**Impact of Coronavirus disease 2019 (COVID-19) vaccination on menstrual bleeding quantity: an observational cohort study**

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**Running head**

COVID19 vaccine and menstrual bleeding quantity

**ABSTRACT**

**Objective** Assess whether coronavirus disease 2019 (COVID-19) vaccination impacts menstrual bleeding quantity.

**Design** Retrospective cohort

**Setting** Five global regions

**Populations** Vaccinated and unvaccinated regularly cycling individuals using the digital fertility-awareness application “Natural Cycles”.

**Methods** We used prospectively collected menstrual cycle data and multivariable longitudinal Poisson GEE models, multivariable multinomial logistic regression models, and calculated the adjusted difference between vaccination groups. All regression models were adjusted for confounders.

**Outcome measures** Mean number of heavy bleeding days (fewer, no change, more) and changes in bleeding quantity (less, no change, more) at three time points (first dose, second dose, and post-exposure menses).

**Results** We included 9,555 individuals (7,401 vaccinated, 2,154 unvaccinated). About 2/3 of individuals reported no change in the number of heavy bleeding days regardless of vaccination status. After adjusting for confounders, there were no significant differences in the number of heavy bleeding days by vaccination status. A larger proportion of vaccinated individuals experienced an increase in total bleeding quantity (34.5% unvaccinated, 38.4% vaccinated; 4.0% [0.7, 7.2%] adjusted difference). This translates to an estimated 40 additional people per 1,000 normally cycling individuals who experience more total bleeding quantity following the first vaccine dose due to vaccination. Differences resolved in the cycle post-exposure.

**Conclusion** A small increase in the probability of more total bleeding quantity occurs following the first COVID-19 vaccine dose which resolved the cycle post-vaccination cycle. Total number of heavy bleeding days did not differ by vaccination status. Our findings can reassure the public that any changes are small and transient.

**TWEETABLE ABSTRACT**

In 9,555 people tracking their #periods, for every 1,000 people who receive the #CovidVaccine, an additional ~40 notice an increase in the flow of their next period compared to those that didn’t receive #CovidVaccine. In their next period, flow returns to normal

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**Keywords**

COVID-19 vaccination, menstrual cycle, menstruation, bleeding quantity

**INTRODUCTION**

Menstrual cycles are considered a sign of overall health, a “vital sign” according to the NIH and medical societies (1,2). Experiencing an unexpected change in menstruation can cause concern and even alarm. Public and media reports about a possible link between coronavirus disease 2019 (COVID-19) vaccination and menstrual disturbances (3,4) have highlighted the lack of evidence to respond to such concerns. Menstrual outcomes were not included in COVID-19 vaccine trials (5–8), limiting manufacturer, public health agencies’, and clinicians’ ability to respond to questions about the impact of the vaccine on menstrual health. There are biologically plausible ways in which a vaccine-elicited immune response could cause menstrual changes: cytokine production may transiently interfere with the hypothalamic-pituitary-ovarian axis, which drives the menstrual cycle (9–12) and/or activation of local immune cells in the endometrium could impact tissue repair at this site, potentially increasing menstrual bleeding (13,14). However, individuals naturally experience inherent and normal variations in menstrual cycle duration and bleeding patterns (15,16), making it challenging to isolate COVID-19 vaccination as a cause.

A growing body of evidence demonstrates that COVID-19 vaccination is associated with a small (less than 1 day) increase in cycle length, and no change in menses length (17–21). Other disturbances, such as bleeding quantity or menstrual symptoms, are less well studied. Retrospective studies have identified that bleeding quantity changes may occur with vaccination but these studies are not designed to determine if vaccination is the main factor associated with these changes due to lack of a comparison group and the use of retrospective self-reported data (22–24).

The objective of this study is to estimate the association of COVID-19 vaccination on menstrual bleeding quantity among individuals with normal menstrual cycles (24–38-day cycle lengths and ≤ 8-day menses). We examine changes in the number of heavy bleeding days and in total bleeding quantity using data from a retrospective cohort study using prospectively collected menstrual cycle data and an unvaccinated comparison group.

