Association between COVID-19 vaccination and menstruation: a state of the science review

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► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjsrh-2024-202274).

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Received 9 February 2024
Accepted 25 April 2024
Published Online First 10 June 2024

To cite: Payne LA, Wise LA, Wesselink AK, *et al*. *BMJ Sex Reprod Health* 2024;**50**:212–225.

ABSTRACT

Introduction Menstrual health is a key patient-reported outcome beyond its importance as a general indicator of health and fertility. However, menstrual function was not measured in the clinical trials of COVID-19 vaccines. The purpose of this review was to synthesise the existing literature on the relationship between COVID-19 vaccination and menstrual health outcomes.

Methods A PubMed search to 31 October 2023 identified a total of 53 publications: 11 prospective cohort studies, 11 retrospective cohort studies or registry-based cohort studies, and 31 cross-sectional or retrospective case–control studies.

Results Identified studies were generally at moderate-to-high risk of bias due to retrospective design, interviewer bias, and failure to include a non-vaccinated control group. Nonetheless, the bulk of the literature demonstrates that COVID-19 vaccine is associated with temporary changes in menstrual characteristics (cycle length and flow) and menstrual pain. Follicular phase (at the time of vaccination) is associated with greater increases in cycle length. Evidence suggests temporary post-vaccine menstrual changes in adolescents, abnormal vaginal bleeding in postmenopausal individuals, and a potential protective effect of using hormonal contraception.

Conclusions In this review we found evidence supporting an association between the COVID-19 vaccine and menstrual health outcomes. Given the importance of menstrual function to overall health, we recommend that all future vaccine trials include menstruation as a study outcome. Future vaccine studies should include rigorous assessment of the menstrual cycle as an outcome variable to limit sources of bias, identify biological mechanisms, and elucidate the impact of stress.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Menstrual health data were not collected as part of the clinical trials for the COVID-19 vaccines, and anecdotal reports of menstrual cycle changes after vaccination encouraged independent research to evaluate these outcomes. Individual research studies have evaluated this question, but data have not been summarized in a comprehensive review.

WHAT THIS STUDY ADDS

⇒ We found that most published studies reflected a moderate or high risk of bias due to methodological issues. However, the existing data suggest temporary changes in menstrual cycle length, flow and menstrual pain following COVID-19 vaccination.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ This review suggests the importance of measuring and monitoring the menstrual cycle as a key outcome in future vaccine clinical trials and may also be used to counsel individuals about potential menstrual changes following COVID-19 vaccination.

INTRODUCTION

Half the population will experience menstruation at some point in their lives. Among individuals with a uterus, menstruation occurs for approximately 5–7 days each month for 40 years. Menstrual health, whether characterised in terms of cycle length, days of flow, volume/intensity of flow, regularity or associated symptoms, is a key patient-reported outcome beyond its importance as a general indicator of

health and fertility. Menstrual health outcomes are not routinely included in clinical trials and have not been a consideration for vaccine trials.[1–4] Numerous reports of menstrual disturbances following COVID-19 vaccination, the complete absence of evidence, and the lack of attention to this sex-specific issue contributes to vaccine hesitancy, causes public mistrust, and directly impacts preventable morbidity and mortality (see online supplemental file 1).[5–10] The purpose of this review was to summarise the existing evidence on the relationship between COVID-19 vaccination and menstrual health.

Methods

To identify potentially relevant publications, we used the following search terms in PubMed to identify articles published on or before 31 October 2023: 'COVID-19', 'vaccination', 'vaccine', 'menstruation', 'menses' and 'menstrual changes'. After excluding case series or case reports and publications based solely on postmenopausal individuals, we identified a total of 53 publications: 11 prospective cohort studies, 11 retrospective cohort studies or registry-based cohort studies, and 31 cross-sectional or retrospective case–control studies. These papers were then rated by the co-authors and a research staff member for risk of bias using the ROBINS-E tool, which provides a structured method for evaluating risk of bias in non-randomised epidemiological studies.[11] Authors of any of the included papers were not involved in the risk assessment of these papers. In the results, we have highlighted key studies while summarising the evidence. Additionally, we provide study details for the identified prospective and retrospective cohort studies or registry-based cohort studies in tables 1 and 2, respectively. Study details for cross-sectional studies or retrospective case–control studies are presented in online supplemental file 2.

