

The Relationship between COVID-19 Vaccination and Menstrual Cycle Pattern, a Systematic Review

Ashraf Direkvand-Moghadam

Department of Midwifery, Faculty of Nursing and Midwifery, Ilam University of Medical Sciences, Ilam, Iran.

***Corresponding Author:** Ashraf Direkvand-Moghadam, Department of Midwifery, Faculty of Nursing and Midwifery, Ilam University of Medical Sciences, Ilam, Iran.

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Abstract

Introduction: There has been growing concern about menstrual disturbances during the COVID-19 pandemic, potentially caused by factors such as vaccination, infection, stress, and lifestyle changes. Our understanding of how COVID-19 impacts menstruation is limited, making it challenging to provide evidence-based advice. Menstrual irregularities can lead to anxiety and concerns about vaccination risks. The relationship between the menstrual cycle and COVID-19 effects remains unclear, highlighting the importance of further research to understand the connection and its implications for female health. The aim of the study was to investigate the relationship between COVID-19 vaccination and menstrual cycle pattern.

Materials and Methods: A systematic review, follows the PRISMA guidelines for systematic reviews. The author conducted a literature search across three databases: Pubmed, Scopus, and Web of Science databases from 2019 – 2024. Keywords derived from the Medical Subject Headings thesaurus were employed, specifically: "Menstrual Cycle", "uterine bleeding", "COVID- 19 Vaccine", and "COVID-19 Virus Vaccines". These identified terms were then amalgamated utilizing the Boolean operators AND and OR, with a prerequisite for their presence in the title, abstract, and keywords.

Findings: The review identified 11 articles, including 5 cross-sectional studies and 6 cohort studies. The outcomes assessed in these studies included changes in menstrual cycle duration, frequency, blood quantity, and associated symptoms. The findings indicate that Covid-19 vaccination can lead to menstrual irregularity, delayed periods, heavier or lighter menstrual flow, and changes in cycle length. These menstrual changes were more frequently reported after the second dose of the vaccine compared to the first dose.

Conclusion: The review shows a link between COVID-19 vaccination and menstrual irregularities, with many women experiencing changes in cycle length, flow, pain, and symptoms. More research is needed for better understanding.

Keywords: COVID-19; immunization; menstrual pattern

Introduction

The Covid-19 pandemic, a global outbreak of a highly infectious respiratory disease caused by the novel coronavirus, has created a severe impact on the world, resulting in widespread illness and death, economic downturns, and significant social disruption [1-3]. The mortality of COVID-19 has been a significant global concern. Studies have shown varying mortality rates and impacts of the pandemic [4,5]. The COVID-19 pandemic has significantly impacted global health education and systems [6]. It has exacerbated existing challenges and introduced new ones, such as interrupted supply chains, economic crises, and healthcare system shortcomings [7]. The pandemic has led to a decrease in healthcare revenue, staff layoffs, and furloughs, highlighting the need for coordinated global health responses [8]. The long-term consequences of COVID-19 encompass a wide array of impacts on physical, mental, and economic levels. Physically, COVID-19 can lead to persistent symptoms like muscle weakness, fatigue, and breathing difficulties, affecting

individuals for weeks or months. Mentally, the pandemic has resulted in increased cognitive decline, memory impairment, anxiety, and depressive-like behavior, with a notable impact on mental health [9]. COVID-19 vaccination started in December 2020, with vaccines from Pfizer-BioNTech, Moderna, Oxford-AstraZeneca, and Johnson & Johnson being widely used [10].

COVID-19 vaccination plays a crucial role in preventing severe illness, hospitalization, and death caused by the SARS-CoV-2 virus. Various types of vaccines, including mRNA and vector vaccines, have been developed and approved for public use, showing high efficacy in preventing symptomatic COVID-19 infections [11,12]. Side effects of COVID-19 vaccination can vary based on factors such as the type of vaccine received and individual characteristics. Common side effects include fever, arm pain, myalgia, burning at the injection site, muscle

pain, and joint pain [13]. COVID-19 vaccines have been associated with abnormal uterine bleeding [14] in women [10,15]. Concerns have arisen regarding the adverse effects of COVID-19 vaccines on female reproductive health, leading to investigations on this topic. The Korean Specialized Committee for COVID-19 vaccination-related loss compensation identified abnormal uterine bleeding [14] as a 'suspected related symptom' post-vaccination, allowing affected individuals to claim compensation [10]. A global retrospective cohort study found that COVID-19 vaccination is associated with a small, temporary increase in menstrual cycle length. However, this increase is less than one day and not associated with any change in the number of days of bleeding. In other words, while some individuals may experience slight changes in their menstrual cycles after vaccination, it does not appear to have a significant impact on overall menstrual patterns. Rest assured, this variation is not harmful and does not affect fertility. By employing a systematic review methodology, the study synthesizes existing literature to provide a comprehensive understanding of the relationship between COVID-19 vaccination and menstrual cycle patterns. This approach follows the PRISMA guidelines, ensuring a rigorous evaluation of the available evidence. The aim of the study was to investigate the relationship between COVID-19 vaccination and menstrual cycle pattern.

