BMC Women's Health

SYSTEMATIC REVIEW

Open Access

Prevalence of menstrual alterations following COVID-19 vaccination: systematic review & meta-analysis

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Abstract

Background COVID-19 vaccines can lead to diverse local and systemic side effects, but there is limited evidence concerning their association with menstrual cycle changes. This study aimed to assess the prevalence of menstrual cycle alterations after COVID-19 vaccination among adult women.

Methods We systematically searched the PubMed, Web of Science and Science Direct databases for observational studies that included adult women and investigated the range of menstrual alterations. The quality of the studies was evaluated via the Newcastle–Ottawa scale. All the data were analyzed via Comprehensive Meta-Analysis Software Version 4.0. Forest plots were created to calculate the individual and pooled prevalence rates of different types of menstrual changes and 95% confidence intervals (CI) via fixed-effects and random-effects models, as appropriate. Heterogeneity was assessed with Q statistics and the I^2 test.

Results Eleven studies, encompassing 26,283 adult women, met our eligibility criteria. Among the selected studies, five were cohort studies, five were cross-sectional studies, and one employed a case–control design. The menstrual changes included abnormal cycle duration, dysmenorrhea, irregular cycles, and abnormal cycle flow (heavy and light flow), with pooled percentages of 27.3% (CI: 7.2–64.6%), 22% (CI: 5.2–59.4%), 16% (CI: 5.8–37.2%), 11.7% (CI: 5.8–22%), and 5.5% (CI: 2.3–12.5%), respectively.

Conclusions This review highlights the prevalence of menstrual changes after COVID-19 vaccination and emphasizes the importance of considering menstrual health as an integral part of postvaccination monitoring and health care interventions. However, longitudinal studies are essential for establishing a definitive causal relationship between COVID-19 vaccination and menstrual alterations.

Keywords COVID-19, Vaccine, Menstrual cycle

Background

The COVID-19 pandemic, which emerged in Wuhan, China, in December 2019, created a global health crisis. In response, researchers and public health officials have made substantial efforts to develop vaccines aimed at mitigating the impact of the virus [1]. By late 2020, several vaccines had been successfully developed and authorized for emergency use, resulting in their widespread distribution in early 2021 [2]. Vaccines have

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become the most effective method to curb the pandemic, leading to notable reductions in both the incidence of COVID-19 and associated mortality rates [3, 4]. Despite their effectiveness, vaccine uptake has been impeded by concerns regarding their efficacy, potential adverse effects, and safety, and the expedited nature of their development [5, 6].

Many studies have been conducted to assess the safety, efficacy, and potential adverse effects of COVID-19 vaccines [7, 8]. Among the observed adverse effects, menstrual cycle changes have emerged as a significant concern [9, 10]. This issue has been substantiated by reports from numerous women who experienced unexpected alterations in their menstrual cycles through the Vaccine Adverse Event Reporting System (VAERS) and social media [11, 12]. Furthermore, observational studies commonly reported longer or shorter menstrual cycles, increased irregularity, and heavier bleeding after COVID-19 vaccination [13, 14]. However, these changes were typically short-term and resolved spontaneously in approximately half of the cases [15, 16].

The National Institutes of Health (NIH) agreed to fund five institutes to explore a potential link between COVID-19 vaccination and menstrual cycle changes, including the underlying mechanisms [17]. This could have lead to greater interest from researchers in investigating the prevalence of menstrual changes following COVID-19 vaccination, but few studies have investigated the underlying mechanisms [18]. Thus, it is important to consolidate these diverse findings for a more comprehensive understanding of the impact of COVID-19 vaccination on the menstrual cycle [19]. Therefore, we performed this systematic review and meta-analysis to summarize the available qualitative and quantitative data from observational studies that investigated menstrual cycle changes associated with COVID-19 vaccination in adult women.

Objective

This systematic review was carried out to answer the following research question:

In adult women, is the use of the COVID-19 vaccine associated with menstrual cycle changes compared with no vaccination?

Methods

This review adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement [20].

Eligibility criteria

The criteria for considering relevant studies for this review were as follows:

1. Types of studies

We included observational studies on humans that investigated the association of the COVID-19 vaccine with menstrual changes, including cross-sectional, prospective or retrospective case–control, or cohort studies. We excluded experimental in vitro studies, case reports, review articles, editorials, expert opinions, and preprinted articles. Randomized controlled trials (RCTs) were excluded because our study aimed to determine the pooled prevalence of menstrual changes caused by the COVID-19 vaccine. Additionally, vaccine trials did not prospectively collect data on menstrual health outcomes [21].

2. Types of participants

We included human studies in which participants were adult women aged 18–55 years who were otherwise healthy. We excluded studies with the following participant criteria: aged less than 18 years or more than 55 years; pregnant or lactating participants; participants with hormonal or other pathologies that might cause menstrual changes other than the potential effect of the COVID-19 vaccine.

3. Types of interventions

We sought studies in which participants received at least two doses of COVID-19 vaccines of any type.

4. Outcomes

We included studies examining a range of menstrual abnormalities, which included flow (heavy, light, normal), regularity (regular or irregular), duration of cycle (normal or abnormal), and presence of painful menstruation (dysmenorrhea), regardless of whether these changes were self-reported or clinically measured. We excluded studies that investigated the side effects of the COVID-19 vaccine in general and surveillance reports.

Information sources and search strategy

We systematically searched the PubMed, Science Direct, and Web of Science databases for articles published until July 2023. Moreover, we examined the references of the selected articles to find additional relevant articles. Three authors conducted an independent search via the following search terms: ("COVID-19 vaccine" AND "menstrual cycle" OR, "menstrual irregularities"); we also searched for the most widely used vaccine trade names ("Pfizer" OR "Janssen" OR "AstraZeneca" OR "Moderna", AND "menstrual cycle" OR, "menstrual irregularities"). We

also used the truncation (*) with the same root word (vaccine) to find additional research articles. We used truncation to ensure that all potential variants of the search term were found. No limits were applied to the search results except for studies in humans, publication type, or duration filters (2020–July 2023); however, no language restriction was used.

Selection and data collection process

The citations were retrieved via reference management software (Mendeley). Duplicate citations were removed. All the remaining studies underwent a thorough review process. Two authors independently assessed each study, and a third author reviewed all discrepancies to resolve any disagreements during the initial screening. The initial screening involved scrutinizing titles and abstracts against the predefined eligibility criteria. A structured data collection approach was adopted via a Google Excel spreadsheet (Supplementary Tables 1–4). This sheet included essential study information such as the author's name, year of publication, country of origin, study design, sample size, participant age, inclusion criteria, exclusion criteria, administered vaccine, reported outcomes and results. This methodical process ensured the systematic compilation of relevant data from the selected studies.