RESULTS

Cycle length

Cycle length is a distinct measurement defined as the time period from the first day of the last menstrual period until the day before the next menses starts. The bulk of research on COVID-19 vaccination and menstrual health has been focused on cycle length as it is a well-defined and, often, routinely tracked outcome. Formal passive reporting systems and public reports described *both* longer and shorter cycle lengths in the cycle during which COVID-19 vaccination occurs.[12 13] The first prospective study to identify an association between COVID-19 vaccination and temporary alterations to menstrual cycle length was a retrospective cohort study of prospectively tracked menstrual cycles in approximately 4000 US-based individuals.[14] The study utilised de-identified period tracking data from the Food and Drug Administration (FDA)-cleared menstrual tracking application Natural Cycles to compare cycle length differences between vaccinated and unvaccinated individuals. The population analysed had to be not recently pregnant, naturally cycling (no use of hormones) and demonstrate normal menstrual cycle length pre-vaccination. As compared with the unvaccinated control group, vaccinated individuals experienced a slightly longer cycle of less than 1 day after vaccination. A subsequent study broadening the population to include individuals outside the United States confirmed the findings with data from nearly 20 000 individuals and additionally found that for most individuals the increase in cycle length resolved in the cycle following vaccination.[15]

Although the average cycle length change observed in these population analyses was small, there were individuals in both the vaccinated and unvaccinated groups who experienced a greater magnitude of change. Of the total, 1342 participants experienced a change in cycle length of eight or more days, comprising 6.2% of vaccinated individuals and 5.0% of unvaccinated individuals. Individuals who were younger and who had a longer cycle length before vaccination were more likely to experience the increase. This study also found no difference in the type of COVID vaccine (eg, mRNA, attenuated virus, etc.) and no change in menstrual cycle length (eg, days of bleeding).

With regard to menstrual cycle phase at the time of vaccination, one retrospective cohort study of individuals using a menstrual tracking application demonstrated that individuals who received vaccine in the follicular phase were more likely to experience a cycle length disturbance then those who received vaccine in the luteal phase.[16] This study was not designed to determine causation as it did not include a control group or use a validated ovulation date.

Much less is known about the extent to which adolescent girls experience menstrual cycle changes following COVID-19 vaccination – likely given the greater difficulties in studying this vulnerable population. One study included 39 adolescent girls (aged 12–16 years) and assessed menstrual regularity following vaccination. Although this study did not include a control group, the data showed that eight girls (of the 23 with pre-vaccine regular cycles) reported some kind of menstrual irregularity 3 months post-vaccination.[17] A separate study in Norway asked mothers of both vaccinated and unvaccinated adolescent girls to retrospectively report any menstrual cycle disturbances in their daughters.[18] The data showed mothers reported more menstrual disturbances (shorter and longer cycles, increased pain, and increased heavy bleeding) in the girls who had been vaccinated compared with those who were not, although the authors mentioned that menstrual disturbances were common in both groups.

The published literature has continued to demonstrate that COVID-19 vaccination is associated with a slightly longer average cycle length among reproductive-aged individuals who prior to vaccination

Table 1 Prospective cohort studies of premenopausal individuals

First author (reference)	Publication year	Study design	Location	Sample size	Age of participants	Study period	Vaccine types	Outcome(s)	Control variables	Main results	Overall risk of bias rating
Alvergne[19]	2022	Two cohorts: retrospective+prospective	UK	Prospective: 79 Retrospective: 1273	≥18 years	Retrospective: 7/2021–10/2021 Prospective: not provided	Pfizer, Moderna, AstraZeneca, Janssen	Timing and flow of menses	None	▶ Post-vaccine menses: 2.3 days late on average (prospective cohort) ▶ No meaningful change in flow ▶ No association by brand - those on progestogen-only contraception: more likely to report heavy flow	High
Bouchard[58]	2022	Prospective cohort	North America	76	18–42 years	Not provided	Pfizer or Moderna mRNA vaccines	Prospectively collected daily diary data on: cycle length, days of flow, volume, luteal phase length, signs of ovulation. Secondary outcomes: perceived menstrual changes attributed to vaccination	None (time-invariant variables controlled as part of pre–post design)	75 women provided 588 cycles for analysis (227 pre-vaccine cycles, 145 vaccine cycles, 216 post-vaccine cycles). 22% perceived changes in their menstrual cycle post-vaccination but there were no significant differences in menstrual cycle length or days of flow comparing pre-vaccine, vaccine and post-vaccine cycles	Moderate
Chiang[20]	2023	Prospective cohort study	Taiwan	20	≥20 years	Not provided	Moderna, Pfizer, AstraZeneca	Cycle length, bleed length	None (pre–post design)	Bleed length: 6.08 (pre) vs 6.45 (first dose) vs 6.00 days (second dose). Cycle length: 29.42 (pre) vs 30.84 (first dose) vs 30.30 days (second dose)	High
Duijster[59]	2023	Prospective cohort event monitoring study+spontaneous reports	The Netherlands	13 567	16–55 years	1/2/2021–29/3/2022	AstraZeneca, Janssen, Moderna or Pfizer vaccine	Amenorrhoea/oligomenorrhoea, dysmenorrhoea, heavy menstrual bleeding, intermenstrual bleeding, irregular bleeding, reduced blood loss, and withdrawal blood loss abnormal	Age	Increased odds of any menstrual abnormality for Janssen (OR 1.83; 95% CI 1.33 to 2.49), Moderna (OR 2.44; 95% CI 1.86 to 3.20) and Pfizer (OR 3.04; 95% CI 2.36 to 3.93) vs AstraZeneca. Most menstrual abnormalities (63.8%, n=352) occurred after second dose of vaccination vs first dose (36.2%). Overall, median time to resolution of abnormalities was 7 days (IQR 4–14 days)	Moderate
Edelman[15]	2022	Prospective cohort study	Global	19 622	18–45 years	10/2020–11/2021	Pfizer, Moderna, AstraZeneca, Janssen	Cycle length, menses length	Age, BMI, education, parity, relationship status, global region	Adjusted difference (β) in change in cycle length between vaccinated and unvaccinated: first dose: 0.71 (95% CI 0.47 to 0.96); second dose: 0.56 (95% CI 0.28 to 0.84). After second dose: −0.11 (95% CI −0.33 to 0.10). Adjusted difference in change in menses length for vaccinated vs unvaccinated:first dose: 0.07 (95% CI 0.00 to 0.13); second dose: 0.13 (95% CI 0.06 to 0.20)	Low

