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An investigation into the effects of COVID-19 vaccines on Iranian women's menstrual cycle

Ali **Hosseini Nasab** [1], Shahrzad **Sanjari** [2], Mohammad Reza Mohammadi **Soleimani** [3], Katayoun **Alidousti** [4,*]

[1] Infectious and Tropical Research Center, Kerman University of Medical Sciences, Kerman, Iran.
[2] Student Research Committee, School of Nursing and Midwifery, Shahroud University of Medical Sciences, Shahroud, Iran.
[3] Department of Psychology, Kerman Branch, Islamic Azad University, Kerman, Iran.
[4] Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran.

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***Corresponding author**: Katayoun **Alidousti**, MSc. Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Haft-Bagh Highway, Kerman, Iran 7616913555.
Email: xalidoosti@kmu.ac.ir; kalidousti@gmail.com.
ORCID: 0000-0002-1206-4912.

ABSTRACT

Objective. The COVID-19 virus disrupts the renin-angiotensin system by reducing the expression of angiotensin-2 converting enzyme receptors in host cells, inducing an inflammatory response. This system regulates ovarian follicular development and ovarian steroid hormone production. So, this study has been conducted to examine the possible effects of COVID-19 vaccines on the menstrual cycle of Iranian women.
Materials and Methods. In this retrospective cohort study, an online researcher-made questionnaire containing 32 multiple-choice questions was used over one month to investigate the possible changes in the menstrual cycle after receiving COVID-19 vaccines among 916 eligible women aged 18 to 45 years.
Results. The mean age of participants was 34.34 ± 8.37 years, 77.79% were married, and 61.47% were government employees. The highest number of participants (n = 377, 39.68%) had been vaccinated with the Sinopharm. The most common menstrual disorder (n = 189) was menorrhagia. Most menstrual disorders were due to the AstraZeneca and Sinopharm vaccines. The chance of polymenorrhoea after receiving the Sputnik vaccine was 1.88 times higher than AstraZeneca (OR 1.88 and p = 0.04, 95%CI 1.02-3.46). The chance of hypermenorrhoea after the AstraZeneca vaccination was 2.77 times higher than after the Sputnik (OR 2.77 and p = 0.01, 95%CI 0.18-0.74).
Conclusions. Regardless of the type of vaccine, females subjected to COVID-19 may experience self-limiting menstrual abnormalities. Awareness of women before receiving the vaccine prevents further worries and uninformed judgments that negatively impact public attitudes.

INTRODUCTION

In December 2019, a new beta-coronavirus (COVID-19) with symptoms of respiratory involvement appeared in Wuhan, China, and spread rapidly worldwide [1]. SARS-CoV-2 affects various body organs, such as the gastrointestinal tract, nervous system, skin, olfactory, cardiovascular, liver, and reproductive organs, with a possibility of permanent damage. Angiotensin-2 converting enzyme (ACE2) receptors, as the entry points of the virus into the cell, are essential components of the renin-angiotensin system (RAS) [2]. The ovarian renin-angiotensin system regulates ovarian follic-

ular development and the production of ovarian steroid hormones [3, 4].
Vaccination is a fundamental strategy to prevent diseases. Today, the best option to fight the spread of COVID-19 is to use an effective and safe vaccine [5]. After vaccination, the most common side effects were high temperature, fatigue, headache, muscle pain, and pain at the injection site. These minor side effects were resolved within a few days [6]. Additionally, unexpected menstrual changes are not listed as a symptom, but women of all ages are increasingly coming with these changes after the COVID-19 vaccine. Menstrual disorders following the COVID-19 vaccine have severely affected the quality of life of women. Concerns have been raised about a possible link between vaccination against COVID-19 and future fertility [7].
A study on Japanese women revealed that the length of the menstrual cycle became longer after receiving the COVID-19 vaccines. The maximum side effects of the COVID-19 vaccine were seen when the vaccination was done during the menstrual period. The side effects were minimized if the vaccination was done during ovulation [8].
In a study by Ma *et al*. (2020) on men in the reproductive age range of 24-49 years with moderate to severe disease, an increase in LH levels and a decrease in testosterone levels were observed among patients in the COVID-19 group [5].
A systematic review showed that women's most significant problem related to menstruation after contracting the COVID-19 disease was the high amount of bleeding and the lengthening interval between periods. These changes were not associated with the severity of the disease [9].
Studies have indicated that menstrual irregularities follow a typical coronavirus-induced infection. This disorder can be due to the direct effect of the virus on the sexual organ, mental disorders caused by the disease [10], the impact of the virus on the body's defense mechanisms, and the production of various immune mediators.
Since the periods of recurrence and long-term complications of the disease are not known. Women of reproductive age may have children in the future and disrupt pregnancy. Antibody screening is not cost-effective in our country [11], so it is better to investigate vaccine problems and complications at the beginning of work. Furthermore, the best possible way should be provided to reduce side effects and increase willingness to receive the vaccine.
To date, no comprehensive study has been performed on the effect of COVID-19 vaccination on the menstrual cycles of Iranian women. Due to the prevalence of immunization in different age groups, it seems necessary to evaluate the possible effects of COVID-19 vaccines on the menstrual cycle in natural infections with this virus.

