

Association Between Covid-19 Vaccination and Alterations in the Menstrual Cycle

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Abstract:

The COVID-19 pandemic, declared in March 2020 by the WHO, prompted global health strategies, including mass vaccination campaigns. In record time, vaccines were developed with various biotechnological platforms (mRNA, viral vectors and inactivated viruses), which demonstrated high efficacy in reducing hospitalizations and deaths from SARS-CoV-2. Its adverse effects were mostly mild and transient. However, as immunization progressed, anecdotal reports emerged about possible alterations in the menstrual cycle, such as changes in the duration, intensity of bleeding, frequency between cycles and atypical premenstrual symptoms. Although in cases such as the HPV vaccine this possibility had already been raised, a direct causal relationship has not been established.

Objective: To analyze the possible association between vaccination against COVID-19 and menstrual alterations in Mexican university women.

Materials and methods: Observational, longitudinal and analytical study by means of a digital survey applied between August and December 2024 to women over 18 years of age, active or graduated from the FES Iztacala, with regular cycles and at least one dose of COVID-19 vaccine. Those who had factors that altered their menstruation were excluded. The survey collected general data, pre- and post-vaccination menstrual characteristics, lifestyle, and vaccine type.

Results: 59.8% of the participants reported menstrual alterations. The main changes were in bleeding intensity (82.6%), period length (55.4%), and frequency (31.5%). Physical and emotional symptoms were also reported.

Conclusions: The results suggest a possible temporal association without serious clinical consequences.

Keywords: COVID-19; vaccination; women; menstrual cycle; menstrual alterations; bleeding

Abbreviations

- COVID-19: Coronavirus Disease 2019.
- RT-PCR: reverse transcription polymerase chain reaction
- VUM: Variant under monitoring
- VOI: Variant of interest
- VOC: Variant of concern

1.Introduction

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus, a type of coronavirus (Image. 1)

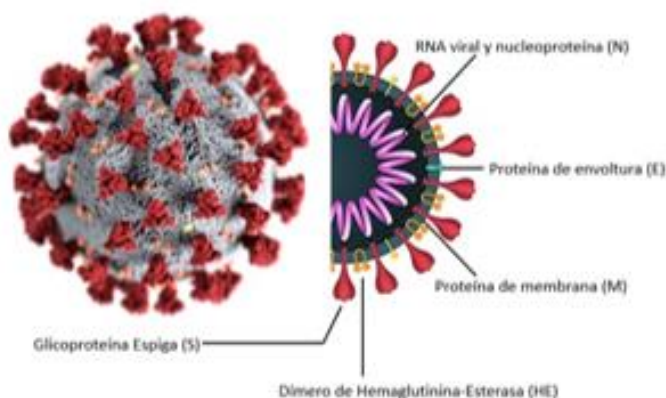


Image 1: Viral structure of the Coronavirus. Reproduced from "COVID-19, the viral disease that spread in the world" (Cedillo-Barrón, 2020).

(Table. 1) that mainly affects the respiratory tract and can cause flu-like symptoms. At the end of December 2019, in the city of Wuhan, China, multiple cases of pneumonia of unknown origin were reported, which were later attributed to this new viral agent. The high transmission capacity of the

virus [1] —mainly through respiratory droplets and contaminated surfaces— led to its rapid spread worldwide, which triggered a health emergency in a short period of time.

NAME:	"Coronavirus", Coronaviridae, subfamily Orthocononavirinae.
MEDICAL OF IMPORTANCE:	<i>Alphacoronavirus</i> , <i>Betacoronavirus</i> , <i>Gammacoronavirus</i> , and <i>Deltacoronavirus</i> .
VIRAL STRUCTURE:	Spherical structure (11-13nm in diameter) surrounded by an envelope with projections in the form of peaks or spikes, which gives them an appearance similar to that of a crown - hence their name coronavirus.
PROTEIN STRUCTURE:	They maintain a helically symmetrical capsid formed by the nucleocapsid protein (N) and are surrounded by a lipid envelope in which three proteins are found: protein E (envelope), protein M (membrane) and protein S (spike).
TRANSMISSION:	Respiratory droplets when coughing, talking or sneezing, aerosols, contaminated surfaces.
INCUBATION PERIOD:	1-2 to 12 days.
COMMON SYMPTOMS:	Runny and runny nose, cough, fatigue, sore throat and headache, fever, chills and malaise, shortness of breath (dyspnea).
DIAGNOSIS:	Preliminary diagnosis: Present the picture of symptoms and have been exposed to contagion. Confirmatory diagnosis: By real-time RT-PCR.
Note. Made from: Weiss-Leibowitz, (2020); Gibson (2022); Valverde-Temoche, (2021) [2-4]	

Table 1: General information about the Coronavirus.