Continued

Table 1 Continued

First author (reference)	Publication year	Study design	Location	Sample size	Age of participants	Study period	Vaccine types	Outcome(s)	Control variables	Main results	Overall risk of bias rating
Edelman[14]	2022	Prospective cohort study	US	3959	18–45 years	10/2020-9/2021	Pfizer, Moderna, Janssen	Cycle length, menses length	Age, race/ ethnicity, BMI, parity, relationship status, education	Cycle length: first dose: β=0.64 (0.27 to 1.01); second dose: β=0.79 (0.40 to 1.18); Days of flow: first dose: β=0.08 (–0.04 to 0.19); second dose: β=0.08 (–0.04 to 0.20)	Low
Gibson[16]	2022	Prospective cohort study	US	9652	≥18 years	11/2019–1/2022	Moderna, Pfizer, Janssen	Cycle length	Age, BMI, seasonality	All vaccinations: first dose of mRNA vaccine (0.50 days, 95% CI 0.22 to 0.78); second dose of mRNA vaccine (0.39 days, 95% CI 0.11 to 0.67); Janssen vaccine: 1.26 days longer (95% CI 0.45 to 2.07) than pre-vaccination cycles. Follicular phase vaccination: first dose of mRNA vaccine (0.97 days, 95% CI 0.53 to 1.42); second dose of mRNA vaccine (1.43 days, 95% CI 1.06 to 1.80); Janssen dose (2.27 days, 95% CI 1.04 to 3.50)	Low
Mohr-Sasson[17]	2023	Prospective cohort	Israel	35	12–16 years	6/2021–7/2021	Pfizer	Change in: cycle regularity, cycle length, cycle intensity, AMH during 3-month period	Age, BMI, side effects	31.8% of regularly menstruating girls had irregular periods after vaccination; 50% of pre-menarcheal girls reported menarche on 3-month follow-up; AMH levels not appreciably different pre- and post-vaccination	High
Rogers[23]	2022	Prospective cohort	UK	11 475	18–59 years	2/2021–10/2021	AstraZeneca, Pfizer, SpikeVax	Cycle changes	None	Reported HR for first dose of AstraZeneca (reference) with second dose of AstraZeneca, first dose of Pfizer, and second dose of Pfizer. All null	Moderate
Wang[21]	2022	Prospective cohort study	US and Canada	3858	21–56 years (all premenopausal)	4/2020–11/2021	mRNA and adenovirus-vector	Cycle length	Sociodemographic and behavioural factors±pandemic stressors	Vaccination was associated with longer cycles after vaccination (0–6 months: OR 1.67 (95% CI 1.05 to 2.64); 7–9 months: OR 1.43 (95% CI 0.96 to 2.14); >9 months: OR 1.41 (95% CI 0.91 to 2.18)) and among those whose cycles were short, long or irregular before vaccination (OR 2.82 (95% CI 1.51 to 5.27); OR 1.10 (95% CI 0.68 to 1.77) for those with normal length, regular cycles before vaccination). mRNA and adenovirus-vectored vaccines were both associated with this change	Low

Continued

Table 1 Continued

First author (reference)	Publication year	Study design	Location	Sample size	Age of participants	Study period	Vaccine types	Outcome(s)	Control variables	Main results	Overall risk of bias rating
Wesselink[22]	2023	Prospective cohort study	US and Canada	1137	21–45 years	6/2021–8/2022	Moderna, Pfizer, Janssen	Cycle regularity, cycle length, bleed length, heaviness of bleed and menstrual pain	Sociodemographic, lifestyle, medical and reproductive factors	Participants had 1.1-day longer cycles after the first dose of vaccine (95 % CI 0.4 to 1.9) and 1.3-day longer cycles after the second dose (95 % CI 0.2 to 2.5). Associations were attenuated at the second cycle post-vaccination. There was little association with cycle regularity, days of flow, menstrual volume or pain	Low

AMH, anti-Müllerian hormone; BMI, body mass index; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; mRNA, messenger RNA; OR, odds ratio; UK, United Kingdom; US, United States; β, mean difference.

had regular cycles.[16 19–22] We now know the COVID-19 vaccine is associated with changes in cycle length, at least in adult populations, and although a small change in menstrual cycle length may not be meaningful to healthcare professionals and researchers as it does not signify the need for a clinical workup or intervention, the significance of this body of research is that unanticipated, even small disturbances for a key patient outcome like menstrual health can trigger an exponential rise in concerns, as has been the case with the COVID-19 vaccine.

