We analyzed data collected by the menstrual cycle tracking smartphone application
43 Lunar App^A. This application allows users to track their menstrual cycle and menses,
44 recording beginning and end dates, their pain intensity and blood loss quantity during
45 menses (more, equal, or less than usual), and their Covid-19 vaccination status.

46 The database contained 28,876 users and 162,529 cycles. The distribution of the
47 percentages of users' age ranges was: 18-24, 11.85%; 25-34, 49.15%; 35-44, 28.56%;
48 45-54, 8.31%; other, 2.13%. We filtered the database, keeping only users who had
49 reported their vaccination status and at least five consecutive cycles. We considered
50 first doses or monodoses of the vaccine for the analysis, and we removed incomplete
51 and/or wrong data. After this filtering process, we ended up with 371 users and 1855
52 cycles, registered between September 2020 and February 2022. The relatively small
53 size of the final sample is caused by the imposed restrictive inclusion and exclusion
54 criteria, to ensure the maximum attainable data quality.

55 For the analysis, we employed the self-controlled case series method.³ Each participant
56 in our cohort was a control and a case before and after getting the covid-19 vaccine,
57 respectively. Our primary outcome was menstrual cycle length change in days.
58 Secondary outcomes were menses length change in days, and variations in the usual
59 blood quantity and pain intensity during the menses. We stratified the analysis of all
60 outcomes by the phase of the menstrual cycle of the user at vaccination time. We
61 considered the luteal phase as the period between menstruation and the 14 days prior
62 to it,⁴ due to the relative robustness of this phase. We considered the rest of the cycle
63 as follicular phase. The distribution of the medians (over each user) of cycle lengths
64 before the vaccine had a median value of 28 days, with a (5, 95) interpercentile range
65 of (22, 34) days.

66 For calculating the menstrual cycle length change, we computed the difference
67 between the median length of the three cycles before the vaccine and the length of
68 the cycle in which the vaccine was given (4th cycle), for each user. Then, we computed
69 the median over all the users, as well as the 95% confidence intervals of the point
70 estimate. We used medians because the data was not normally distributed. We
71 proceeded similarly for the menses length, but employing data from the 5th cycle. For
72 the blood loss quantity and pain intensity, we computed the differences in the

73 percentages of cycles with abnormalities in each endpoint before and after the
74 vaccine, and the 95% confidence intervals of the point estimates. Users reported
75 abnormalities when they had more or less blood loss quantity or pain intensity than
76 usual during menses. We employed Wilcoxon signed-rank and Chi-squared tests for
77 statistical hypothesis testing of medians and proportions, respectively. Statistical
78 significance was set at $p < 0.005$. The participants of this study provided their consent to
79 the treatment of their data with menstrual or reproductive health research purposes,
80 upon registration in the app. The app does not gather information about the usage of
81 contraception or cycle control methods, and this is a potential limitation of our study,
82 as it could affect the outcomes.

83 **Results**

84 We observed an increase of the median cycle length 0.5 (0.0, 1.0) days (p -value <0.005)
85 for all individuals, with 8.08% of the individuals having an increase of 8 or more days,
86 which is considered clinically significant⁵. We observed no variation in menses length,
87 in line with results previously reported in the literature.² In addition, we observed no
88 significant variations in the percentages of cycles with abnormal blood loss or pain
89 intensity.

90 Furthermore, the stratified analysis showed an association between the phase of the
91 menstrual cycle of the individual at vaccination time and the cycle length change. Thus,
92 individuals vaccinated during follicular phase showed a median increase cycle length of
93 1 (0.0, 1.0) day (p -value <0.005), with 11.82% of the users having an increase of 8 or
94 more days. Individuals vaccinated during luteal phase showed no change (see Table 1).

95 **Conclusion**

96 Our results show an association between the phase of the menstrual cycle at
97 vaccination time and the change in cycle length. Thus, vaccination during the luteal
98 phase would have a protective effect over Covid-19 vaccine-related menstrual cycle
99 disorders, compared to vaccination during the follicular phase. The presented results
100 suggest considering the phase of the menstrual cycle for the design of future Covid-19
101 vaccination policies, recommending vaccination during the luteal phase.

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119 Tables:

120 Table 1

	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)	<0.005	1.0 (0.0,1.0)	<0.005	0.0 (0.0,1.0)	0.961
Menses length	0.0 (0.0,0.0)	0.010	0.0 (0.0,0.0)	0.101	0.0 (0.0,0.0)	0.049
Percentage of cycles with abnormal blood loss during menses	-2.88 (-7.75,2.00)	0.149	-3.76 (-10.90,3.37)	0.202	-1.98 (-8.60,4.64)	0.459
Percentage of cycles with abnormal pain intensity during menses	-0.45 (-5.70,4.80)	0.827	-1.08 (-8.70,6.55)	0.720	0.18 (-7.02,7.38)	0.948

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122 Table 1. Covid-19 vaccine association with menstrual cycle disorder.