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

Authors:
Mr. Borja VELASCO-REGULEZ
MSc, Artificial Intelligence Research Institute, Barcelona, Catalonia, Spain.

Dr. Jose L. FERNANDEZ-MARQUEZ
PhD, University of Geneve, Geneve, Switzerland

Dr. Nerea LUQUI
MD, Holy Cross and Saint Paul Hospital, Barcelona, Catalonia, Spain.

Dr. Jesus CERQUIDES
PhD, Artificial Intelligence Research Institute, Barcelona, Catalonia, Spain.

Ms. Analia FUKELMAN

Dr. Josep PERELLÓ
MD, Autonomous University of Barcelona, Barcelona, Catalonia, Spain.

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

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**Main text:**

**Objective**

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

**Study Design**

We analyzed data collected by the menstrual cycle tracking smartphone application Lunar App. This application allows users to track their menstrual cycle and menses, recording beginning and end dates, their pain intensity and 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 users’ age ranges was: 18-24, 11.85%; 25-34, 49.15%; 35-44, 28.56%; 45-54, 8.31%; other, 2.13%. We filtered the database, keeping only users who had reported their vaccination status and at least five consecutive cycles. We considered first doses or monodoses of the vaccine for the analysis, and we 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 the analysis, we employed the self-controlled case series method. 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. 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 as the period between menstruation and the 14 days prior to it, due to the relative robustness of this phase. We considered the rest of the cycle as 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 three cycles before the vaccine and the length of the cycle in which the vaccine was given (4th cycle), for each user. Then, we computed the median over all the users, as well as 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 employing data from the 5th 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 Wilcoxon signed-rank and Chi-squared tests for statistical hypothesis testing of medians and proportions, respectively. Statistical significance was set at p<0.005. The participants of this study provided their consent to the treatment of their data with menstrual or reproductive health research purposes, upon registration in the app. 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 of the median cycle length 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. We observed no variation in menses length, in line with results previously reported in the literature. 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 the cycle length change. Thus, individuals vaccinated during follicular phase showed a median increase cycle length of 1 (0.0, 1.0) day (p-value<0.005), with 11.82% of the users having an increase of 8 or more days. Individuals vaccinated during luteal phase showed no change (see Table 1).

**Conclusion**

Our results show an association between the phase of the menstrual cycle at vaccination time and the 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, recommending vaccination during the luteal phase.

**References:**


5 Male V. Menstruation and covid-19 vaccination. BMJ 2022;376:o142

Web references:

Tables:

Table 1

<table>
<thead>
<tr>
<th></th>
<th>All vaccinated individuals</th>
<th>Individuals vaccinated during follicular phase (186; 50.13%)</th>
<th>Individuals vaccinated during luteal phase (185; 49.87%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change</td>
<td>P-value</td>
<td>Change</td>
</tr>
<tr>
<td>Cycle length</td>
<td>0.5 (0.0,1.0)</td>
<td>&lt;0.005</td>
<td>1.0 (0.0,1.0)</td>
</tr>
<tr>
<td>Menses length</td>
<td>0.0 (0.0,0.0)</td>
<td>0.010</td>
<td>0.0 (0.0,0.0)</td>
</tr>
<tr>
<td>Percentage of cycles with abnormal blood loss during menses</td>
<td>-2.88 (-7.75,2.00)</td>
<td>0.149</td>
<td>-3.76 (-10.90,3.37)</td>
</tr>
<tr>
<td>Percentage of cycles with abnormal pain intensity during menses</td>
<td>-0.45 (-5.70,4.80)</td>
<td>0.827</td>
<td>-1.08 (-8.70,6.55)</td>
</tr>
</tbody>
</table>

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