Cycle irregularity/missed periods/intermenstrual bleeding

Studies investigating altered menstrual patterns (ie, missed periods, intermenstrual bleeding and cycle irregularity) remain sparse. These outcomes, specifically missed periods and cycle irregularity, overlap somewhat with one another and with cycle length outcomes and may be viewed and defined differently by patients and the scientific community. Intermenstrual bleeding is more straightforward to define, any bleeding that occurs outside of menses, but the data have not been available prospectively or have been inconsistently tracked by patients. Just three prospective cohort studies in the United States and the UK have reported on pre- and post-vaccination menstrual cycle characteristics; all concluded that COVID-19 vaccination was not associated with a change in menstrual regularity.[21–23] Additionally, one Swedish national register-based cohort study found that COVID-19 vaccinations were not associated with incident menstrual cycle irregularity that was “at least of sufficient concern to warrant seeking medical care” among premenopausal women.[24]

The evidence is less clear regarding any impact of COVID-19 vaccination on other bleeding disorders. Evidence from any longitudinal studies is absent. We found seven cross-sectional surveys of individuals reporting missed periods and intermenstrual bleeding after receiving COVID-19 vaccination (especially in subsequent and booster doses compared with the first dose).[25–31] However, none of the studies was able to ascertain the extent to which these findings were attributable to a natural menstrual variation, selection bias, or causally affected by the vaccines given the cross-sectional study design.

At the present time, the current evidence is insufficient to determine if COVID-19 vaccination is associated with cycle irregularity or other altered menstrual patterns.

Flow effects/bleeding intensity, quantity and duration

Menstrual flow is truly a patient-oriented outcome where the patient determines what is heavy or light; thus any reported change from an individual’s baseline is the outcome of interest.[32] Reported menstrual flow effects around COVID-19 vaccination have been mainly retrospectively collected but duration of menses

Table 2 Retrospective cohort studies or registry-based cohort studies of premenopausal individuals

First author (reference)	Publication year	Study design	Location of study	Sample size	Age of participants	Study period	Vaccine types	Outcome(s)	Control variables	Main results	Overall risk of bias rating
Alahmadi[41]	2022	Retrospective cohort study	Saudi Arabia	673	18–45 years	1/2021–1/2022	Moderna, AstraZeneca, Pfizer-Biotech	Menstrual length, days of flow, volume, pain regarding pre- and post-COVID-19 vaccination	None (pre–post comparison)	Changes in menstruation after both vaccine doses were observed for 47%: 23% more pain after first dose and 21% after second dose. Moderna vaccine was associated with greatest changes (65.4%), AstraZeneca was associated with fewest changes (44.9%). Duration of changes in cycles after vaccination (one dose or both) was <1 month for 42% and ≥3 months for 27.1%. Vaccination was associated with minor and transient increase in menstrual pain	High
Barabás[51]	2022	Retrospective cohort study	Hungary	1563	18–65 years	Recruited: 9/2021–12/2021 Data collected: 2019–2022	Pfizer, Moderna, AstraZeneca, Sputnik, Janssen, Sinopharm	Cycle length, menses length, cycle regularity	None	40.4% reported menstrual changes: 29.9% shorter cycles; 22.2% longer cycles; 13.9% missed period; 7.8% prolonged bleeding; 12.2% irregular bleeding; 4.3% heavier bleeding; 2.8% strong menstrual cramps; 2.0% period reappearance	High
Bisgaard Jensen[49]	2023	Registry-based cohort study	Denmark	13 648	16–65 years	5/2021–12/2021	Pfizer-BioNTech, Moderna, other or mixed	Longer menstrual cycle, shorter menstrual cycle, heavier menstrual bleeding, lighter menstrual bleeding, more regular menstrual cycle, more irregular menstrual cycle, menstrual absence, prolonged bleeding, shortened bleeding, menstrual pain, intermenstrual bleeding, 2-monthly menstrual bleedings, duration of any menstrual changes	Vaccine symptoms, prior COVID-19 infection, concerned about vaccine, stress, age, smoking, health, use of hormonal contraception; alcohol use, physical activity, weight, pre-vaccination menstrual regularity, vaccine type	30% women reported any menstrual change (95% CI 29.31 to 30.86). Less than 10% of women reported either longer or shorter cycles, heavier or lighter bleeding, more regular or irregular cycles, or other menstrual changes	High