Material and method

2.1 Study design

A systematic review, was conducted, incorporating studies, adhering to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) standard and utilizing the PICO strategy (16). The aim of this investigation was to uncover empirical evidence regarding the correlation between COVID-19 vaccination and menstrual patterns.

The studies selected were required to meet the inclusion criteria after a thorough assessment of their title and abstract, resulting in 15 articles being included in the review.

Databases

All articles published in English in the Pubmed, Scopus, and Web of Science databases from 2019 - 2024 were utilized for this study.

Search strategy

Keywords derived from the Medical Subject Headings thesaurus were employed, specifically: "Menstrual Cycle", "uterine bleeding", "COVID-19 Vaccine", and "COVID-19 Virus Vaccines". These identified terms were then amalgamated utilizing the Boolean operators AND and OR, with a prerequisite for their presence in the title, abstract, and keywords.

Inclusion and Exclusion criteria

Both cohort and Cross-sectional studies that discussed the Menstrual Cycle and COVID- 19 Vaccines were included. The systematic reviews were excluded.

Database	n
PubMed/Medline:	10
Scopus:	3
ISI Web of Science:	4

A visual representation of the study selection process can be observed in the flow diagram (Figure 1).

Characteristics of the selected studies

The studies included in this systematic review were Cross-sectional studies, published between 2019 and 2024. Of the 11 studies, 3 were

Study selection process

Firstly, using the Rayyan QCRI programme [17], two researchers screened titles and abstracts for relevance, and removed duplicates. Subsequently, a full-text reading of the articles that apparently met the inclusion criteria took place. The selection process was carried out based on the approval of two researchers.

Data extraction

The PICO strategy was used to extract data such as the general characteristics of the studies and their sample (author, year of publication, country, type of study design, place where the study was conducted, age group, sample size, Types of Vaccines Administered and Number of doses), data collection tools, and the main results.

Risk of bias measurement tool

The evaluation of the risk of bias in the included studies was conducted using the Cochrane Handbook of systematic reviews of interventions [18]. This particular tool examines seven domains, with each domain being assessed using one of three potential outcomes: "High risk" [19], "low risk" (+), and "unclear risk" (?). The domains utilized for the assessment of bias risk included selection bias, performance bias, detection bias, attrition bias, reporting biases, and additional sources of bias that allowed for the identification of unaddressed biases deemed significant.

Quality of the evidence

The Grading of Recommendations, Assessments, Development and Evaluation (GRADE) [20] system was utilized to evaluate the evidence quality of the findings presented in the studies. This framework delineates the evidence quality as the degree of certainty in the accuracy of an effect estimate necessary for formulating a recommendation. Evaluation of evidence quality encompasses considerations such as study bias, variability, a- lack of precision, bias in publication, surrogate outcomes, and additional variables affecting evidence quality.

Results

The process of study identification and selection was conducted meticulously. During the identification phase, a comprehensive search across various computerized databases yielded a total of 17 articles. Subsequently, after removing duplicate and unrelated titles, 11 remaining studies were scrutinized to determine adherence to the inclusion criteria. Upon evaluation, articles fulfilled the criteria, leading to a thorough examination of their full texts. Ultimately, following a detailed analysis, studies were included 11 in this systematic review [21-31].

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developed in Saudi Arabia [21-23], 5 in U.S [24-26, 28, 31] 1 in Japanese[27], 1 in Brazil [29], and 1 in Iran [30]. The aggregate of the initial sample size, comprising the 11 articles included, combines a total of 20670 individuals. The characteristics of the studies and the sample are detailed in Table 1.