The rapid spread of SARS-CoV-2 affected millions of people on all continents, causing the collapse of numerous health systems, profound economic disruptions, and significant transformations in social life. On March 11, 2020, the World Health Organization (WHO) officially declared COVID-19 a pandemic, with more than 118,000 cases in 114 countries and a growing number of deaths.[5]

Given the urgency to find effective solutions, care measures were implemented to stop the spread of the virus – such as confinement, mandatory use of face masks and distancing – which drastically modified social dynamics. Subsequently, the scientific community and technological development managed to authorize and distribute various vaccines from different pharmaceutical companies in less than a year around the world; This advance not only marked a key event in the history of vaccinology, but

also demonstrated the potential of global scientific cooperation in the face of health emergencies.

In Mexico, according to the Ministry of Health, between 2020 and 2023, at least six waves of COVID-19 infections were recorded. Each one presented different clinical and epidemiological characteristics, evidencing changes in the transmission capacity of the virus, mainly due to the appearance of new variants, with Delta and Omicron being the most predominant in the population.[6] (Table 2) The vaccination process against COVID-19 in Mexico began in December of that same year (2020), with the application of the first doses to health personnel in Mexico City. The strategy was implemented in stages, prioritizing the most vulnerable groups and was extended by age phases until May 2022. As of March 2021, more than 75 million vaccines against COVID-19 had been administered in Mexico. Of

these, 85%, that is, 64 million have a complete scheme, and 11 million have at least one dose, which represents 15%. [7]

VARIANT	PLACE OF IDENTIFICATION	GLOBAL CIRCULATION PERIOD	DESIGNATION ACCORDING TO IMPACT ON POPULATION
Alpha	United Kingdom	December 2020 - mid-2021	VOC
Beta	South Africa	Late 2020 - Mid 2021	VOC
Gamma	Brazil	Early 2021 - Mid 2021	VOC
Delta	India	April 2021 - end of 2021	VOI: April 2021 VOC: June 2022
Omicron	South Africa	November 2021 - present	VUM: November 2021 VOC: March 2023
<p>*Variant under monitoring (VUM): Investigate whether this variant may pose an additional threat to global public health.</p> <p>*Variant of interest (VOI): Describe a variant with changes that are known to affect the behavior of the virus and its potential impact on people's health (increased ability to spread).</p> <p>*Variant of concern (VOC): This is a variant defined as VOI but also meets the following criteria: a.) It can cause a detrimental change in the severity of the disease. b.) can have a substantial impact on the ability of health systems to care for COVID-19 patients. C.) significant decrease in the effectiveness of available vaccines to protect against severe disease.</p>			
Note. Adapted from: <i>Historical working definitions and primary actions for SARS-CoV-2 variants</i> , 2023. [8]			

Table 2: Variants of the SARS-CoV-2 virus that occurred during the pandemic.

Vaccines, as fundamental tools in health care, represent an immunological strategy that allows the body to generate specific defenses against infectious agents without exposing itself to the effects of the disease. In the context of the COVID-19 pandemic, the different vaccine platforms (mRNA, viral

vectors, inactivated viruses, and protein subunits) demonstrated high efficacy in preventing severe forms of the disease (95%–85%) depending on the dosage regimen and population. (5, 6, 7) (Table 3)

VACCINES	DIGITAL PLATFORM	MECHANISM OF ACTION
Pfizer-BioNTech and Moderna	Messenger RNA (mRNA)	They introduce genetic instructions for cells to produce the virus's S protein, triggering an immune response.
AstraZeneca, Sputnik V, Janssen and Patria	Non-replicating viral vector	They use a harmless modified virus to carry genetic information from SARS-CoV-2.
Sinovac	Inactivated virus	It contains the complete virus that has been inactivated (killed) although it cannot cause disease, the immune system recognizes it and generates defenses.
Abdala and Soberana*	Protein subunit	It includes specific fragments of the virus (such as the S protein) along with adjuvants that enhance the immune response.
*The Abdala, Soberana 02 and Soberana Plus vaccines are vaccines that have been produced externally but have been authorized for use in Mexico.		
Note. Made from: "Vaccine Information," Ministry of Health, Mexico. [12].		