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Table 2 Continued

First author (reference)	Publication year	Study design	Location of study	Sample size	Age of participants	Study period	Vaccine types	Outcome(s)	Control variables	Main results	Overall risk of bias rating
Caspersen[18]	2023	Population-based cohort study	Norway	7565	12–15 years	8/2021–10/2021	Comirnaty vaccine	Mother's report of daughter's periods before vs after vaccination: (1) heavier bleeding than usual, (2) prolonged menses, (3) shorter interval between menses than usual, (4) longer interval between menses than usual, (5) spotting between menses and (6) greater menstrual pain	None (self-matched case series study)	RR for heavier bleeding 1.60 (95% CI 1.43 to 1.80); RR for prolonged bleeding 1.39 (95% CI 1.22 to 1.59); RR for shorter interval 1.19 (95% CI 1.07 to 1.32); RR for longer interval 1.15 (95% CI 1.05 to 1.27); RR for spot bleeding 1.06 (95% CI 0.92 to 1.23); RR for stronger period pain 1.14 (95% CI 1.04 to 1.26); RR for period pains without bleeding 1.00 (95% CI 0.90 to 1.11); RR for other pelvic symptoms 0.97 (95% CI 0.76 to 1.25)	High
Darney[33]	2023	Retrospective cohort study	Five global regions	9555	18–44 years	10/2020–5/2022	Pfizer, Moderna, AstraZeneca, Janssen, Covishield and Sputnik, Covaxin, Sinopharm and Sinovac	Mean number of heavy bleeding days and changes in bleeding quantity at three time points (first dose, second dose and post-exposure menses)	Age, race, ethnicity, parity, BMI, education, relationship status, region.	About 66% reported no change in heavy bleeding days, regardless of vaccination status. Little difference in heavy bleeding days by vaccination status. A larger proportion of vaccinated individuals experienced increases in total bleeding quantity (34.5% unvaccinated, 38.4% vaccinated; β=4.0%, 99.2% CI 0.7 to 7.2)	Low
Dellino[60]	2022	Retrospective cohort study	Italy	100	18–45 years	4/2021–4/2022	Pfizer, Moderna, AstraZeneca	Late period, abnormal uterine bleeding	None	23% had menstrual delay, 77% had AUB	High
Hallberg[61]	2022	Registry-based cohort study	Sweden	1.6 million	15–49 years	12/2020–1/2022	Pfizer, Moderna, AstraZeneca	ICD-10 codes: N91 (absent, scanty, rare menstruation), N92 (excessive, frequent, irregular menstruation), N93 (other abnormal uterine/vaginal bleeding)	None	Standardised incidence ratios (comparing with unvaccinated patients in 2019): N91: 0.93 (0.86 to 1.00); N92: 1.04 (1.01 to 1.07); N93: 1.23 (1.17 to 1.28)	High
Hasdemir[62]	2023	Retrospective cohort study	Turkey	258	"Reproductive-aged women"	Not provided	CoronaVac, Pfizer	"Menstrual dysregulation"	None	Prevalence of new-onset menstrual dysregulation following vaccination was 20.6% and it differed compared with baseline. Menstrual pattern returned to normal in 59.6% of vaccinated women	High

Continued

Table 2 Continued

First author (reference)	Publication year	Study design	Location of study	Sample size	Age of participants	Study period	Vaccine types	Outcome(s)	Control variables	Main results	Overall risk of bias rating
Ljung[24]	2023	Registry-based cohort study	Sweden	2 946 448	12–74 years	12/2020–2/2022	BNT162b2, mRNA-1273, ChAdOx1 nCoV-19, AZD1222	Healthcare contact (admission to hospital or visit) for menstrual disturbance or bleeding before or after menopause (ICD-10 codes N91, N92, N93, N95)	Age, country of birth, employed in healthcare, marital status, education, health-seeking behaviours, comorbidity, and treatments	Postmenopausal: highest risks observed after third dose, in 1–7-day risk window (HR 1.28, 95% CI 1.01 to 1.62) and 8–90-day risk window (HR 1.25, 95% CI 1.04 to 1.50). There was a 23–33% increased risk after 8–90 days with BNT162b2 and mRNA-1273 after the third dose, but association with ChAdOx1 nCoV-19 was unclear. Premenopausal: no association with menstrual disturbances or bleeding	Moderate
Trogstad[63]	2023	Retrospective cohort study (Norwegian Young Adult Cohort)	Norway	39 772	18–30 years	5/2021–10/2021	Data from National Immunisation Registry (SYSVAK). Pfizer, Moderna, AstraZeneca (through 3/2021 only)	Menstrual disturbances (heavier bleeding than usual, prolonged bleeding, shorter interval between menstruations, longer interval between menstruations, spot bleedings, stronger pain during menstruation, period pain without bleeding) before and after the first and second dose of COVID-19 vaccine.	Self-controlled case series design	In the first cycle after vaccination: increased occurrence of unusually heavy and prolonged bleeding, spot bleeding, interval changes, and increased pain during periods vs last cycle prior to vaccination. The association was strongest for heavy menstrual bleeding increasing from 8% before vaccination to 14–15% after vaccination, corresponding to RR of 1.90 (95% CI 1.69 to 2.13 after first vaccine dose; RR 1.84, 95% CI 1.66 to 2.03 after second dose). The association between vaccination and menstrual disturbances did not differ by vaccine brand, use of hormones, or history of gynaecological conditions	Moderate