Data items

All outcomes for which data were obtained were self-reported menstrual changes in terms of flow (heavy, normal, light), which was normal between 20 and 90 mL, approximately 1 and 5 tablespoons; regularity (interval variations between cycles, where the average is to have periods every 28 days); duration of menstruation (number of bleeding days, where normal is between 2 and 7 days); and duration of cycle (first day of period to the day before the next one, where normal is from 23 to 35 days). Studies have reported menstrual changes via different measurements, such as frequency and the risk ratio. Therefore, we have entered data on positive events to calculate individual and pooled event rates to ensure consistency.

Study risk of bias assessment

In this review, the methodological quality of various types of studies, including cohort and case–control studies, was evaluated via the Newcastle–Ottawa scale [22]. For cross-sectional studies, a modified version of the Newcastle–Ottawa scale was used as suggested in a previous systematic review [23]. Two independent reviewers conducted the assessments, and a third reviewer resolved any disagreements through mutual consensus. Notably, the overall quality of the studies was not used as a basis for exclusion in this review. Instead, the primary focus was on conducting a comprehensive assessment of postvaccination menstrual changes across the selected studies.

Synthesis methods

All the data were analyzed via Comprehensive Meta-Analysis Software Version 4.0. Forest plots were created to calculate the individual and pooled prevalence of different types of menstrual disorders, 95% confidence intervals (CIs) were calculated for both fixed effects and random effects, and heterogeneity was assessed with Q statistics and the I^2 test. The cutoff values for the I^2 statistic were used to classify heterogeneity as very low (0–25%), low (25–50%), moderate (50–75%), or high (>75%). Publication bias was assessed via funnel plots and Begg's adjusted rank correlation test. A P value < 0.10 was considered to indicate publication bias.

Results

Study selection

The PubMed search produced 65 articles, the Web of Science search yielded 54 articles, and ScienceDirect provided 330 articles. A manual search for relevant articles resulted in the identification of 14 articles. After excluding articles that did not meet the inclusion criteria and removing duplicate citations, 83 articles were identified for thorough retrieval and examination. At this stage, three articles were excluded because they were preprints [24–26]. Among the remaining 80 articles, 69 were excluded for several reasons related to participants, interventions, study design, and scope of the studies. These included studies that involved adolescents, peri/postmenopausal, breastfeeding, and pregnant women; studies with unclear pregnancy and/or lactation status; studies that involved women with known hormonal or pathological conditions that affect menstruation; studies with unspecified menstrual changes; studies with unstated COVID-19 vaccine types; studies that reported COVID-19-related adverse events, including menstrual changes, without specifying the type of change; and other reasons, such as study design (experimental, quasiexperimental, mixed-method) or studies of menstrual changes with different scopes, such as fertility and endometriosis. Thus, 11 studies were included for the final review, synthesis of evidence, and assessment of the risk of bias [27–37]. The process of selection and exclusion is shown in the PRISMA flow chart (Fig. 1).

Study characteristics

The 11 studies that were selected included 26,283 participants. Among the selected studies, diverse research designs were used. Specifically, five studies adopted

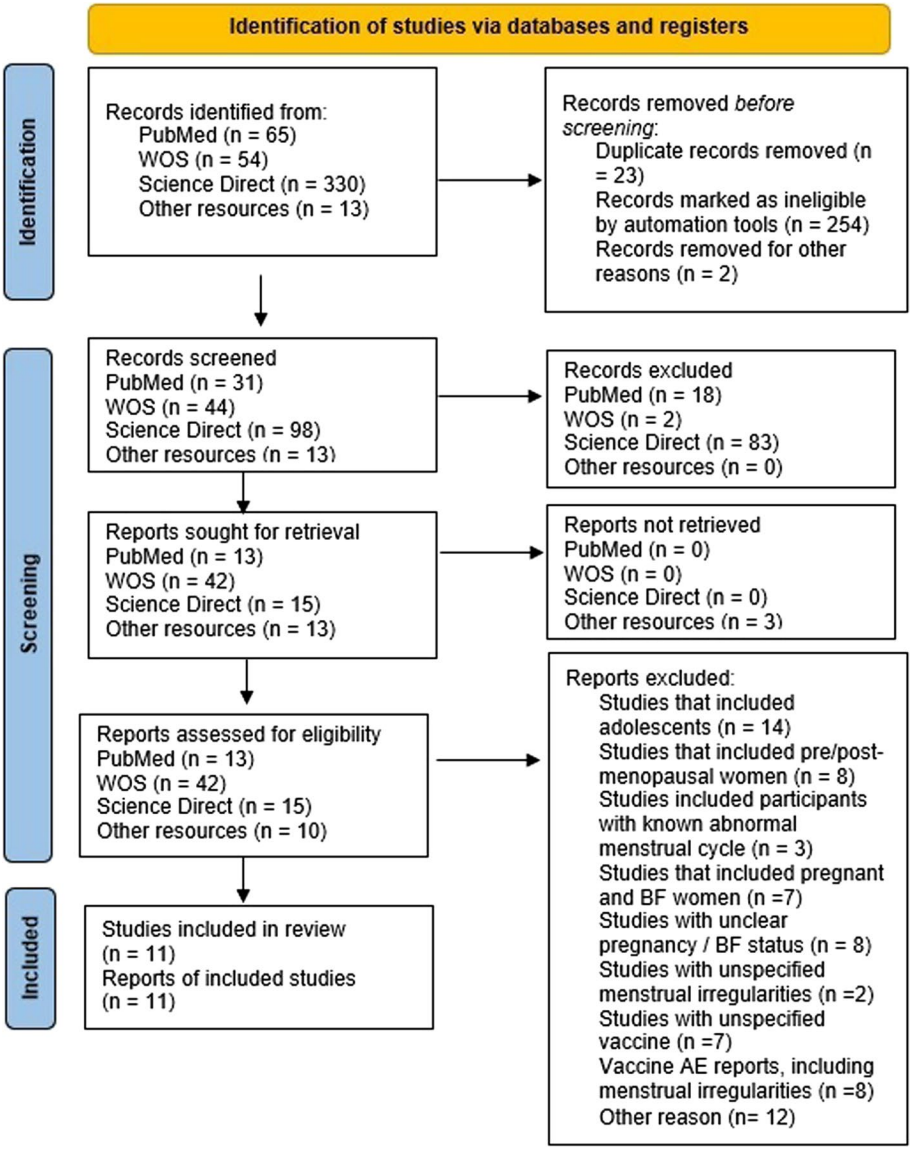

Fig. 1 PRISMA flowchart

a cohort design; one study employed a case–control approach. Additionally, five studies utilized a cross-sectional design. For details of the study design, participant demographics, type of vaccine administered, and specific outcomes, please refer to Table 1 for a comprehensive overview.