MATERIALS AND METHODS

We conducted a retrospective cohort analysis of possible menstrual cycle changes following COVID-19 vaccinations. In Iran, there were six different kinds of injectable vaccine. They included Sputnik, AstraZeneca, Sinopharm, Barakat, Bharat, and Pasteur.
According to World Health Organization (WHO), several COVID-19 vaccines using different platforms, such as viral vectors, inactivated virus modalities, and messenger ribonucleic acid (mRNA), have successively obtained emergency clinical use authorization for the prevention of SARS-CoV-2 infections [12].
Covaxin is a whole-inactivated virus-based COVID-19 vaccine developed by Baharat Biotech in collaboration with the Indian Council of Medical Research - National Institute of Virology.
COVIran Barakat is a COVID-19 vaccine developed in Iran by Shifa Pharmed Industrial Group, a subsidiary of the Barkat Pharmaceutical Group. It is an inactivated virus-based vaccine. Iranian authorities have authorized its emergency use.
Sputnik V is an adenovirus viral vector vaccine for COVID-19 developed by the Gamaleya Research Institute of Epidemiology and Microbiology in Russia. It is the world's first registered combination vector vaccine for the prevention of COVID-19, having been registered on 11 August 2020 by the Russian Ministry of Health.
AstraZeneca plc is a British-Swedish multinational pharmaceutical and biotechnology company with its headquarters at the Cambridge Biomedical Campus in Cambridge, England. It has been involved in developing the Oxford-AstraZeneca COVID-19 vaccine.
Sinopharm BIBP COVID-19 vaccine, also known as BBIBP-CorV, is a whole inactivated virus COVID-19 vaccine developed by Sinopharm's Beijing Institute of Biological Products (sometimes written as Beijing Bio-Institute of Biological Products.
The statistical population included women of childbearing age (aged 18 to 45 years) in southeast-

ern Iran in 2021. The study samples were women who had received at least one dose of COVID-19 vaccination. Online sampling was performed on eligible women.

Patient and public involvement

Inclusion criteria included: women aged 18 to 45 years old who were not pregnant with no gynaecological diseases affecting the level of female sex hormones (premature ovarian failure, polycystic ovary syndrome, endocrine disorders, like hypothyroidism and pituitary adenoma), regular period cycles 21-35 days long, average volume and amount of bleeding before administration of the COVID-19 vaccine, had experienced no stressful events from 3 months before receiving the vaccine until the completion of the questionnaire and no weight change in comparison with before vaccine administration.

Sample size

Out of 1,520 people who completed the questionnaire, 604 were removed as they did not satisfy the inclusion criteria (pre-vaccination menstrual irregularities, experiencing stressful events, taking hormonal drugs, diseases such as PCOS, thyroid disorders, or taking emergency contraceptive pills). Finally, 916 people were recruited for the study.

Research tool

The research tool used was a researcher-made online questionnaire containing 32 multiple-choice questions. The first part of the questionnaire examined age, occupation, education, marital status, body mass index, concomitant disorders of women, use of hormonal and non-hormonal medications, number of previous pregnancies and abortions, contraceptive methods before and after vaccination, fertility status (or pre-menopause), and the type of COVID-19 vaccine received. The second part of the questionnaire was extracted from an article and examined the PMS, dysmenorrhoea, and menstrual status before and after vaccination, including the length of menstrual cycles, the number of bleeding days, and, in case of irregular menstrual cycles or abnormal uterine bleeding, the length of the irregularity/abnormality [13]. The questions were designed so that the answers were yes or no.
This questionnaire was designed to be filled out only once for each respondent. The survey was only available for 30 days in Persian (from October 30, 2021 to November 30, 2021) and was distributed through social media platforms.