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Table 2 Continued

First author (reference)	Publication year	Study design	Location of study	Sample size	Age of participants	Study period	Vaccine types	Outcome(s)	Control variables	Main results	Overall risk of bias rating
Wong[48]	2022	Retrospective cohort study (vaccine surveillance)	US	62 679	≥18 years	12/2020–1/2022	Pfizer, Moderna, Janssen	Menstrual irregularities or vaginal bleeding	None	63 815 respondents reported on menstrual irregularities or vaginal bleeding, which included 62 679 female respondents (1.0% of 5 975 363 female respondents aged ≥18 years). Common themes identified included timing of menstruation (70 981 (83.6%) responses) and severity of menstrual symptoms (56 890 (67.0%) responses). Other themes included menopausal bleeding (3439 (4.0%) responses) and resumption of menses (2378 (2.8%) responses)	Moderate

AUB, abnormal uterine bleeding; CI, confidence interval; HR, hazard ratio; ICD-10, International Classification of Diseases, 10th Revision; OR, odds ratio; RR, relative risk; US, United States; β, mean difference.

or number of bleeding days have been more available prospectively as they are tracked routinely by individuals and are a main data point captured by menstrual tracking applications.

A large-scale investigation of 9555 menstruating individuals (7401 vaccinated and 2154 unvaccinated) who tracked menstrual cycles using an app found no differences in number of heavy bleeding days, although vaccinated individuals did report greater total bleeding quantity in the cycle when the vaccine was received.[33] Other studies have found no significant changes in self-reported menstrual flow in a large prospective and retrospective sample of women[19] and no differences in relative risk of reporting "heavier" or "lighter" periods in those vaccinated compared with those who were not.[34] Similar self-report studies have found no differences in menstrual flow following vaccination.[35] However, contradictory findings have also been published suggesting there are changes to menstrual flow following vaccination, with many participants reporting "heavier" menstrual flow.[12 36 37] These findings also have support from research demonstrating changes to menstrual flow following vaccination,[31 38] although there have also been a mix of reported changes including "heavier" and "lighter" flow.[39] Despite these mixed findings, the UK Medicines and Healthcare products Regulatory Agency (MHRA) determined that "heavy flow" be included as a potential vaccine side effect, given the strength of the evidence supporting this outcome, and Pfizer and Moderna product information has now added this as a possible side effect.[40]

Menstrual pain and endometriosis

Menstrual pain is a self-reported outcome measure, defined as pain and discomfort in and around the pelvic region that begins with the onset of menstruation. Data on menstrual pain and COVID-19 vaccination are limited, although existing studies do suggest increased menstrual pain after COVID-19 vaccination, affecting around 20–40% of menstruating people after vaccination; estimated prevalence was similar after both the first and second vaccination dose.[28 41–43] Heterogeneity by type of vaccination in relation to post-vaccination menstrual pain experience remains inconclusive.[39 41] However, a longitudinal study that included pre-pandemic and pre-vaccination follow-up data did not observe that menstrual cycle pain complaints varied appreciably according to vaccination status.[22] Importantly, post-vaccination change in menstrual pain could also be attributed to background variability in menstrual pain driven by, for example, between-cycle fluctuations, age-related menstrual changes or pandemic-related stress.[44] Unlike menstrual length and regularity, menstrual pain and other menstruation-related symptoms can be perceived differently when reported in real time versus recalled and influenced by the format of questions, increasing the risk of misclassification or recall bias.

One of the most common medical conditions associated with menstrual pain is endometriosis. Endometriosis is a disease where the lining of the uterus (the endometrium) grows outside of the uterus. Endometriosis is associated with other painful conditions including dyspareunia, dysuria and dyschezia, and can be a source of chronic pelvic pain. It is associated with inflammatory processes, and thus, individuals with endometriosis may be particularly susceptible to effects from the COVID-19 vaccine. Emerging research suggests that people with endometriosis immunised with SARS-CoV-2 mRNA vaccines perceived worsening menstrual cycle abnormalities – namely fatigue, pain and regularity disorders – compared with those without a history of endometriosis.[43 45] Among people with endometriosis, those taking hormonal treatment reported less change in menstrual-associated symptoms,[43] suggesting a possible protective or stabilising effect of oestrogen or progesterone. Notably, in these studies, endometriosis was confirmed by either transvaginal sonography or by hospital record, so it is not clear if participants received surgical confirmation of endometriosis at any point, which is the gold standard for diagnosis.