**METHODS**

We conducted a retrospective cohort study using vaccination and menstrual cycle data from individuals using the fertility awareness application Natural Cycles (Natural Cycles USA Corp, New York). Cycle data ranged from October 2020 to May 2022; initial COVID-19 vaccinations were received between January 2021 and April 2022. Individuals who use Natural Cycles prospectively track their physiologic data as a non-hormonal pregnancy prevention or planning method and cannot be using a hormonal contraceptive method concurrently. Details on variables tracked by Natural Cycles are reported elsewhere (15). Users may consent to the use of their de-identified data for research, and remove their consent if desired. Individuals who had consented to the use of their data for research purposes were sent an in-app message explaining that their data could be used for studies about the COVID-19 vaccine and requesting their vaccination status (yes/no) and if yes, vaccination details. In order to be eligible for study inclusion, individuals must have given consent for use of their anonymized data and reported their vaccination information. We included individuals ages 18 to 45 years who were at least three cycles post-pregnancy or from use of hormonal contraception, not menopausal by self-report, and who had a normal pre-vaccination menstrual cycle (average length of 24-38 day and menses length of 8 days or less).

Every individual contributed menses data from a minimum of four consecutive cycles. For vaccinated individuals, we included the three menses immediately prior to vaccination, and at least the menses associated with the first vaccine dose (designated as “first dose menses”). If available, we also included menses data from the cycles associated with the second vaccine dose (“second dose menses”), as well as the cycle and menses following vaccination (“post-exposure menses”) to assess potential resolution of changes. If an individual was vaccinated during their menses, that menses was designated as ‘first dose menses’ (or ‘second dose menses, respectively), if they were vaccinated after completion of their menses, the following menses was designated as the ‘first or second dose menses’. For unvaccinated individuals (control group), we included menses data from four to six cycles from a similar time period, depending on the amount of data recorded, to serve as the notional pre-vaccination period, first dose menses, second dose menses, and post-exposure menses. Individuals without data beyond menses associated with the first vaccination dose were excluded from the analyses of later time points.

Individuals using the Natural Cycles application can choose whether or not they want to track their menstrual ‘flow’ or menstrual bleeding quantity; it is not a required variable thus many individuals have no or incomplete data for menstrual bleeding quantity. We excluded individuals with more than one day of missing bleeding quantity data during the three-pre-vaccination menses or during the three post-vaccination menses of interest. Thus, in total, individuals were allowed up to four days of missing bleeding quantity data to be included in the final dataset: one during the pre-vaccination period and one for each of the post-vaccination menses analyzed.

Our primary exposure was COVID-19 vaccination, as reported by individuals using the Natural Cycles application: individuals recorded their vaccination date(s) or confirmed their unvaccinated status. We also classified vaccinated individuals by their vaccine’s mechanism of action: mRNA (Pfizer-BioNTech, Moderna), adenovirus vector (Astrazeneca, Johnson & Johnson/Janssen, Covishield, Sputnik), and inactivated virus (Covaxin, Sinopharm, Sinovac). One individual who received the protein subunit-mediated Novavax vaccine could not be classified with the other vaccine mechanisms and was therefore grouped with individuals with unspecified vaccine brand.

Individuals report their daily bleeding quantity as “spotting”, “light”, “medium”, or “heavy”. We assessed menstrual bleeding quantity in two ways: the number of heavy bleeding days and the total bleeding quantity, i.e., the ordinal sum of bleeding scores with spotting scored as 1, light as 2, medium as 3, and heavy as 4. For each post-vaccination menses (first dose menses, second dose menses, and post-exposure menses), we calculated the within-individual change from the median of the three-pre-vaccination menses. We then categorized the change in the number of heavy bleeding days as fewer days, no change, or more days, and categorized change in total bleeding quantity as less bleeding, no change, or more bleeding. We therefore had 2 outcomes measured at three timepoints each (the first dose menses, second dose menses, and post-exposure menses):1) the change in number of heavy bleeding days and 2) the change in total bleeding quantity. We used a Bonferroni-adjusted significance level of 0.008 to account for multiple comparisons for these six total outcomes and thus report 99.2% confidence intervals. No relevant core outcome set exists or is in development to address menstrual changes and therefore none were used for these analyses.