Study registration, ethical and methodological standards

This manuscript was derived from project code No. 400000874 and was approved by the Ethics Committee of Kerman University of Medical Sciences, Iran (the code of ethics No. Kmu.ac.ir.1400.594). Written informed consent was obtained to enter the study. The study's objectives were described to all women. This study also conformed to the Enhancing the Quality and Transparency of health Research (EQUATOR) network guidelines.

Statistical analysis

The analysis was performed using SPSS software version 17 with central indices and dispersion and ratio equality test, chi-square, t-test, and one-way analysis of variance.

RESULTS

The average age of participants was 34.34 ± 8.37 years, and the majority were 30 to 40 years (40.84%). The majority (77.79%) were married, and 61.47% were government clerks. Most participants (75.79%) had a university education. The most commonly used contraceptive method (37.79) was the natural method. In terms of the type of injectable vaccine, 108 (11.37%) had been vaccinated with Sputnik, 310 (32.63%) with AstraZeneca, 377 (39.68%) with Sinopharm, and 155 (16.32%) with other vaccines (Barakat, Bharat, and Pasteur) (**Table 1**).
After vaccination, 149 women (15.68%) developed polymenorrhoea, 147 (15.47%) oligomenorrhoea, 157 (16.53%) hypermenorrhoea, 88 (9.26%) bleeding less than 30 ccs, 189 (19.89%) menorrhagia, and 112 (11.79%) metrorrhagia; according to collected data, 47 participants (4.95%) hypomenorrhoea, 823 people (86.63%) had no change in menstrual pain, 127 women (13.37%) had increased dysmenorrhoea, and 18 participants (1.89%) developed amenorrhoea. In terms of symptoms of premenstrual syndrome, 754 women (79.36%) reported no change in symptoms, and 196 people (20.63%) reported increased symptoms (**Table 2**).

Table 1. *Demographic characteristics of the participants (n = 950).*

Variable		Frequency	Percent
Marital status	Single	177	18.63
	Married	739	77.79
	Widow	34	3.58
Job	Housekeeper	311	32.74
	Self-employment	55	5.79
	Employee	584	61.47
Education	High school	73	7.68
	Diploma	157	16.53
	College education	720	75.79
Type of vaccine received	Sputnik	108	11.37
	AstraZeneca	310	32.63
	Sino pharm	377	39.68
	Others	155	16.32
Contraceptive use	DEPO	5	0.53
	IUD	55	5.79
	Withdrawal	359	37.79
	LD or HD	30	3.16
	Minipill	1	0.11
	Condom	223	23.47
	Non	277	29.16
Breastfeeding status	No	903	95.05
	Yes	47	4.95
Age	< 20	45	4.74
	20 -30	282	29.63
	30-40	388	40.84
	40-50	222	23.37
	>50	13	1.37

Table 2. *Status of vaccination complications on menstrual cycle (n = 950).*

Variable		Frequency	Percent
Polymenorrhoea	Yes	149	15.68
	No	801	84.32
Oligomenorrhoea	Yes	147	15.47
	No	803	84.53
Hypomenorrhoea	Yes	47	4.95
	No	903	95.05
Hypermenorrhoea	Yes	157	16.53
	No	793	83.47
Bleeding less than 30 cc	Yes	88	9.26
	No	862	90.74
Menorrhagia	Yes	189	19.89
	No	761	80.11
Metrorrhagia	Yes	112	11.79
	No	838	88.21
Amenorrhoea	Yes	18	1.89
	No	932	98.11
Dysmenorrhoea	Without change	823	86.63
	Increased	127	13.37
PMS	Without change	754	79.36
	Increased	196	20.63

Out of the 149 women who developed polymenorrhoea after receiving the vaccine, 59 (39.6%) had been vaccinated with AstraZeneca. Most women with oligomenorrhoea (36.7%) had been immunized with Sinopharm. Among the 47 people with hypomenorrhoea, the majority (36.2%) were vaccinated with AstraZeneca, and 38.2% of those who had hypermenorrhoea after vaccination had been immunized with Sinopharm. Among 88 patients with bleeding less than 30 ccs, the majority (39.8%) had been vaccinated with Sinopharm. However, menorrhagia was more common (34.9%) in those receiving the AstraZeneca vaccine. Metrorrhagia was more common during the menstrual cycle following receiving the AstraZeneca vaccine (34.8%) than other vaccines. Among the 196 people who developed PMS symptoms or experienced worsened symptoms after receiving the vaccine, the majority (33.7%) had been vaccinated with AstraZeneca, but onset or exacerbation of dysmenorrhoea (34.6%) was seen after vaccination with Sinopharm. Most cases of amenorrhoea (50%) were seen following the administration of other vaccines (Barakat, Bharat, and Pasteur) (**Table 3**). Almost all participants stated that the disorders were temporary and had resolved within three months.