Postmenopausal individuals

The diagnosis of menopause is quite clear, diagnosed 12 months after an individual's last period. Although one small study of 64 postmenopausal Lebanese women found no evidence of vaginal bleeding following receipt of the COVID-19 vaccine,[46] many larger studies examining population data have found evidence of a slightly increased risk of bleeding in postmenopausal women. In an examination of clinical records of 485 644 postmenopausal women, there was a small but statistically significant increase in the likelihood of receiving an abnormal bleeding diagnostic code in the 16 weeks following COVID-19 vaccination.[47] However, the authors note that this temporary increase was so small that it translated to fewer than 1 in 1000 women experiencing this change. Another study of over 1.5 million Swedish postmenopausal women also reported a small but significantly increased risk of bleeding, particularly after receiving a third dose of the vaccine.[24] An evaluation of reports of COVID-19 vaccine side effects to "v-safe" – an independent and voluntary vaccine monitoring system for individuals in the United States – found that approximately 4% of the 84 943 responses of menstrual disturbances reported postmenopausal bleeding.[48] Additionally, a supplementary analysis of 14 577 Danish self-reported postmenopausal women showed 2% (n=347) reported some "menstrual changes" following vaccination.[49] Postmenopausal women, by definition, are not menstruating, although the authors did not clarify the specific "menstrual" changes reported by postmenopausal women. Taken together, it does appear that many postmenopausal individuals experienced some abnormal vaginal bleeding following COVID-19 vaccination and this information is critically important information for this population to know when considering the potential side effects of the COVID-19 vaccination.

Hormonal contraception users

Hormonal contraception encompasses a wide range of methods, method delivery systems and dosing, and can contain only progestogen or oestrogen combined with a progestogen. The few studies that have specifically evaluated the impact of hormonal contraception on menstrual cycle changes following COVID-19 vaccination have suggested that hormonal use has a protective effect against changes to the menstrual cycle but not all studies are able to differentiate between different methods.

One large study including prospective and retrospectively collected self-report data found a delay in the menstrual period following vaccination of 0.37 days, which was a smaller delay than in those not using hormonal contraception. There were no significant changes to menstrual flow following vaccination in those using hormonal contraception generally; although when type of hormone was analysed separately, those using progesterone-only hormones reported heavier flow following vaccination.[19] A separate study also reported heavier menstrual flow post-vaccine among those using hormonal contraception, although type of hormonal contraceptive was not analysed separately. Those using hormonal treatments also reported more breakthrough bleeding.[12] However, one additional study reported *fewer* menstrual cycle changes and less bleeding changes following each of the first and second dose vaccinations in those using hormonal contraceptives compared with those who were not.[43]

Stress

The term "stress" is a broad and wide-ranging term that encompasses a number of areas related to psychological distress, worry or concern.[50] Many different measures can reflect different aspects of stress including depression, anxiety, perceived stress and COVID-19 pandemic-related stress. There have been mixed results with regard to the impact of psychological stress on menstrual disturbances following receipt of the COVID-19 vaccine. Wang and colleagues reported that adult vaccinated women had a higher risk of increased cycle length compared with unvaccinated women, and this finding persisted after accounting for pandemic-related stress, which was assessed as depression, anxiety, posttraumatic stress, perceived stress and worry about COVID-19.[21] Similarly, another study found no relationship between perceived stress and vaccination status or menstrual cycle characteristics.[22] However, another study found that changes in menstrual cycle characteristics were correlated with symptoms of depression, suggesting that the menstrual

cycle effects of the vaccine may be related to changes in mood.[51] However, these inconsistent findings may result from different assessments of stress and how those measures related to changes in the menstrual cycle.

Long/short pre-vaccination cycles

Almost all of the research published to date is focused on individuals with regular pre-vaccination menstrual cycles.[32] The restriction of analyses to this 'normal' cycle population was by design, otherwise it would have been impossible to determine if an actual signal existed due to the vaccine. Individuals with baseline irregular cycles did report menstrual disturbances through official passive reporting systems (Vaccine Adverse Event Reporting System, VAERS) and social media-based surveys. However, due to the inherent increased variability with irregular cycles, it will be a challenge to determine what changes are due to the vaccine.

AREAS OF FUTURE RESEARCH

Optimisation of study design and risk of bias

Cross-sectional and retrospective case–control studies, which select participants after both vaccination and menstrual changes have already occurred, are more prone to selection bias than prospective studies because selection is more likely to be dependent on both exposure and outcome. Another common concern about many studies is that participants were asked to report data on changes in menstruation in relation to vaccination, or participants were asked to provide data on vaccination and menstrual changes on the same questionnaire, both of which are likely to increase potential for spurious positive associations. The studies at lowest risk of bias are those that: (1) did not select participants in a way that depended on outcome status, (2) collected data prospectively in time (ie, vaccination data were collected before data on the occurrence of menstrual changes), (3) included a comparison group of non-vaccinated participants and (4) followed participants for at least two menstrual cycles to assess the extent to which menstrual changes persisted over time. Ideally, a study would use vaccine data on brand, dose and dates from a population vaccine registry (gold standard), but only a small subset of studies had access to vaccination records. Nevertheless, studies that collected data proximal in time to the occurrence of vaccination are likely to have reasonably valid exposure classification. Prospective cohort studies in which participants were asked to report any changes in menstruation attributed to vaccination should still be considered at relatively higher risk of bias. Overall, based on these criteria, there is a moderate-to-high risk of bias in the vast majority of published studies on this topic.