Table 3: Types of COVID-19 vaccine authorized and applied in Mexico and their mechanism of action.

Due to the little experience with these vaccines, the health authorities established a surveillance system from the beginning to identify possible adverse effects. Although most of the reported symptoms were mild and temporary — such as pain at the injection site, fever, fatigue, headache, muscle aches — [13,14] the speed of the process also showed less common side effects, particularly with regard to variables related to female reproductive health, as testimonies began to emerge related to changes in the duration, frequency and characteristics of their menstruation after receiving one of the vaccines against COVID-19.

The lack of scientific studies at the Mexican population level on the relationship between the vaccine and the modification of menstrual cycles reduces the ability to address the concerns expressed and provide adequate guidance to menstruating people regarding the possible effects of vaccination. Therefore, the objective of this study is to analyze whether there is an association between the application of the COVID-19 vaccine and menstrual alterations in Mexican university women, particularly those linked to the university community of the Iztacala Faculty of Higher Studies.

2. Materials And Methods

2.1 Type And Design Of The Study

According to the Supo taxonomy (2012) [15], the present study corresponds to an observational, longitudinal, analytical and prospective design, with a relational level of research.

2.2 Population And Sample

The population was composed of Mexican women between 19 and 35 years old, active or graduated from a bachelor's degree from the Iztacala Faculty of Higher Studies (UNAM).

A simple random sampling was used with a convenience technique, recognizing the possibility of self-selection bias, since participation was voluntary and through an online form. To reduce biases, strict inclusion and exclusion criteria were established (Table 4), and any participant with a history that could affect their menstrual pattern was excluded.

The sampling was random, with a convenient technique.

2.3 Inclusion And Exclusion Criteria

These were defined based on literature that points to various factors capable of modifying the menstrual cycle, such as the use of contraceptives, emotional alterations or hormonal disorders. [16].

- Inclusion criteria: (Table 4)
 - Mexican women over 18 years of age.
 - Regular menstrual cycle (frequency between 21 and 35 days, duration between 2 and 8 days, moderate flow).
 - Active status or graduate of the FES Iztacala.
 - Have received at least one dose of the COVID-19 vaccine.
- Exclusion criteria:
 - Use of contraceptive methods.
 - Pregnancy or breastfeeding.
 - Presence of insomnia, stress, anxiety, or depression.
 - Inadequate diet.
 - Hormonal diseases.

2.4 Data Collection

Data collection was carried out through a digital survey of our own elaboration, not standardized, specifically designed according to the objectives of this study. The questionnaire was implemented through the Google Forms (<https://forms.gle/grS5p2YiV2jXiGez6>) platform under the title "Association between the COVID-19 vaccine and alterations in the menstrual cycle of students of the Iztacala Faculty of Higher Studies". The dissemination of the instrument took place between August and December 2024, through social networks such as Facebook, Instagram and WhatsApp. The survey was made up of eight sections:

1. Objective of the survey.
2. Informed consent
3. General data: name, age, semester, degree.
4. Anthropometric assessment: weight, height and BMI.
5. Menstrual pattern prior to vaccination: age of menarche, bleeding characteristics, premenstrual syndrome, gynecological-obstetric history.
6. General evaluation: daily routine and diet.
7. Vaccination information: type and number of vaccine doses administered.
8. Changes in the menstrual cycle after vaccination.

The instrument used was previously validated by expert judgment, in order to ensure its conceptual relevance and clarity in the wording of the items. Subsequently, an internal consistency analysis was performed using **Cronbach's alpha** coefficient, obtaining a value of **0.932**, which indicates a

statistically excellent reliability. However, the questionnaire did not incorporate objective clinical indicators or validated psychometric scales for the assessment of specific emotional symptoms, such as anxiety or depression.

2.5 Legal Ethical Aspects

In the development of the research, the ethical and legal principles that govern the participation of human beings in academic studies were fully respected. Each participant was duly informed about the objectives, procedures, expected benefits and possible risks of the study, thus guaranteeing their right to make free and conscious decisions about their participation. As a fundamental part of the ethical process, each participant signed a digital informed consent, which recorded voluntary participation, the possibility of withdrawing at any time without consequences, the confidentiality of the information provided and the exclusive use of the data for academic and scientific purposes. In this way, compliance with the ethical standards of respect, autonomy and confidentiality in the treatment of information was ensured.