Author	Year of publication	Country or Project	Type of study design	Age group	Sample size	Types of Vaccines Administered	Number of doses
Al-Furaydi, A et al (21)	2023	Saudi Arabia	Cohort	18-45	338	Pfizer/BioNTech Moderna Oxford/AstraZeneca	Two doses
Aljehani, AM et al (22)	2023	Saudi Arabia	Cross-sectional	Over 17 year	535	Any of nine different COVID-19	77 %, three doses 20.7% ,two doses 1.7% , one dose
Almousa IA (23)	2022	Saudi Arabia	Cross-sectional	15-54	343	Not specify the exact types of COVID-19 vaccines	91.3%. two doses 8.7%, one dose
Edelman A,et al (24)	2022	US	Cohort	18-45	3959	Pfizer-BioNTech (Pfizer), 55% Moderna , 35% Johnson & Johnson/Janssen,7%	Not clear, majority two doses
Farland, LV et al (25)	2023	US	Cohort	18-45	2367	Pfizer-BioNTech	Three doses
Gibson, EA et al (26)	2022	US	Cohort	?- <20-> 50	9652	Pfizer-BioNTech, 55% Moderna, 37% Johnson & Johnson (J&J), 8%	Pfizer-BioNTech and Moderna, two doses Johnson & Johnson, one dose
Kajiwara, Sh(27)	2023	Japanese	Cross-sectional	18-22	247	Moderna, 90% Pfizer, 10%	Two doses
Laganà, AS et al (28)	2022	US	Cross-sectional	15-49	164	AstraZeneca Pfizer-BioNTech Moderna	Two doses
Marcelino, A et al (29)	2024	Brazil	Cross-sectional	20-39	1012	-	Two doses
Hosseini Nasab, A et al (30)	2024	Iran	Cohort	18-45	916	Sinopharm,39.68% AstraZeneca, 32.63% Sputnik,11.37% Barakat, Bharat, and Pasteur, 16.32%	-
Wesselink, AK et al (31)	2023	US	Cohort	21-45	1137	Pfizer-BioNTech Moderna	Two doses

Table 1: The description of studies that met our eligibility criteria

This systematic review encompasses 11 studies, which display a notable disparity in the results. These discoveries can be classified into 5 primary principles.

1. Prevalence of -menstrual irregulaiting

In 7 studies [21-23, 25, 28, 29] prevalence of menstrual changes were reported. A study was conducted on adult Saudi women to evaluate the correlation between vaccination and menstrual cycle irregularities. The findings revealed that 63.9% of the women experienced fluctuations in their menstrual cycle after receiving either the initial or subsequent dose [21]. A recent study found that 41.7% of 223 participants reported changes in their menstrual cycle after receiving the COVID-19 vaccine. The percentage increased to 44.1% after the second dose. Prevalence of changes varied between doses, with some types of changes increasing and others decreasing [22]. A prospective cross-sectional study examined 344 women. A majority of the participants (60.3%) reported experiencing various menstruation irregularities post Covid-19 vaccination. Among them, 14% reported longer menstrual frequencies exceeding 35 days, and 10.2% reported shorter menstrual frequencies less than 25 days [23]. A recent study investigated the potential impact of COVID-19 vaccination on menstrual cycles in a group of 545 participants, revealing that 25% experienced changes in their cycle. Notably, the majority of these changes were observed after the second dose, with 56% of participants reporting changes at this stage, compared to 18% after the first dose, and 14% after the third [25]. A recent research project in Japan showed that there were minor discrepancies in menstrual cycle duration before and after vaccination, with variances of 1.9 ± 3.0 , 1.6 ± 2.8 ($p = 0.557$), and $2.5 \pm$

3.8 ($p = 0.219$) days noted pre-vaccination, post-first dose, and post-second dose respectively [27]. Another study reported that approximately 50-60% of women experienced menstrual irregularities after the first COVID-19 vaccine dose, slightly increasing to 60-70% after the second dose, with most cases resolving within two months [28]. A study reported that 29.9% of women experienced menstrual changes after COVID-19 vaccination, indicating a notable proportion of participants affected [29].

Type of menstrual irregulaiting

COVID-19 vaccines can lead to self-limiting menstrual abnormalities in Iranian women, with the most common disorders being menorrhagia, polymenorrhoea, and hypermenorrhoea [30]. Another study involved 1,137 participants, showed a delay in menses and a higher prevalence of long menstrual cycles post-vaccination [27]. A research study analyzed changes in the menstrual cycle among a cohort of 3,959 participants. Overall, the administration of the COVID-19 vaccine showed a correlation with a slight alteration in the length of the cycle. This amounted to less than a day for each vaccine dosage cycle when compared with cycles prior to vaccination. Specifically, the initial dosage resulted in a 0.71 day extension, while subsequent dosages led to a 0.91 day extension (20). In another study, common alterations reported by participants included irregular menstrual cycles (43%), increased menstrual discomfort or cramps (30%), and unusually heavy or prolonged bleeding (31%) [21]. A study of 9,652 participants and 128,094 menstrual cycles found that COVID-19 vaccines slightly increased the average length of menstrual cycles. The average cycle length increased by 0.50 days and 0.39 days for initial and second doses of mRNA vaccines,