Risk of bias in studies

Assessment of quality for the five cohort studies revealed one study of good quality (7 points), whereas the remaining studies were of fair quality (3–4 points) owing to a lack of unexposed controls, ascertainment of exposure, and adequate follow-up. On the other hand, one cross-sectional study was of fair quality (5 points), whereas four studies were of poor methodological quality (2–4 points) owing to the lack of information on nonrespondents, ascertainment of exposure to the COVID-19 vaccine, and assessment of outcomes via self-reports. The details are shown in Tables 2, 3, and 4.

Key findings on menstrual cycle changes associated with COVID-19 vaccination

The studies included in our analysis did not provide data on the overall prevalence of menstrual cycle changes. Instead, they provide information specific to various types of menstrual alterations. Therefore, we generated

Table 1 Study characteristics

Author (year) [ref]	Country	Study design	Age	Inclusion criteria	Exclusion criteria	Vaccine(s) administered (*n*)	Results (%)/Vaccine
Farland (2022) [27]	United States	Cohort	18–45 years	Women 18–45 years old Menstruating With and without a history of SARS-CoV-2 infection Living in Arizona, USA	Pregnant Peri or postmenopausal Hysterectomy or oophorectomy Did not receive two doses of Pfizer-BioNTech or Moderna vaccines or one dose of Janssen vaccine.	mRNA Pfizer-BioNTech (Moderna), vector (Janssen)	24.8% of patients reported alterations in their menstrual cycles following vaccination. The majority (56.3%) noticed these changes after their second dose of the vaccine, compared to the first dose (18%) and the third dose (14%). The most frequently reported changes were irregular menstruation (43.0%), increased premenstrual symptoms (34.1%), increased menstrual pain/cramps (30.4%), and abnormally heavy bleeding (31.1%).Participants previously had an average cycle length of 27 days (SD = 6.1; median = 28) before receiving the COVID-19 vaccine. While their cycles averaged 29 days (SD = 14; median = 31) after vaccination, for those who reported a change in menstrual flow before vaccination, 11% reported spotting, 37% light bleeding, 41% moderate bleeding, and 11% heavy bleeding. After vaccination, these averages changed to 15% spotting, 26% light bleeding, 48% moderate bleeding, and 11% heavy bleeding.
Matar (2022) [28]	Jordan, Palestine, Syria, Egypt, Sudan, and Libya	Cross-sectional	Above 18 years	Women over 18 years old Menstruating	Pregnant /Breastfeeding women Taking OCPs Using IUD Had endometriosis Had PCOS	mRNA (Moderna), Viral vector (Johnson & Johnson/Janssen, AstraZeneca)	Women who received one or more doses of COVID-19 vaccine had significantly higher frequencies of tiredness (89.7%), pelvic pain (85.6%), back pain (82.9%), and thigh pain (63.9%) compared to unvaccinated individuals. Participants who were fully vaccinated had higher frequencies of all of the following: back pain (82.3%), nausea (44.2%), tiredness (90.5%), pelvic pain with periods (85.3%). Menstrual irregularity was statistically significantly observed after Johnson & Johnson vaccine, followed by Sinopharm, Moderna, and AstraZeneca.
Namiki (2022) [29]	Japan	Cross-sectional	Above 18 years	Females over 18 years old Medical experts Received Pfizer–BioNTech vaccine	No consent Males Postmenopausal females Contradictory answers Pregnant women Breastfeeding	mRNA (Pfizer-BioNTech)	The frequency of abnormal bleeding following the first dose was 0.6% and increased following the second (1.0%) and third dose (3.0%). The frequency of irregular menstrual cycles also increased from 1.9% following the first dose to 4.9% and 6.6% following the second and the third doses, respectively.

Table 1 (continued)

Author (year) [ref]	Country	Study design	Age	Inclusion criteria	Exclusion criteria	Vaccine(s) administered (*n*)	Results (%)/Vaccine
Quejada (2022) [30]	Colombia	Cross-sectional	18–41 years	18–41 years old Vaccinated against COVID-19 Normal cycles according to FIGO before vaccination Normal cycles and bleeding despite the use of hormonal contraceptives (combined or progestin-only)	Pregnant or lactating (in the last 6 months) History of diseases that produce menstrual irregularities or early menopause such as anorexia, bulimia, polycystic ovary syndrome, hypothyroidism, obesity (Body Mass Index (BMI) > 30), or low weight (BMI < 18) Hysterectomy or oophorectomy High performance athletes Women who had COVID-19 in the last year	mRNA (Pfizer-BioNTech, Moderna), Viral vector (Johnson & Johnson/Janssen, Oxford-AstraZeneca), inactivated virus (Sinovac), Others (Clover, Sputnik, CanSino, Sinopharm)	Overall, 25% reported that the cycle became infrequent (> 38 days), while 22.28% indicated that it was frequent (< 24 days), and 9.23% reported amenorrhea. These menstrual changes were observed more with Pfizer and Sinovac vaccines. In relation to the duration of the menstrual cycle, (65.2%) had normal ranges (< 8 days), 26.08% had prolonged cycle (> 9 days), and only (8.69%) reported amenorrhea. The menstrual flow was reported as abnormal by 69% of participants, being heavy (41.8%), light (20.65%), and absent in 6.52%. 30.97% of participants described the menstrual volume as normal after vaccination. When discriminating by the type of vaccine: 9.23% vaccinated with Pfizer reported light volume, while the others reported predominantly heavy cycles (with J&J/Janssen Sinovac, Moderna, and AstraZeneca).
Edelman (2022) [31]	United States	Cohort	18–45 years	18–45 years old At least three cycles post pregnancy or post use of hormonal contraception Normal prevaccination menstrual cycle lengths Contributed six consecutive cycles of data	Menopausal Received the Oxford/AstraZeneca vaccine	mRNA (Pfizer-BioNTech, Moderna), Viral vector (Janssen), unspecified	In the first vaccine cycle, the percentage of participants who experienced a clinically significant change in cycle length did not differ by vaccination status (4.3% for unvaccinated vs. 5.2% for vaccinated). During the second vaccine cycle, a slightly higher percentage of participants had a change in cycle length (4.6% unvaccinated vs. 6.5% vaccinated). The increases in cycle length for both the first and second vaccine cycles were reported more among individuals who received both vaccine doses within a single cycle (cycle four). 10.6% had an increase in cycle length of 8 days or more compared with 4.3% in the unvaccinated cohort.
Trogstad (2023) [32]	Norway	Cohort	18–30 years	Received two COVID-19 vaccine doses at least 6 weeks prior to completing the questionnaire	Received three vaccine doses Inconsistency between self-reported vaccination and registry information Reported not to menstruate Unvaccinated Received the first vaccine dose less than 6 weeks prior to completing the questionnaire	mRNA (Pfizer-BioNTech, Moderna), Viral vector (Janssen, Oxford-AstraZeneca)	Overall, The prevalence of any reported menstrual disturbance was 38.8% after the first vaccine dose. The prevalence of heavy bleeding was 13.6% in the cycle after the first dose, and 15.3% after the second vaccine dose. The prevalence of prolonged menstrual bleeding was 12.5% after the first dose, and 14.3% after the second dose. Increased risk of heavier menstrual bleeding than usual after both first and second doses, RR = 1.90 (95% CI 1.69–2.13) and RR = 1.84 (95% CI 1.66–2.03), respectively. Increased risks after both the first and second dose for prolonged bleeding (RR = 1.46 (95% CI 1.31–1.61) for dose 1 and 1.71 (95% CI 1.55–1.89) for dose 2). Increased risks after both the first and second dose for shorter interval (RR = 1.32 (95% CI 1.19–1.46) for dose 1 and 1.57 (95% CI 1.42–1.73) for dose 2). Increased risks after both the first and second dose for stronger period pain (RR = 1.35 (95% CI 1.24–1.47) for dose 1 and 1.62 (95% CI 1.49–1.77) for dose 2). For spot bleeding, only a slight increase was observed after the first dose.