The chance of polymenorrhoea after vaccination in women vaccinated with the Sputnik vaccine was 1.88 times higher than AstraZeneca (OR 1.88 and p = 0.04, 95%CI 1.02-3.46). However, the chance of polymenorrhoea in women vaccinated with AstraZeneca was 3.7 times higher than in those immunized with Sinopharm (OR 0.27 and p = 0.00, 95%CI 0.15-0.48). The chance of polymenorrhoea after vaccination in women who did not use any contraceptive method was 1.7 times higher than in women who used the withdrawal method (OR 1.7 and p = 0.05, 95%CI 1.01-2.87). The chance of polymenorrhoea after vaccination in women over 50 years was 7.1 times higher than those aged 20 to 30 years (OR 0.14 and p = 0.00, 95%CI 0.04-0.49), 5.2 times higher than those aged 30-40 years (OR 0.19 and p = 0.01, 95%CI 0.06-0.65) and 6.66 times higher than those aged 40-50 years (OR 0.15 and p = 0.00, 95%CI 0.04-0.52).

The chance of hypermenorrhoea after vaccination in women who had received AstraZeneca was 2.77

Table 3. *Frequency of menstrual cycle disorders in different type of COVID-19 vaccine received.*

Variable	AstraZeneca n (%)	Sputnik n (%)	Sino pharm n (%)	Others n (%)
Polymenorrhoea	59 (39.60)	31 (20.81)	21 (14.09)	38 (25.5)
Oligomenorrhoea	49 (33.3)	13 (8.8)	54 (36.7)	31 (21.1)
Hypomenorrhoea	17 (36.2)	10 (21.3)	16 (34)	4 (8.5)
Hypermenorrhoea	56 (35.7)	14 (8.9)	60 (38.2)	27 (17.2)
Bleeding less than 30 cc	30 (34.1)	14 (15.9)	35 (39.8)	9 (10.2)
Menorrhagia	66 (34.92)	17 (9)	53 (28)	53 (28)
Metrorrhagia	39 (34.8)	10 (8.9)	38 (33.9)	25 (22.3)
Amenorrhoea	3 (16.7)	1 (5.6)	5 (27.8)	9 (50)
Dysmenorrhoea	46 (36.2)	15 (11.8)	44 (34.6)	22 (17.3)
PMS	66 (33.7)	30 (15.3)	60 (30.6)	40 (20.4)

times higher than in those who received Sputnik (OR 0.36 and p = 0.01, 95 CI 0.18- 0.74).

The chance of bleeding less than 30 cc after vaccination in women with a university education was 7.79 times higher than in women without a high school diploma (OR 7.79 and p = 0.01, 95%CI 1.65-36.81). The chance of bleeding less than 30 ccs after vaccination in women who had no contraceptive method was 5.13 times higher than the natural method (OR 5.13 and p = 0.00, 95%CI 2.77-9.52). The chance of menorrhagia after vaccination in women without a high school diploma was 2.77 times higher than those with a diploma (OR 0.36 and p = 0.01, 95%CI 0.17-0.75) and 3.44 times higher than those with university education (OR 0.29 and p = 0.00, 95%CI 0.14-0.62). The chance of menorrhagia after vaccination in women who had received AstraZeneca was twice higher than in Sinopharm (OR 0.5 and p = 0.00, 95%CI 0.31-0.81). However, in those who got other vaccines, it was 2.29 times higher than AstraZeneca (OR 2.29 and p = 0.00, 95%CI 1.44-3.64). The chance of menorrhagia after vaccination in women who used the natural contraceptive method was 16.6 times that of IUDs (OR 0.06 and p = 0.01, 95%CI 0.01-0.43), while the chance of menorrhagia in women who did not use any contraceptive method was 1.76 times that of the natural contraceptive method (OR 1.76 and p = 0.01, 95%CI 1.13-2.73).