2.6 Data Analysis

Using the IBM SPSS Statistics software platform, an internal validation analysis was performed, which included construct and reliability analysis of the instrument, obtaining a Cronbach's alpha of 0.932, which indicated excellent reliability. Subsequently, a descriptive analysis was applied using measures of frequency, central tendency and variability. For the inferential analysis, the Chi-square test of Independence was used. A value of $p \leq 0.05$ was considered statistically significant.

3.Results

Due to the exploratory nature of the study, non-probabilistic convenience sampling was used. Participation was voluntary and only those people who met the inclusion criteria and completed the survey in its entirety during the data collection period were considered. In this context, data from 176 Mexican women in an average age range of 19 to 35 years (mean age 22.98) were analyzed. Most of the responses came from residents of Mexico City (48.3%) and the State of Mexico (46.6%), which together represented 94.9% of the sample.

Following the exclusion criteria¹, the following were excluded from the total (n=176) (Table 4)

- 84 women with irregular cycles since before vaccination,
- 51 women who use contraception or hormone therapy,
- 11 women who suffer from a hormonal disease,
- 56 women who maintain an inadequate diet,
- 21 women who suffered from disorders such as insomnia, stress, anxiety or depression.

Thus, the final sample was composed of 92 women who met the inclusion criteria.

PARTICIPANTS	INCLUSION CRITERIA	EXCLUSION CRITERIA 1
	<ul style="list-style-type: none"> ● Over 18 years old ● Regular menstrual cycle ● Belonging to the Iztacala Faculty of Higher Studies ● Have received at least one dose of the COVID-19 vaccine 	<ul style="list-style-type: none"> ● Use of contraceptive methods ● Breastfeeding or pregnancy ● Insomnia, stress, anxiety, or depression ● Inadequate nutrition ● Hormonal disease.
n= 176	n= 92	n= 84

Note. ¹ These were defined based on literature that points to various factors capable of modifying the menstrual cycle, such as the use of contraceptives, emotional alterations or hormonal disorders.[17].

Table 4: Participating population based on inclusion and exclusion criteria.

Of the 100% of the population, 39.2% of the women who responded to this survey are graduates and 60.8% are studying one of the bachelor's degrees taught at the Iztacala Faculty of Higher Studies, of which nursing (47.7%), psychology (21.6%) and medicine (10.8%) are the careers in which there were the largest number of participants.

Distribution of vaccines applied

Of the sample analyzed (n=92) and who reported having been vaccinated against COVID-19, the following were applied: *I. Messenger RNA vaccines* 27.2% (n=25): such as Pfizer-BioNTech 15.2% (n=14) and Moderna 12% (n=11). *II. Viral vector vaccines* 65.2% (n=60): AstraZeneca 21.7% (n=20), Sputnik V 42.4% (n=39) and Janssen with 1.1% (n=1) and *III. Vaccines with inactivated virus* such as Sinovac with 7.6% (n=7). (Table 5). Regarding the dosage schedule, 64.1% have a complete dose schedule (3-4 doses), 34.8% with 1-2 doses and only one person (1.1%) reports having received a 5th dose. (Table 6.)

	VACCINE	FREQUENCY	PERCENTAGE	VALID PERCENTAGE	CUMULATIVE PERCENTAGE
VALID	PFIZER BIONTECH	14.0	15.2	15.2	15.2
	ASTRAZENECA	20.0	21.7	21.7	36.9
	SPUTNIK V	39.0	42.4	42.4	79.3
	SINOVAC	7.0	7.6	7.6	86.9
	JANSSEN	1.0	1.1	1.1	88.0
	MODERN	11.0	12.0	12.0	100.0
		92.0	100.0	100.0	

Table 5. Distribution of vaccines applied as first and second doses.

	DOSE	FREQUENCY	PERCENTAGE	VALID PERCENTAGE	CUMULATIVE PERCENTAGE
VALID	1-2 DOSES	32	34.8	34.8	34.8
	3-4 DOSES	59	64.1	64.1	98.9
	5 OR MORE DOSES	1	1.1	1.1	100.00
		92.0	100.0	100.0	

Alterations in the menstrual cycle

Table 6. Distribution of application of dosage schedule.