Table 1 (continued)

Author (year) [ref]	Country	Study design	Age	Inclusion criteria	Exclusion criteria	Vaccine(s) administered (*n*)	Results (%)/Vaccine
							N.B. These changes were further analyzed by vaccine type, with the following results: Heavier menstrual bleeding dose 1 Any vaccine: RR of 1.90 (95% CI 1.69–2.13) Comirnaty: RR of 1.89 (95% CI 1.63–2.18) Spikevax: RR of 1.86 (95% CI 1.54–2.26) Vaxzevria: RR of 2.40 (95% CI 1.29–4.46) Heavier menstrual bleeding dose 2 Any vaccine: RR of 1.84 (95% CI 1.66–2.03) Comirnaty: RR of 1.75 (95% CI 1.52–2.02) Spikevax: RR of 1.92 (95% CI 1.67–2.21) Prolonged menstrual bleeding dose 1 Any vaccine: RR of 1.46 (95% CI 1.31–1.61) Comirnaty: RR of 1.51 (95% CI 1.32–1.73) Spikevax: RR of 1.44 (95% CI 1.22–1.70) Vaxzevria: RR of 1.06 (95% CI 0.62–1.79) Prolonged menstrual bleeding dose 2 Any vaccine: RR of 1.71 (95% CI 1.55–1.89) Comirnaty: RR of 1.65 (95% CI 1.44–1.89) Spikevax: RR of 1.78 (95% CI 1.53–2.06) Shorter interval dose 1 Any vaccine: RR of 1.32 (95% CI 1.19–1.46) Comirnaty: RR of 1.31 (95% CI 1.15–1.48) Spikevax: RR of 1.32 (95% CI 1.12–1.56) Vaxzevria: RR of 1.53 (95% CI 0.91–2.57) Shorter interval dose 2 Any vaccine: RR of 1.57 (95% CI 1.42–1.73) Comirnaty: RR of 1.46 (95% CI 1.26–1.69) Spikevax: RR of 1.67 (95% CI 1.46–1.90) Longer interval dose 1 Any vaccine: RR of 1.07 (95% CI 0.97–1.17) Comirnaty: RR of 1.10 (95% CI 0.98–1.23) Spikevax: RR of 1.01 (95% CI 0.85–1.19) Vaxzevria: RR of 1.08 (95% CI 0.57–2.03) Longer interval dose 2 Any vaccine:, RR of 1.24 (95% CI 1.13–1.37) Comirnaty: RR of 1.22 (95% CI 1.06–1.42) Spikevax: RR of 1.26 (95% CI 1.11–1.44) Vaginal spotting dose 1 Any vaccine:, RR of 1.09 (95% CI 1.01–1.17) Comirnaty: RR of 1.13 (95% CI 1.02–1.25) Spikevax: RR of 1.01 (95% CI 0.89–1.13) Vaxzevria: RR of 1.32 (95% CI 0.89–1.94) Vaginal spotting dose 2 Any vaccine: RR of 1.49 (95% CI 1.37–1.62) Comirnaty: RR of 1.47 (95% CI 1.30–1.65) Spikevax: RR of 1.51 (95% CI 1.35–1.70)

Table 1 (continued)

Author (year) [ref]	Country	Study design	Age	Inclusion criteria	Exclusion criteria	Vaccine(s) administered (*n*)	Results (%)/Vaccine
							Stronger period pains dose 1 Any vaccine: RR of 1.35 (95% CI 1.24–1.47) Comirnaty: RR of 1.32 (95% CI 1.18–1.46) Spikevax: RR of 1.45 (95% CI 1.25–1.68) Vaxzevria: RR of 1.14 (95% CI 0.78–1.67) Stronger period pains dose 2 Any vaccine: RR of 1.62 (95% CI 1.49–1.77) Comirnaty: RR of 1.50 (95% CI 1.33–1.69) Spikevax: RR of 1.75 (95% CI 1.55–1.98)
Wesselink (2023) [33]	United States	Cohort	21–45 years	21–45 years old Resided in the United States or Canada Trying to conceive without the use of fertility treatment	Received first dose before enrollment	mRNA (Pfizer-BioNTech, Moderna), Viral vector (Janssen, Oxford-AstraZeneca)	Overall, 15% reported irregular menstrual cycles at baseline. On first and second follow-up after first dose, the prevalence of irregular cycles was 22.7% and 20.4%, respectively. Mean typical menstrual cycle length reported at baseline was 28.6 days among those with regular cycles. Mean cycle length in unvaccinated menstrual cycles was 29.6 days compared with mean cycle length in the first (30.9 days) and second (30.3 days) cycles after the first vaccine dose. The prevalence of short menstrual cycles (less than 24 days) did not show significant variation based on vaccination status. The prevalence of long menstrual cycles (more than 38 days) increased from 5.9% in unvaccinated individuals to 11.1% in the first cycle following the first dose, then decreased to 7.3% in the second cycle following the first dose. The prevalence of bleeding lasting 7 days or more and the need for 20 or more tampons/pads was similar regardless of vaccination status. The prevalence of menstrual pain requiring medication was 29.8% in unvaccinated follow-up questionnaires and increased to 34.8% and 31.9% in the first and second follow-up questionnaires after the first dose, respectively.