respectively. Cycles that received the single J&J dose showed an average increase in length of 1.26 days [22]. In a study woman who received two doses of the vaccine during a single menstrual cycle, the variance manifested as 1.3 ± 3.5 and 3.9 ± 3.3 days' pre- and post-vaccination respectively. Adverse reactions were most severe and frequent during menstruation, with symptoms like headache and chills being notably impacted, before subsiding during ovulation [23].

3. Causes of menstrual irregulating

Factors like high stress levels and higher BMI were associated with increased odds of experiencing menstrual changes post-vaccination [25]. A study state that the menstrual irregulating were associated with factors like not using contraception, suggesting a potential link between vaccination and menstrual irregularities in some women [29]. Speculatively, the menstrual irregulating post-vaccination could be due to temporary hormonal variations induced by the inflammatory reaction from the vaccine, affecting the crosstalk between inflammatory homeostasis and menstrual cycle regulation [30]. Vaccination triggers an immune response that can temporarily affect the hypothalamic-pituitary-ovarian (HPO) axis, which regulates hormones involved in the menstrual cycle. Also, the immune response to vaccination may also impact immune cells in the uterine lining responsible for the build-up and breakdown of endometrial tissue, potentially increasing menstrual flow [31].

4. Time for reverts menstrual cycle to normal pattern

Irregularities in menstrual cycle following COVID-19 vaccination are typically self-resolving and last up to three months, irrespective of vaccine type [30]. Post COVID-19 vaccination, menstrual irregularities normalize within two months in about half of cases, indicating a potential reversion to normal patterns [21]. After COVID-19 vaccination, menstrual cycle length typically returns to normal within 1-2 cycles following vaccination, indicating a temporary effect on menstrual cycle characteristics [31]. However some studies did not provide a specific timeframe for the resolution of menstrual changes post-COVID-19 vaccination [22,25].

5. Interfering factors for menstrual irregulating

A study based on self-reports of menstrual cycle reported the absence of significant variances among the different types of vaccines or body mass [20]. It emphasizes the importance of educating women before vaccination to prevent unwarranted concerns and negative public perceptions, also, the immune response to the vaccine, rather than a specific component, may be responsible for menstrual irregularities [30].

Recommendations for the future

Due to the high prevalence of menstrual disorders post-vaccination, ongoing monitoring of pre- and post-vaccination menstrual cycles is recommended to track any changes over time [21,25]. Another study said that there is a potential relationship between menstrual changes and socioeconomic factors, contraceptive use, and body mass index post-COVID-19 infection or vaccination, therefore, it highlights the importance of considering these factors when assessing menstrual health in women who have been infected with SARS-CoV-2 or vaccinated against COVID-19, indicating a need for further investigation into these associations [29].

Discussion

The current study presents several novel insights into the effects of COVID-19 vaccination on menstrual health. Here are the key points highlighting its novelty: The study addresses a growing concern regarding menstrual disturbances during the COVID-19 pandemic, which may be influenced by vaccination, infection, stress, and lifestyle changes. This is particularly relevant as the pandemic has led to increased anxiety and uncertainty among women regarding their reproductive health. The present study highlights specific menstrual irregularities associated with

COVID-19 vaccination, such as alterations in cycle length. A significant portion of women reported experiencing changes in their menstrual cycles after the first dose. Specifically, 51.1% of women noted alterations in their cycles following this initial vaccination [21]. In another study, 41.7% of women reported menstrual changes after the first dose, which increased to 44.1% after the second dose [22]

Based on the results of a study, women who experienced menstrual changes after COVID-19 vaccination, the highest rates were observed in women who received the Pfizer/BioNTech vaccine, with 83.8% reporting disturbances after the first dose after the second dose, 36.9% of women reported no changes in their menstrual cycles, indicating that a considerable number still experienced alterations. The data also suggested that 47.2% of participants noted that the effects of the vaccination were still noticeable three months after the second dose [21].