After the administration of the COVID-19 vaccine, 59.8% (n=55) of the women surveyed consider that there were alterations in their menstrual cycle. Specifically, 55.4% (n=51) of the women reported changes in the **duration of menstruation**, 31.5% (n= 29) in the **frequency between cycles**, and 82.6% (n=76) in **bleeding intensity**. After comparing the menstrual pattern

of the participants prior to vaccination with the changes reported after vaccination, significant differences were recorded in the duration of menstruation (p=0.000), the frequency between cycles (p=0.000) and the intensity of bleeding (0.001). (Table. 7).

REPORTED CHANGES	VALUE OF SIGNIFICANCIA ¹
DURATION OF MENSTRUATION	.000
FREQUENCY BETWEEN CYCLES	.000
INTENSITY OF BLEEDING	.001

¹note. ¹ Chi-square test of independence – Statistical significance value p ≤ 0.05

Table 7. Comparison between normal menstruation pattern versus changes reported after COVID-19 vaccination.

When comparing the intensity of physical and psychoemotional symptoms before and after COVID-19 vaccination, significant changes were observed in the significance variables (p<0.05). Regarding *emotional symptoms*, *significant* differences were found before vaccination in anxiety (p=0.005), depression (p=0.002), crying (p=0.046), mood swings (p=0.009), anger (p=0.001), appetite change (p=0.007) and changes in libido (p=0.035). In the *post-vaccination period*, only crying (p=0.033), insomnia (p=0.030), and

lack of concentration (p=0.001) were present. In physical *symptoms, prior to vaccination*, differences were found in breast sensitivity (p=0.000), acne (p=0.000) and constipation (p=0.003). In the *post-vaccine period*, significance was observed in headache (p=0.011), weight gain (p=0.036), abdominal swelling (p=0.013), breast tenderness (p=0.018) and diarrhea (p=0.000) (Table 8)

	BEFORE AND AFTER MENSTRUATION	PRE-VACCINE	POST-VACCINE
EMOTIO NAL	ANXIETY	.005	.858
	DEPRESSION	.002	.579
	CRYING	.046	.033
	IRRITABILITY	.203	.310

	MOOD CHANGE	.009	.359
	ANGER	.001	.178
	APPETITE CHANGE	.007	.346
	INSOMNIA	.675	.030
	SOCIAL ISOLATION	1.000	.436
	LACK OF CONCENTRATION	.346	.001
	CHANGES IN LIBIDO	.035	.650
PHYSICAL	NAUSEA, DIZZINESS	.458	.263
	HEADACHE	.290	.011
	FATIGUE	.428	.916
	WEIGHT GAIN	.366	.036
	ABDOMINAL BLOATING	.379	.013
	BREAST SENSITIVITY	.000	.018
	ACNE	.000	.053
	CONSTIPATION	.003	.087
	CRAMPS	.949	.712
	DIARRHOEA	.826	.000
	COLITIS	.225	.752

Note. ¹ Chi-square test of independence – Statistical significance value $p \leq 0.05$

Table 8: Symptoms related to the menstrual cycle: Comparison between pre-vaccine and post-vaccine symptoms.

4. Discussion

The rapid production and distribution of biologics against COVID-19 as a strategy to face the global health emergency limited the time available to comprehensively evaluate their possible side effects in different population groups, particularly women. Historically, similar concerns have been documented about the possible influence of certain immunogens on the menstrual cycle. Such is the case of the vaccine against the human papillomavirus (HPV) reported in 2013[18], the typhoid vaccine in 1913 and the Hepatitis B vaccines in the mid-80s. (13,14) These studies agree that these modifications tend to be mild and transient and a conclusive cause-and-effect relationship has not been found, so they do not imply a long-term risk or affect fertility.

Although the physiological mechanisms involved are not yet fully understood, several studies have documented transient modifications in the menstrual cycle associated with vaccination. For example, research published in JAMA Network Open (18) identified slight (<1 day) increases with receipt of an influenza vaccine, with or without a COVID-19 vaccine, but statistically significant increases in cycle length, particularly when vaccine application coincided with specific phases of the cycle, suggesting a possible influence of the immune response. For their part, Al Shahrani et al. (2024) (16) They conducted a meta-analysis that revealed that 27.3% of women presented alterations in the duration of the cycle after immunization, while 11.7% reported an increase in bleeding volume and 5.5% a decrease in bleeding. Likewise, it was observed that about 22.1% experienced dysmenorrhea. In general, these studies agree that there may be a temporary lengthening of the cycle from one to two days, with a tendency to normalize in subsequent cycles.