Table 1 (continued)

Author (year) [ref]	Country	Study design	Age	Inclusion criteria	Exclusion criteria	Vaccine(s) administered (*n*)	Results (%)/Vaccine
Kumar (2023) [34]	India	Cross-sectional	18–45 years	18–45 years old Received two doses of either COVISHIELD or COVAXIN vaccine with or without a booster dose Had previous three regular cycles before vaccination	Unvaccinated or not fully vaccinated Had previously irregular cycles Pregnant Immediate postpartum or postaborted pregnancy, lactating, on hormonal or IUCD contraceptives On anticoagulants/antipsychotic drugs Currently suffering from COVID-19 infection With comorbidities like diabetes, thyroid disorders, hyperprolactinemia, tuberculosis, autoimmune diseases, morbidly obese Acutely ill patient Not willing to be a part of the study	Recombinant (COVISHIELD), inactivated virus (COVAXIN)	Regularity of menstrual cycle: COVAXIN: Regular (92.8%), irregular (7.2%) COVISHIELD: Regular (94.7%), irregular (5.3%) Duration of menstrual bleeding (days): COVAXIN: ≤5 days (78.1%), > 5-≤7 days (20.6%), > 7-≤10 days (0.9%), > 10-≤15 days (0.3%), > 15 days (0.16%) COVISHIELD: ≤5 days (77.8%), > 5-≤7 days (21.4%), > 7-≤10 days (0.4%), > 10-≤15 days (0.3%), > 15 days (0.02%) Change in menstrual bleeding flow COVAXIN: Yes (6.1%), No (93.9%) COVISHIELD: Yes (5.0%), No (95.0%) If yes, then COVAXIN: excessive (55.3%), scanty (44.7%), amenorrhea (3–5 months) (0%) COVISHIELD: excessive (48.4%), scanty (50.2%), amenorrhea (3–5 months) (1.3%) Number of Pads/Days COVAXIN: 0–2 (30.2%), 3–4 (44.6%), 5–6 (23.8%), 7–8 (1.4%) COVISHIELD: 0–2 (14.3%), 3–4 (65.2%), 5–6 (19.8%), 7–8 (0.58%) New Onset Passage of Clots COVAXIN: Yes (9.2%), No (90.8%) COVISHIELD: Yes (7.5%), No (92.5%) Menstrual cycle Length: COVAXIN: 28–30 days (92.5%), < 20 days (3.2%), > 38 days (4.3%) COVISHIELD: 28–30 days (94.9%), < 20 days (1.5%), > 38 days (3.6%) New onset/worsening of menstrual symptoms before, during, or after the menstrual cycle: COVAXIN: Yes (10.8%), No (89.2%) COVISHIELD: Yes (13.1%), No (86.0%) If yes, then the symptoms were as follows COVAXIN: Severe dysmenorrhea (58.5%), dysmenorrhea + diarrhea (0%), severe lower backache (13.3%), lower abdominal pain (19.3%), weakness and body aches (1.5%), vaginal pain (1.5%), excessive white discharge (0.7%), others (5.2%) COVISHIELD: Severe dysmenorrhea (54.3%), dysmenorrhea + diarrhea (0.3%), severe lower backache (8.5%), lower abdominal pain (17.7%), weakness and body aches (10.6%), vaginal pain (1.7%), excessive white discharge (0.7%), others (6.1%)

Table 1 (continued)

Author (year) [ref]	Country	Study design	Age	Inclusion criteria	Exclusion criteria	Vaccine(s) administered (*n*)	Results (%)/Vaccine
Alvergne (2023) [35]	United Kingdom	Case control	28–43 years	Over 18 years Had ever menstruated Currently lived in the UK Gave informed consent for the use of their data	Did not have a period in the 12 months preceding survey Postmenopausal or transitioning Breastfeeding or pregnant Those who selected "Other changes", those who contributed text to the effect of "too early to say" when describing menstrual disturbances following COVID-19 vaccination Who lived outside the UK	Viral vector (Oxford-AstraZeneca)	82% reported no changes to their menstrual cycles 6.2% reported more disruption 1.6% reported less disruption Current smokers were 1.3 times as likely to report any changes Those with positive COVID-19 disease history were 37–46% as likely to report menstrual changes
Hasdemir (2023) [36]	Turkey	Cohort	19–49 years	19–49 years old Health care providers who were a member of Celal Bayar University Medical School and Hospital Vaccinated with inactivated (CoronaVac) and mRNA-based (Pfizer-BioNTechVR) vaccine	Being pregnant Postpartum or breastfeeding Having systemic illnesses (chronic renal failure, cancer, or major psychiatric diseases) that could affect the menstrual pattern Having hematological disorders Thyroid disease Hyperprolactinaemia History of hysterectomy and/or oophorectomy Current and/or prior SARSCoV-2 infection	Combined (Pfizer-BioNTech), inactivated virus (CoronaVac)	The prevalence of menstrual dysregulation following vaccination was 20.6%, varying by age group: 19–29 (12.9%), 30–39 (21.5%), and 40–49 (27.7%). Regarding menstrual pattern changes after vaccination, 22.2% reported dysregulation, while 77.8% did not. The prevalence of menstrual dysregulation by dose was first dose (3.5%), second dose (6.6%), third dose (5.0%), and 4th dose (20.0%). Types of menstrual dysregulation included hypermenorrhea (33.3%), oligomenorrhea (35.2%), menorrhagia (22.2%), and hypomenorrhea (9.3%).
Kajiwara (2023) [37]	Japan	Cross-sectional	18–22 years	18–22 years old Enrolled at a medical university	Participants with an irregular menstrual cycle Participants with a menstrual cycle length not in the range of 20–40 daysParticipants with insufficient data on their normal menstrual cycle before or after vaccine uptake	mRNA (Pfizer-BioNTech, Moderna)	Increase in menstrual cycle length: After the first vaccination 1.6 ± 2.8 days After the second vaccination: 2.5 ± 3.8 days Women who received two doses of the vaccines within a single menstrual cycle: increase length after vaccination: 3.9 ± 3.3 days The severity and proportion of side effects following the second dose of the vaccine were highest during the menstrual period and lowest during the ovulation period.