Biological mechanisms

While we still do not know the mechanism for vaccine-induced menstrual changes, in retrospect it is not surprising that temporary changes to the menstrual cycle could occur with vaccination. Prior evidence exists demonstrating that the reproductive and immune systems 'cross-talk', and a large body of literature has demonstrated the role of oestrogen receptors and their impact on immune function,[52 53] although the extent to which the reverse is true (ie, influence of immune responses on oestrogen) is not well documented. The menstrual cycle is orchestrated through the hypothalamic–pituitary–ovarian (HPO) axis with a series of well-timed hormonal events.[54] The follicular phase of the menstrual cycle or the first half of the menstrual cycle prior to ovulation is the portion of the cycle that is the most variable in its duration while the luteal phase is a consistent duration (typically 14 days).[55] It is quite plausible that both stress and inflammation would impact the balance of ovarian hormones that determine menstrual cyclicity.[56] Future research exploring these potential mechanisms is warranted.

DISCUSSION

This review has summarised the existing literature on the relationship between COVID-19 vaccination and menstrual cycle changes. Overall, data from published studies indicate small transient changes in menstrual cycle length (ie, longer cycle length) following vaccination. Additionally, there is some evidence that other menstrual characteristics such as menstrual pain, menstrual flow and intermenstrual bleeding also occur following vaccination. Less is known about how these effects impact unique populations, including postmenopausal individuals and adolescents, although the limited data available suggest that breakthrough bleeding or menstrual cycle changes, respectively, may occur. Data from several studies suggest estrogen-containing hormonal contraception may protect against changes, which may be due to combined hormonal contraception's inherent, dominant effect on the endometrium or perhaps a unique oestrogen-inflammatory interaction. Additionally, preliminary evidence exists suggesting that menstrual cycle phase at the time of vaccination impacts the degree of menstrual changes, although much more research is needed in this area. The role of stress and long/short pre-vaccination cycles is much less clear due to the very limited data available.

Despite the range of studies included in this review, outcome measures varied from study to study, likely reflecting the lack of established measures for assessing menstrual characteristics or use of whatever data were available in attempts to try to answer the question. Although efforts have been made to provide guidelines for menstrual cycle outcome measures,[57] this remains a significant gap in menstrual-related research. Additionally, lack of standardised measures creates further obstacles for future clinical trials to evaluate and assess the impact of interventions on the menstrual cycle. The menstrual cycle is a significant indicator of women's health outside of fertility and pregnancy, and the lack

Box 1 Additional educational resources (Source)

Sharp GC, Fraser A, Sawyer G, *et al*. The COVID-19 pandemic and the menstrual cycle: research gaps and opportunities. *Int J Epidemiol*. 2022 Jun 13;51(3):691-700. doi: 10.1093/ije/dyab239
NIH COVID-19 website. https://covid19.nih.gov/news-and-stories/covid-19-vaccines-and-menstrual-cycle.
COVID-19 vaccination and menstruation. https://www.science.org/doi/10.1126/science.ade1051

of attention to this critical health indicator suggests much work is still needed to address women's health disparities (Box 1).

We now have a solid evidence base from data over the past 3 years demonstrating the impact of the COVID-19 vaccine on the menstrual cycle. However, it should be noted that the majority of these papers are published in obstetrics/gynaecology or low-impact health journals. The lack of publication of vaccine/menstrual cycle papers in general medical journals suggests that much of academic medicine does not see this information as important for public health. Unfortunately, many providers and members of the public may not learn about these results because of decreased visibility or availability of the published articles. General medical journals may want to reconsider publication priorities in light of the impact of women's health outcomes on public health; given the paucity of evidence in the field, even a small or negative finding is important for both patients and providers. Going forward, we encourage the measurement and monitoring of menstrual health as a key outcome in future clinical trials.

Competing interests LAP has served as a consultant for Bayer Healthcare and Mahana Therapeutics. LAW receives in-kind donations from Swiss Precision Diagnostics (home pregnancy tests) and fertility-tracking apps (Kindara) for primary data collection in PRESTO. LAW also receives consulting fees from the Gates Foundation and AbbVie, Inc. SAM has received institutional grants from AbbVie, Inc., National Institutes for Health (NIH), Department of Defense, and the Marriott Family Foundation and received honoraria from the University of British Colombia, WERF, Huilin Shanghai, and University of Kansas Medical Center. SAM has also received travel support from the Society for Reproductive Investigation, ESHRE 2022, FWGBD 2022, University of Michigan, Massachusetts Institute of Technology, ASRM 2022, LIDEA Registry, Taiwan Endometriosis Society, SEUD, and thr Japan Endometriosis Society. SAM has participated on advisory boards for AbbVie, Roche, Frontiers in Reproductive Health, Abbott, Human Reproduction, and LIDEA Registry. ABE received royalties from Up To Date.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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