We included sociodemographic information collected by Natural Cycles using in-app messages. Individuals using the app are required to input some demographic variables (age, country of residence), other data is optional (BMI), while additional sociodemographic data is voluntary as part of research requests and thus, not supplied by all app users. As such, some sociodemographic variables have a large amount of non-ignorable missing data (See **TABLE S1** for details on missingness). As a result, we included missing as a category in multivariable analyses. We classified age at the beginning of the first cycle as 18-24, 25-29, 30-34, 35-39, or 40-44 years. Individuals reported their race and ethnicity as Asian, Black, Hispanic, Middle Eastern or North African, Native Hawaiian or Pacific Islander, or white. Due to small sample sizes, we collapsed race and ethnicity categories into a binary variable for multivariable analyses. We categorized global region as United Kingdom and Channel Islands, Europe, United States and Canada, Australia and New Zealand, or other. Individuals from Sweden made up the majority of users in Europe (51%), while those from Brazil made up the majority of users in the “other” category (62%). We grouped body mass index (BMI) into underweight, normal weight, overweight, and obese categories and collapsed the underweight and normal weight groups for multivariable analyses due to small sample sizes. We also included parity (nulliparous versus parous), education (at least an undergraduate or higher degree versus less education), and relationship status (in a steady relationship or not).

The Oregon Health & Science University Institutional Review Board (Study #00023204, approved 8/6/21) and the UK’s Reading Independent Ethics Committee (Study #230721, approved 7/23/21) approved the study protocol. De-identified data were used under a data use agreement with Natural Cycles USA Corp, New York. No members of the public were directly involved in this analysis, although the research was developed in response to public reports of menstrual disturbances following COVID-19 vaccination.

*Analysis*

We examined sociodemographic characteristics of the study sample, by vaccination status and overall. We compared the changes in the number of heavy bleeding days and total bleeding quantity for the first dose, second dose, and post-exposure menses using Pearson’s chi-squared test, adjusting p-values to reflect our significance level of 0.008. We then created histograms of the raw, uncategorized change in number of heavy bleeding days and total bleeding quantity by vaccination group. We developed multivariable longitudinal Poisson general estimating equation (GEE) models for all three heavy bleeding days outcomes. GEE models included an offset for menses length, and an interaction between time (pre-/post-vaccination) and vaccination status to determine the effect of vaccination, i.e., the adjusted difference in the change in number of heavy bleeding days between vaccination groups. We then plotted the predicted number of heavy bleeding days before and after vaccination for both groups. For the three total bleeding quantity outcomes, we developed multivariable multinomial logistic regression models using no change as the base outcome, then calculated the adjusted predicted probability of each outcome (less bleeding, no change, more bleeding) for each vaccination group and the adjusted difference between groups. All regression models were adjusted for age, race and ethnicity, parity, BMI, education, relationship status, and global region. Models for the second dose menses and post-exposure menses were also adjusted for time between the first and second vaccine doses.