Table 2 Quality assessment of studies using the Newcastle–Ottawa scale for assessing cohort studies

Study ID	Selection				Comparability[a]	Outcome			Total (9)
	Representativeness of exposed cohort (+)	Selection of the nonexposed cohort (+)	Ascertainment of exposure (+)	Absence of outcome of interest at start (+)	(++)	Assessment of outcome (+)	Length of follow-up (+)	Adequacy of follow-up (+)	
Hasdemir (2023) [36]	-	-	-	+	-	+	+	-	3
Trogstad (2023) [32]	+	-	+	-	-	-	+	-	3
Edelman (2022) [31]	-	-	-	+	+	-	+	-	3
Farland (2022) [27]	+	-	-	+	+	-	-	+	4
Wesselink (2023) [33]	+	+	-	+	++	-	+	+	7

[a] Comparability of cohorts on the basis of the design or analysis

+ Represents the number of scores

Table 3 Quality assessment of studies using the Newcastle–Ottawa scale for assessing case–control studies

Study ID	Selection				Comparability[a]	Outcome			Total (9)
	Representativeness of the case (+)	Adequacy of case definition (+)	Selection of controls (+)	Definition of controls (+)	(++)	Ascertainment of exposure (+)	Same method of ascertainment for cases and controls (+)	Nonresponse rate (+)	
Alvergne (2023) [35]	+	-	+	+	+	-	+	-	5

[a] Comparability of cases and controls on the basis of the design or analysis

+ Represents the number of scores

Table 4 Quality assessment of studies using a modified Newcastle–Ottawa scale for assessing cross-sectional studies

Study ID	Selection				Comparability[a]	Outcome		Total (9)
	Representativeness of sample (+)	Sample size (+)	Nonrespondents (+)	Ascertainment of the exposure (+)	(++)	Assessment of outcome (++)	Statistical test (+)	
Kajiwara (2023) [37]	+	-	-	-	-	-	+	2
Quejada (2022) [30]	+	+	-	-	-	-	-	2
Kumar (2023) [34]	+	+	-	-	-	+	+	4
Namiki (2022) [29]	+	-	-	-	++	-	+	4
Matar (2022) [28]	+	+	-	-	++	-	+	5

[a] Comparability of subjects in different outcome groups on the basis of design or analysis

+ Represents the number of scores

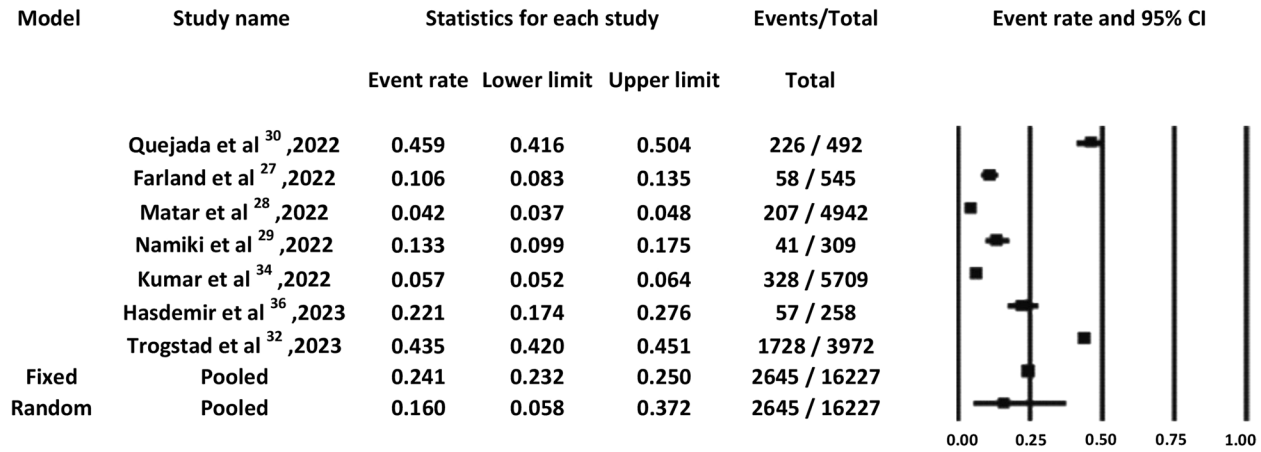

Fig. 2 Forest plot of irregular cycles after COVID-19 vaccination

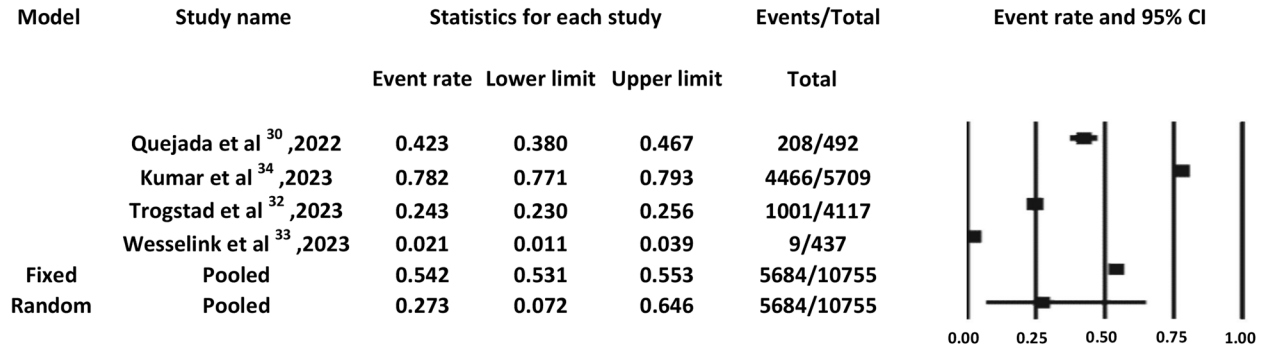

Fig. 3 Forest plot of abnormal cycle duration after COVID-19 vaccination

multiple forest plots categorizing menstrual cycle changes into irregular cycles, abnormal cycle duration, abnormal menstrual flow, and dysmenorrhea.