A study found that the menstrual cycle length tended to be slightly longer after the second dose of the vaccine. In participants who received both doses within the same menstrual cycle, there was a significant delay in menstruation [27]. Participants in the study received up to three doses of the COVID-19 vaccine. The report highlights that changes in the menstrual cycle were most frequently reported after the second dose, with 56% of those who experienced changes noting them after this dose. In comparison, 18% reported changes after the first dose and 14% after the third dose [25]. In a study, however, the specific brands or types of vaccines (e.g., Pfizer, Moderna, AstraZeneca, etc.) are not mentioned in the study's contexts, but also, the findings primarily discuss the impact of vaccination on menstrual cycles, with 294 women (29.9%) reporting changes after vaccination [29]. A study reported various menstrual disorders following vaccination, with the most common being menorrhagia. Other disorders included: Hypermenorrhoea, Metrorrhagia, Polymenorrhoea, Oligomenorrhoea, Amenorrhoea. The chance of experiencing polymenorrhoea was 1.88 times higher after receiving the Sputnik vaccine compared to AstraZeneca. Additionally, the likelihood of hypermenorrhoea was 2.77 times higher after AstraZeneca vaccination compared to Sputnik [30].

A study reported 60% of vaccinated women have been changes in frequency and flow [23]. In another study, the most common issues included irregular menstruation (43%), increased premenstrual symptoms (34%), increased menstrual pain or cramps (30%), and abnormally heavy or prolonged bleeding (31%) [25]. The authors of a study analyzed the impact of COVID-19 vaccination on menstrual cycle length, focusing on the number of doses received and the types of vaccines administered. They reported a small increase in menstrual cycle length associated with the first and second doses of Pfizer-BioNTech and Moderna vaccines, with an average increase of 0.50 days and 0.39 days, respectively. The Johnson & Johnson vaccine was associated with an average increase of 1.26 days compared to pre-vaccination cycles [26]. In a study, after the first dose, menstrual irregularities were reported by 94 women, while after the second dose, 84 women reported similar issues. The irregularities were noted to occur in varying durations post-vaccination, with some lasting more than two months [28].

Conclusion

The review indicates a significant association between COVID-19 vaccination and menstrual irregularities, with a notable proportion of women reporting changes in their menstrual cycles following vaccination. These changes encompass variations in cycle length, flow, pain, and an increase in pre- and post-menstrual symptoms. Further research is needed to understand the mechanisms behind vaccine-associated menstrual changes and to provide healthcare professionals and the public with robust data on this topic.

Strengths of the Study

Comprehensive Literature Search: The study utilized a thorough search strategy across multiple reputable databases (Pubmed, Scopus, and Web

of Science) from 2019 to 2024. This approach ensured a wide range of relevant articles were considered, enhancing the robustness of the findings.

Large Sample Size: The review included a total of 11 studies with an aggregate sample size of 20,670 individuals. This large sample size increases the statistical power of the findings and allows for more reliable conclusions regarding the effects of COVID-19 vaccination on menstrual cycles.

Diverse Study Locations: The studies included in the review were conducted in various countries, including Saudi Arabia, the U.S., Japan, Brazil, and Iran. This geographical diversity helps to generalize the findings across different populations and cultural contexts.

Adherence to PRISMA Guidelines: The systematic review followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines, which are designed to improve the transparency and reproducibility of systematic reviews. This adherence adds to the methodological rigor of the study

Focus on Relevant Outcomes: The review specifically examined menstrual cycle patterns, including cycle length, flow, and associated symptoms. By focusing on these relevant outcomes, the study addresses a significant area of concern for many individuals affected by vaccination.

Call for Further Research: The study highlights the need for additional research to explore the underlying biological mechanisms and the impact of different vaccine types on menstrual health. This acknowledgment of gaps in knowledge encourages ongoing investigation in this important area.

Weaknesses of the Study

Variability in Study Designs: The included studies in the review were primarily cross-sectional, which limits the ability to establish causality between vaccination and menstrual changes. Cross-sectional studies provide a snapshot in time but do not track changes over time or establish a cause-and-effect relationship.

Sample Size and Diversity: Although the review included a total of 11 studies with a combined sample size of 20,670 individuals, the diversity of the populations studied may not fully represent all demographics. Most studies were conducted in specific regions, such as the U.S. and Saudi Arabia, which may limit the generalizability of the findings to other populations or settings.

Potential Biases: The review acknowledges the possibility of biases in the included studies, such as self-reporting bias, where participants may inaccurately report their menstrual cycle changes. This can lead to variability in the data and affect the reliability of the findings.

Lack of Control for Confounding Factors: The studies did not consistently control for confounding factors that could influence menstrual cycles, such as stress, lifestyle changes, and pre-existing health conditions. This lack of control may skew the results and make it difficult to isolate the effect of vaccination on menstrual patterns.

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