We conducted nine sensitivity analyses to confirm our results. First, we compared sociodemographic characteristics of individuals included in the study to those who were excluded due to missing bleeding quantity data. Second, we compared the change in number of heavy bleeding days and total bleeding quantity for the first and second dose menses by the vaccine’s mechanism of action (mRNA, adenovirus vector, or inactivated virus) and by timing of vaccination (during menses versus after menses). Third, although the data did not meet the missing at random assumption required for imputation techniques, we completed 500 iterations of imputation and weighting with covariate balancing propensity scores using bootstrapped standard errors to confirm that our findings were not biased by missing data or by differences in the characteristics of the vaccination groups. Fourth, we excluded any individuals with polycystic ovarian syndrome (PCOS), endometriosis, or thyroid disorder (n = 454). Fifth, we excluded any individual who used emergency contraception during the study period (n = 472). Sixth, we excluded individuals with any pre-vaccination cycles outside the normal length of 24-38 days (n = 1,420). Seventh, we excluded individuals who had received both vaccine doses since their previous menses (n = 422), Eighth, we excluded individuals with any missing bleeding quantity data during the pre-vaccination menses, or first dose, second dose, or post-exposure menses (n = 4,090 for first dose menses, n = 3,050 for second dose menses, n = 3,020 for post-exposure menses). Finally, we included individuals with pre-vaccination menses lengths of nine or ten days (who had previously been excluded; n = 93). We used Stata 15.1 (StataCorp, College Station, TX) for all analyses.

**RESULTS**

Out of 42,095 users, 9,555 individuals (7,401 vaccinated and 2,154 unvaccinated) representing 229,320 menses met the inclusion criteria (**FIGURE 1**). The overall cohort was under the age of 35 (80.4%), nulliparous (77.4%), had at least a college degree (67.8%), and was in a steady relationship (69.7%; **Table 1**). Most individuals were located in the United Kingdom (32.4%), Europe (31.2%) or the United States and Canada (30.1%). Among vaccinated individuals, the majority received mRNA vaccines: 66.7% Pfizer-BioNTech and 17.9% Moderna. Vaccinated individuals were more likely to have at least an undergraduate degree (71.4% compared to 55.3% among unvaccinated). Characteristics of individuals included in the study were similar to those excluded for missing bleeding quantity data (**TABLE S2**). The sample size for the vaccinated group was considerably smaller for the second dose menses (n = 5,288; **FIGURE 1**) for a variety of reasons. Some individuals (2.0% of vaccinated) received the single dose Johnson & Johnson/Janssen vaccine, some did not receive or did not record information about their second dose (22.6%), and some (3.1%) received their second dose after their last cycle of tracked data.

The unadjusted change in the number of heavy bleeding days reported did not differ between the vaccinated and unvaccinated control group for any of the post-vaccination menses (**TABLE 2, FIGURE S1**). Regardless of vaccination status (actual or notional) for the first dose menses, second dose menses, and post-exposure menses, approximately 60% of individuals experienced no change, while approximately 20% experienced fewer heavy bleeding days and 20% experienced more heavy bleeding days. After adjustment in multivariable models, there were still no significant differences by vaccination status during the first and second dose menses (**FIGURE 2**).

When examining the change in total bleeding quantity pre- and post-vaccination (less bleeding, no change, or more bleeding), we found differences between the vaccinated and unvaccinated control groups (**TABLE 2, FIGURE S2**). Vaccinated individuals were more likely to report more bleeding overall than their unvaccinated counterparts during both the first dose menses (38.3% versus 34.8%, p = 0.027) and the second dose menses (39.8% versus 35.5%, p < 0.001). The proportion of individuals who experienced no change in total bleeding quantity was roughly 18% for both vaccinated and unvaccinated groups at both time points. The differences between groups were no longer statistically significant in the post-exposure cycle. After adjustment in multivariable models, the predicted probability of experiencing more total bleeding quantity was higher in the vaccinated group compared to the unvaccinated control group: 4.0% higher (99.2% CI: 0.7 – 7.2%) for the first dose menses and 3.8% higher (99.2%: 0.2 – 7.3%) for the second dose menses (**TABLE S3**). This translates to approximately 40 additional people per 1,000 normally cycling individuals who will experience more total bleeding quantity due to vaccination. Again, this difference was no longer significant in the post-exposure menses: 2.8% higher for vaccinated individuals (99.2%: 0.8% lower – 6.3% higher; data not shown).

We found no major differences in the change in number of heavy bleeding days or total bleeding quantity when comparing individuals who received an mRNA vaccine to those who received an adenovirus vector vaccine during either the first or second dose menses (**FIGURES S3 & S4**). The number of individuals who received an inactivated virus (n = 44 for first dose menses and n = 31 for second dose menses) was too small to draw conclusions. We also found no meaningful differences in our outcomes when examined by timing of vaccination (during menses versus after completion of menses; **FIGURES S5 & S6**).