Prevalence of irregular cycles after COVID-19 vaccination

Seven studies were included in the analysis of the incidence of irregular circulation cycles after COVID-19 vaccination. Overall, the pooled prevalence was 16% (95% CI: 5.8–37.2%). There was high heterogeneity among the included studies ($I^2 = 100\%$; $Q = 2576$; P value < 0.001), as shown in the forest plot (Fig. 2). However, no publication bias was found in any of the studies ($p = 0.440$) according to Begg's adjusted rank correlation test.

Prevalence of abnormal cycle duration after COVID-19 vaccination

Figure 3 shows the forest plot for the pooled prevalence of abnormal cycle duration after COVID-19 vaccination. Four studies were included in the analysis of the prevalence of abnormal cycle duration after COVID-19 vaccination. Overall, the pooled prevalence was 27.3% (95% CI: 7.2–64.6%). There was highly significant heterogeneity among the included studies ($I^2 = 100\%$; $Q = 2658$; P value < 0.001). No publication bias was found in any of the studies ($p = 0.248$) via Begg's adjusted rank correlation test.

Prevalence of abnormal menstrual flow after COVID-19 vaccination

Figure 4 shows the forest plot for the pooled prevalence of heavy flow after COVID-19 vaccination, in which seven studies were included. Overall, the pooled incidence was 11.7% (95% CI: 5.8–22%), and there was highly significant heterogeneity among the included studies ($I^2 = 100\%$; $Q = 1116$; P value < 0.001). No publication bias was found in any of the studies ($p = 0.326$) via Begg's adjusted rank correlation test. Furthermore, five studies were included in the analysis of the prevalence of light menstrual flow after COVID-19 vaccination. Overall, the pooled prevalence was 5.5% (95% CI: 2.3–12.5%). There was highly significant heterogeneity among the included studies ($I^2 = 99\%$; $Q = 317$; P value < 0.001). No publication

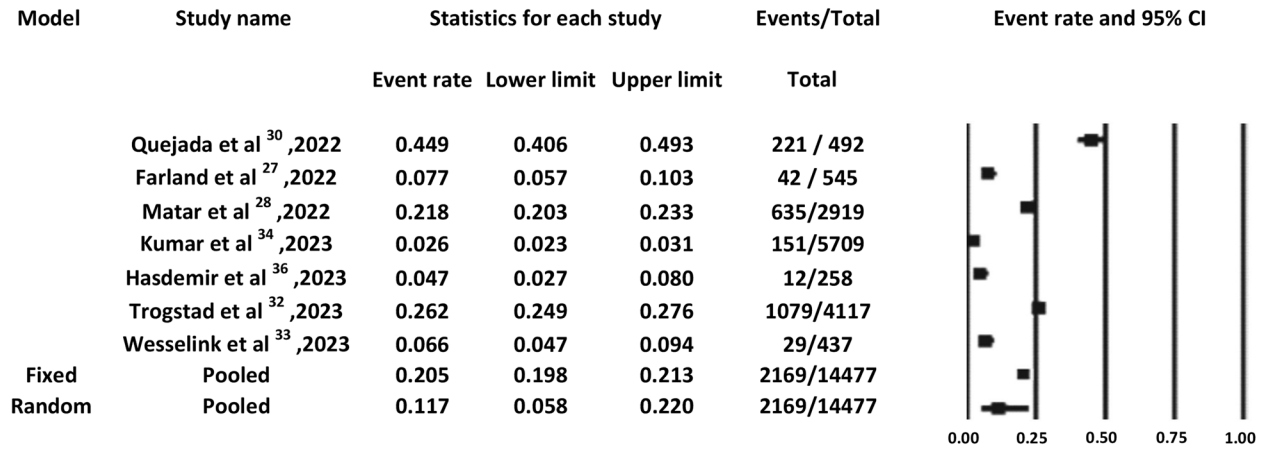

Fig. 4 Forest plot of heavy menstrual flow after COVID-19 vaccination

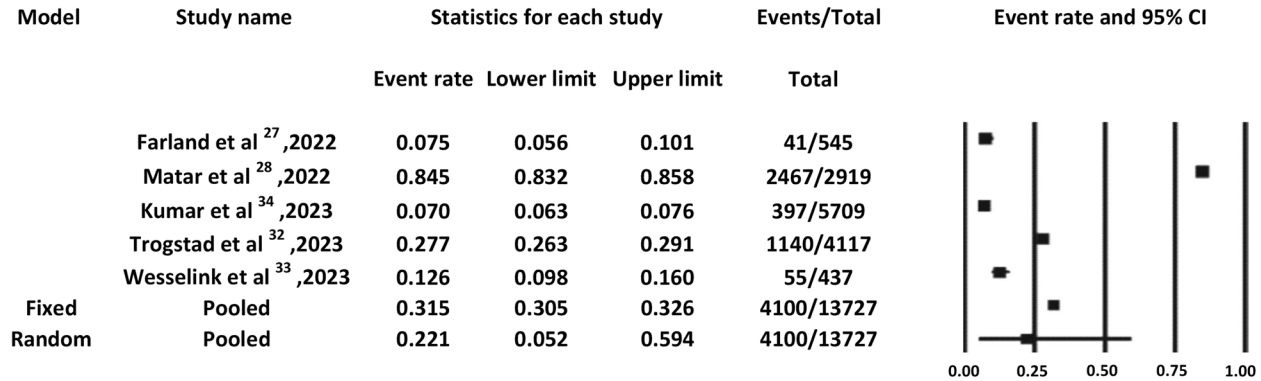

Fig. 5 Forest plot of dysmenorrhea after COVID-19 vaccination

bias was found in any of the studies ($p=0.312$) via Begg's adjusted rank correlation test.

Prevalence of dysmenorrhea after COVID-19 vaccination

Figure 5 shows the forest plot for the pooled prevalence of painful menstruation (dysmenorrhea) after COVID-19 vaccination, in which five studies were included for data analysis. Overall, the pooled prevalence was 22.1% (95% CI: 5.2–59.4%). There was highly significant heterogeneity among the included studies ($I^2=100\%$; $Q=3764$; P value <0.001). No publication bias was found in any of the studies ($p=0.164$) via Begg's adjusted rank correlation test.