The data obtained in this research show that a considerable proportion of the participants manifested menstrual alterations after receiving the COVID-19 vaccine: Approximately 6 out of 10 participants experienced modifications in their menstrual cycle. The most frequent changes included variations in bleeding intensity (82.6%), period length (55.4%), and frequency between cycles (31.5%). The fact that more than half of women experienced some modification in their menstruation underscores the importance of including menstrual health as a component in post-vaccination surveillance, especially considering the emotional and physical impact these changes can have on women's quality of life.

Although the reported symptoms do not imply serious clinical consequences, their frequency and distribution allow us to observe a possible common

response at the population level. In addition, the magnitude of the effects reported in this sample seems slightly higher than that observed in other national studies, for example, in a cross-sectional study carried out at the ABC Hospital in Mexico City it showed that 48.1% of vaccinated women reported some menstrual alteration. Among the most frequent were menorrhagia (20.7%) and increased menstrual pain (27.4%).[19] In this context, the results of this study provide additional evidence from a specific population – Mexican university women – that until now has been underrepresented in the scientific literature.

From an emerging perspective, research has emerged that has begun to explore the role of regulatory proteins such as Sirtuin 1 [20] involved in key cellular functions, including hormonal stability. It has been suggested that this protein may be affected by SARS-CoV-2 and, possibly, by the immunological stimuli associated with vaccination, which opens up new routes to understand menstrual alterations from a molecular approach. Although this line is still in its infancy, it could have therapeutic implications in the future.

In short, although the documented menstrual alterations seem transitory, it is essential that they are recognized and incorporated into post-vaccination surveillance systems because the menstrual cycle is a sensitive indicator of body balance, and their study contributes not only to improving the quality of clinical follow-up, but also to strengthening the confidence of the female population in immunization campaigns.

5. Conclusions

The results of this study support the existence of a temporal association between vaccination against COVID-19 and alterations in the menstrual cycle in Mexican university women. The main modifications reported included variations in bleeding intensity, period length, and frequency between cycles, with statistical significance. Although these alterations do not imply a serious clinical risk nor have they been shown to affect fertility, they can produce significant functional, emotional and social impact that should not be underestimated. Its high prevalence in the sample analysed highlights the importance of including menstrual health as part of post-vaccination pharmacovigilance, especially in young populations and those of reproductive age in order not to generate alarm or reduce confidence in vaccination campaigns.

6. Limitations of the Study

This study has several limitations that must be considered when interpreting its results. First, the observational and cross-sectional design, based on a self-administered survey, carries an inherent risk of memory bias and subjectivity in the responses, since it depends exclusively on the individual perception of the participants regarding the changes in their menstrual cycle. Objective clinical measurements were not included, such as hormone levels, ultrasounds, or gynecological evaluations, that would validate the symptoms reported from a biomedical point of view.

Likewise, the lack of longitudinal follow-up represents an important limitation, since it was not possible to evaluate the duration, recurrence or resolution of menstrual alterations over time. The research was conducted retrospectively, without collecting data at the time the changes occurred, which may have affected the accuracy of the information obtained.

Another relevant aspect is the variability in exposure conditions. The participants received different types of vaccines (with different biotechnological platforms), at different times of the cycle and with variable intervals between doses, which makes it difficult to establish a clear relationship between a specific biological and the alterations observed. In addition, each dose was considered as a unit of exposure, without homogeneity at the time of application or control over previous hormonal factors, which introduces heterogeneity in the risk periods evaluated.

The sample was made up exclusively of young women, university students and belonging to a single academic institution (FES Iztacala – UNAM), which restricts the generalization of the findings to other population groups, such as older women, women with pre-existing gynecological conditions or from diverse socioeconomic contexts. The use of convenience sampling may also have generated self-selection bias, since those who experienced menstrual alterations were able to feel more motivated to participate in the survey. On the other hand, the exclusion of women with emotional disorders, inadequate diet, or hormonal diseases – conditions that are common during the pandemic – reduces the possibility of observing how these factors interact with the effects of vaccination on the menstrual cycle. Finally, the absence of a control group (unvaccinated women or women with different schedules) prevents direct comparisons that allow a stronger association between immunization and menstrual changes to be established.

Taken together, these limitations underscore the need for larger studies, with long-term follow-up, objective clinical assessment, and diverse population representativeness, in order to better understand the relationship between COVID-19 vaccines and menstrual health.

Conflict Of Interest

There is no conflict of interest.

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