The sensitivity analysis imputing missing data and weighting the sample to balance vaccination groups on all sociodemographic variables did not alter our unadjusted or adjusted results in a meaningful way (**TABLE S4**). Nor did the sensitivity analyses excluding individuals 1) with PCOS, endometriosis, or thyroid disorders, 2) who used emergency contraception, 3) with pre-vaccination cycle lengths outside the normal range, 4) who received two vaccine doses prior to a single menses, or 5) with any missing bleeding quantity data. The final sensitivity including individuals with slightly longer pre-vaccination menses lengths (9-10 days) also did not change results.

**DISCUSSION**

**Main Findings**

We used prospectively tracked menstrual cycle bleeding data to assess changes in the number of heavy bleeding days and total bleeding quantity (menstrual ‘flow’) in individuals who received COVID-19 vaccination as compared with an unvaccinated control group. Overall, about 2/3 of individuals reported no change in the number of heavy bleeding days tracked, regardless of vaccination status. After adjusting for confounders, we found no significant differences in the number of heavy bleeding days by vaccination status. However, a larger proportion of vaccinated individuals experienced an increase in total bleeding quantity. Thirty-five (34.5) percent of unvaccinated individuals experienced more bleeding quantity following the first vaccine dose compared with 38.4% among the vaccinated: a 4.0% (99.2% CI: 0.7 – 7.2%) adjusted increase in the probability of more bleeding quantity following the first vaccine dose in multivariable analyses. For the second dose 35.9% of the unvaccinated compared with 39.7% of the vaccinated experienced more bleeding quantity following vaccination: a 3.8% higher (99.2%: 0.2 – 7.3%) adjusted probability for the second dose menses in multivariable analyses. This translates into an estimated additional 40 people per 1,000 normally cycling individuals (the difference between 342/1,000 unvaccinated and 384/1,000 vaccinated) who will experience more total bleeding quantity with the first vaccine dose due to vaccination. Vaccinated and unvaccinated groups’ bleeding quantity was no longer different by the cycle post-exposure.

**Strengths and Limitations**

Strengths of this study include a large global sample with geographic diversity and prospectively tracked bleeding data – users tracked bleeding quantity each day (versus retrospective self-report perceptions of changes in bleeding previously reported). Our outcome measure used counts of heavy bleeding days, which is less subjective than retrospective reports of “more” or “less” bleeding (as previously reported). We also include an unvaccinated control group which allows us to isolate the relationship of vaccination and menstrual bleeding quantity.

Our study’s limitations include missing data in order to fully understand the racial/ethnic and gender-identity diversity in our sample. Our study population is also of lower BMI and higher education than found in general populations. Our study population includes individuals with normal menstrual characteristics pre-vaccine in order to isolate the association of the COVID-19 vaccine and menstrual bleeding changes. Future studies should focus on key sub-groups including contraceptive users, menopausal individuals, people using gender affirming hormonal therapy, and those with non-clinically normal cycles or menses at baseline.

We recognize that more questions remain regarding different aspects of menstrual bleeding but we are limited by the variables collected within the tracking application. On the one hand, the app utilizes the gold standard for real-time menstrual cycle tracking and identifying heavy bleeding which is based on an individual’s self-assessment (16). On the other hand, the units of our ordinal measure of total bleeding quantity have no real numerical interpretation. However, this outcome enables us to note whether a change in bleeding quantity or ‘menstrual flow’ has occurred or not in relationship to vaccine exposure which is a critical knowledge gap and an important outcome of documented interest to the public. Additionally, individuals are not required to track bleeding quantity data in the app, which limited our sample size. We examined data missingness between included and excluded individuals and found no changes in our results. We have no measure of COVID-19 disease, which may impact bleeding patterns (25–27); and vaccination status is self-report and not verified although we do have dates and vaccine brand, and self-report vaccine status has been shown to be a good surrogate for clinical data.(28)