Discussion

The results of our systematic review and meta-analysis highlight the potential association of COVID-19 vaccination with menstrual cycle changes among adult women. We observed that more than one quarter of women experienced abnormal cycle duration, followed by dysmenorrhea in approximately 22% of women, while abnormal menstrual cycle length and flow were less common. When these findings are compared with the literature on menstrual alterations related to COVID-19 vaccination, our results align with and add context to previous observations [38]. One large prospective study indicated that women who received the COVID-19 vaccine experienced a slight increase in the menstrual cycle length of less than one day after both the first and second doses [21]. Individuals who received the vaccine during the follicular phase of their menstrual cycle were more likely to experience cycle length disturbances than those who received it during the luteal phase [39].

The current review revealed a lower prevalence of heavy menstrual flow than did another meta-analysis, which reported that menorrhagia was the most frequently observed menstrual change, with a pooled prevalence of 24.24% [40]. However, our findings might be explained by novel data suggesting that decreased menstrual volume and a prolonged cycle are consequences of

SARS-CoV-2 infection independent of its severity [41], and four of our included studies involved patients with prior COVID-19 disease [27, 31, 34, 35]. In contrast, a recently published systematic review and meta-analysis did not find a significant difference in the risk of adverse menstrual events between women who received the COVID-19 vaccine and those who did not, but the evidence is limited by significant heterogeneity and a high risk of bias in the included studies [42].

Moreover, the reporting in this SR was limited to certain outcomes; for example, the duration of menstrual changes and linked vaccine type were reported in three prospective cohort studies that followed participants for sufficient periods. Overall, menstrual changes are temporary and typically last for one to two menstrual cycles postvaccination [31, 33, 36]. One recent study revealed that participants who received the booster vaccine dose had an average cycle duration of 1.20 days longer (95% CI: 1.00–1.40), which persisted from the second to the fourth cycle after receiving the mRNA vaccine [43]. When the vaccination types were compared, the group that received only CoronaVac reported a higher rate of menstrual irregularities than did the groups that received both CoronaVac and BioNTech, with 32.2% and 19.1%, respectively ($p=0.033$) [36]. Sensitivity analyses comparing menstrual cycle changes by vaccine brand did not significantly vary among the vaccinated cohorts that received the Pfizer-BioNTech vaccine (55%), the Moderna vaccine (35%), or the Johnson & Johnson/Janssen vaccine (7%) [33].

Although the current review did not explore potential causal relationships, it is important to note that various pandemic-related factors can lead to temporary changes in the menstrual cycle [44]. Several intrinsic mechanisms have been proposed to clarify the link between significant immune challenges, such as vaccination, and the menstrual cycle [45, 46]. These mechanisms involve immune activation in response to diverse stimuli, including immunological influences on the hormones that regulate the menstrual cycle [47, 48]. Furthermore, immune cells in the uterine lining play crucial roles in the build-up and breakdown of this tissue during each menstrual process [49]. Other extrinsic factors that could contribute to menstrual changes include stress related to the pandemic, lifestyle changes due to the pandemic, and infection with SARS-CoV-2 [18, 50]. Reaching a definitive conclusion regarding the direct link between these changes and a specific type of COVID-19 vaccine presents a significant challenge. This challenge arises from various factors, including differences in study designs, research methods, and subjectivity in reporting these outcomes. Moreover, early assessments of adverse events in COVID-19 vaccine trials were focused primarily on systemic and major adverse events [51, 52].

This review was based on an extensive search, pooling data from studies with different populations, and applying strict eligibility criteria to eliminate studies with potential confounding factors. We calculated both individual event rates and combined event rates via appropriate statistical methods. These qualities can be considered strengths of the analysis. Thus, this study may provide valuable insights into menstrual alterations in adult women after COVID-19 vaccination. Nevertheless, it is essential to interpret the results cautiously due to certain limitations. First, there was a moderate to high risk of bias for some of the included studies, owing to the study design, reliance on self-reported outcomes, short follow-up periods, and lack of control groups. Second, we observed significant heterogeneity in our findings, likely stemming from several factors, including variations in sample size, differences in sampling methods, the diverse nature of the populations studied, and variations in settings and vaccine administration.

Currently, we have sufficient evidence from studies over the past three years indicating the association of the COVID-19 vaccine with temporary menstrual cycle alterations in adult women. However, the exact mechanisms remain unclear; therefore, experimental studies are warranted to determine the temporal link between the COVID-19 vaccine and menstrual cycle changes. The following criteria might optimize the study design and strengthen outcomes: (1) recruitment of unvaccinated controls; (2) inclusion of different age categories, e.g., adolescents and perimenopausal women; (3) the establishment of clinical measures for menstrual characteristics; (4) adequate follow-up of not less than one year after exposure to the COVID-19 vaccine series/booster dose; (4) adjustment for other factors that contribute to menstrual changes.

Finally, it is important to consider the menstrual cycle as a crucial indicator of women's health and not merely fertility/pregnancy-related health. Thus, efforts should be made to increase the awareness of health care providers regarding the latest evidence of the impact of the COVID-19 pandemic on women's health. Moreover, women's concerns about vaccination should be addressed, and proper counseling based on the available evidence should be provided. With respect to public health considerations, although menstrual cycle changes are potential side effects of COVID-19 vaccination, they should not discourage vaccination. Additionally, mechanisms of reporting and monitoring of menstrual health outcomes for future COVID-19 vaccination programs should be strengthened.

Conclusions

This systematic review consolidates the growing body of evidence regarding the potential association of COVID-19 vaccination with menstrual cycle alterations, highlighting abnormal cycle duration and dysmenorrhea as more commonly reported than other menstrual cycle characteristics. However, the evidence is limited by a moderate risk of bias and heterogeneity among the included studies. Thus, further trials are needed to explore causal relationships. While these observed menstrual variations prompt significant considerations for women's health and health care practices, vaccination continues to be advised for women of reproductive age.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12905-024-03349-9.

Supplementary Material 1.

Author contributions

"Conceptualization, A.A.; methodology, N.A2, L.A, and Z.A.; data curation, N.A3, L. A, and R.A.; writing—original draft preparation, A.A, and L.A.; Statistical analysis and synthesis: Dr. Ahmed Hassan (Biostatistician). N.A2 , N.A3 and R.A. prepared all Tables, Z.A prepared Figs. 1, 2, 3, 4 and 5. All authors have read and agreed to the published version of the manuscript."

Funding

This research was funded by Princess Nourah bint Abdulrahman University Researchers Supporting Project number (PNURSP2024R289), Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 9 June 2024 Accepted: 2 September 2024
Published online: 19 September 2024

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