**Interpretation in light of other evidence**

A study using retrospective recall of bleeding quantity changes following COVID-19 vaccination and no comparison group found that 42% of those reporting regular menstrual cycles prior to vaccination reported experiencing heavier bleeding following vaccination relative to their bleeding before vaccination (24). Another study also using retrospective recall of menstrual changes but including unvaccinated pre/post comparison group (surveyed individuals were asked about outcomes before and after vaccination) found that menstrual disturbances did follow vaccination. However, this study also identified that more than a third of their total participants (vaccinated and control) experienced disturbances even prior to vaccination or for controls over a similar time period (22). This finding is consistent with our results that over a third of individuals regardless of vaccination status had more bleeding quantity. A retrospective study without an unvaccinated comparison group reported that menstrual changes were more frequent following the second dose than the first (23); another found no differences in menstrual flow (18)

Our study highlights the importance of an unvaccinated comparator group: bleeding variability was high regardless of receiving a vaccine. With the inclusion of an unvaccinated control group and accounting for confounders, we found no differences in heavy bleeding days by vaccination status, but we did find that a small but significantly larger proportion of vaccinated individuals experienced more totalbleeding quantity in the cycle of their first and second vaccine doses, compared with unvaccinated individuals. This difference resolved by the cycle following exposure to COVID-19 vaccination. Previous research using the Natural Cycles app data found a small increase in cycle length and no difference in menses length associated with COVID-19 vaccination.(20,21) This study adds to the growing body of evidence of time-limited menstrual disturbances associated with COVID-19 vaccination at a population-level of reproductive-aged individuals with previously regular menstrual cycles.

The impact of COVID-19 disease on menstrual disturbances in unvaccinated individuals is less well defined, which is the relevant counterfactual for those hesitant to vaccinate themselves or family members due to concerns about menstrual disturbances. Changes in menstrual cycles were reported by 16% of a cohort who had COVID-19 disease prior to the availability of vaccines (2020); compared with those who had COVID-19 disease and reported there was no change. In two studies carried out prior to the availability of vaccines, 16% (25) or 28% (26) of menstruating people with COVID-19 disease reported menstrual changes, with changes associated with more severe disease. In a cohort of people with Long COVID, more than 30% of menstruating participants reported some kind of menstrual disturbance (27). Those who reported menstrual changes also reported more severe COVID-19 symptoms (25). Finally, COVID-19 disease carries serious morbidity and mortality risks to unvaccinated individuals which must be considered when discussing concerns about menstrual disturbances and vaccination.

Development of core outcome sets and regulatory support to include these core outcomes in future vaccine development studies would aid in providing foundational information on a critical patient-reported outcome.

**CONCLUSION**

We find a small (4.0%) but statistically significant increase in the adjusted probability of more total bleeding quantity following the first COVID-19 vaccine dose compared with an unvaccinated comparison group. This difference resolved by the post-vaccination cycle. We found no difference in total number of heavy bleeding days by vaccination status. Our findings can inform patients and help providers in counseling about what to expect following COVID-19 vaccination.

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**Disclosure of interests**

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**Contributions to authorship**

ABE conceived of the study and secured funding. ABE, ERB, and BGD developed the analysis plan and conducted analyses. BGD and ERB drafted the manuscript. ABE, EB, JTP, AVL, KAM, STC, LH, JA, and VM provided substantive intellectual contributions to the manuscript.

**Details of ethics approval**

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).

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**Tables and Figure Captions**

**Figure 1. STROBE Flow Diagram**

**Table 1. Study participant characteristics (n = 9,250), by vaccination status**

**Table 2. Changes in number of heavy bleeding days from 3 pre-vaccination median to 1st dose menses, 2nd dose menses, and post-exposure menses, by vaccination status**

**Figure 2. Predicted number of heavy bleeding days for the 3 pre-vaccination median and the 1st dose (left), 2nd dose (center), and post-exposure (right) menses**