The chance of metrorrhagia in women who got other vaccines was 2.14 times higher than in Sinopharm (Sinopharm is the reference value). The opportunity of metrorrhagia after vaccination in single women was 1.9 times higher than in married women (OR 0.52 and p = 0.02, 95%CI 0.31-0.88). The chance of dysmenorrhoea in women without a high school diploma was 2.85 times higher than those with a diploma (OR 0.35 and p = 0.01, 95%CI 0.15-0.78) and 3.12 times higher than those with university education (OR 0.32 and p = 0.01, 95%CI 0.14-0.71).

The chance of amenorrhoea in women immunized with other vaccines was 10.85 times that of AstraZeneca (OR 10.85 and p = 0.00, 95%CI 2.43-48.40). The chance of amenorrhoea after vaccination in women who took LD or HD pills was 12.94 times the natural method (OR 12.94 and p = 0.00, 95%CI 2.60-64.35).

The chance of PMS in women who had gotten other vaccines was 1.71 times those vaccinated with AstraZeneca (OR 1.71 and p = 0.03, 95%CI 1.04-2.81). Also, this chance was 5.26 times higher in women who did not breastfeed (OR 0.19 and p = 0.00, 95%CI 0.06-0.58).

DISCUSSION

This study's findings showed that about 13% of participants had experienced menstrual problems regardless of the type of vaccine, which was lower than the results reported by Laganà *et al.*, where 50 to 60% of women of childbearing age had experienced menstrual irregularities after vaccination [14].

The findings indicate that most menstrual abnormalities were due to AstraZeneca and Sinopharm vaccines and affected both the length of the menstrual cycle and the amount of bleeding. Previous studies have also reported menstrual changes after mRNA and adenovirus-based COVID-19 vaccines, suggesting that if there is a link, it may be due to an immune response to the vaccine rather than a specific component of the vaccine [15]. A cross-sec-

tional study of women living in the Middle East and North Africa reported menstrual disturbances such as (delaying/increasing/haemorrhages or pain): 0.98% of Pfizer BioNTech and 0.68% (7/1028) of Oxford-AstraZeneca vaccines [16].

According to our data, 86.63% of participants had no change in their menstrual pain and 16.53% of participants' bleeding rate was more than before as respects a study in Saudi Arabia of 673 women concluded that the COVID-19 vaccination was associated with a slight change that led to more painful periods and increased bleeding [17]. Also, a study in Pakistan on 953 medical students showed that 41.2% of students had experienced dysmenorrhoea, and 58.8% had problems with the frequency and flow of menstruation [18]. Perhaps the reason for the difference in the rate of menstrual pain in these studies is the different types of vaccines received.

In line with our findings, another study in Norway, on 5,688 women, showed a significant increase in the amount of menstrual bleeding, which was higher than before [19].

Our findings are consistent with a preprint of a US survey that found 42% of people with regular menstrual cycles had more bleeding than usual after vaccination [20].

This study found that all menstrual abnormalities, such as bleeding days, bleeding volume, length of the menstrual cycle, dysmenorrhoea, and PMS that did not exist before or were low increased the following vaccination. According to participants' self-report, these complications were resolved within a maximum of 3 months. This result is consistent with previous studies that included 2269 women, 46.7% of whom had menstrual changes, and the symptoms of 86.8% of affected women improved spontaneously within one month without treatment [21].

The current study concluded that almost half of the women complained about menstrual cycle length. In contrast, according to a survey by Arison, the COVID-19 vaccine was linked with a small and temporary change in menstrual cycle length and had no effect on the duration of bleeding [22].

Changes in menstrual cycle length are due to events during the follicular phase and maturation. Therefore, the menstrual cycle phase during which the vaccine was administered can lead to changes in menstrual cycle length. In this study, since most women did not remember which day of the menstrual cycle they had received the vaccine, we could not relate the abnormalities to a specific phase. However, according to Lagana, most women menstruate 1-5 days earlier than expected. This alteration occurred mainly when the first dose of the vaccine was administered during the first 14 days of the menstrual cycle. However, they did not find significant differences in the occurrence of this menstrual irregularity based on when the first vaccine dose was administered [14].

Menstrual changes following vaccination are not so unusual, given that such modifications have been observed for other microbes, like the human papillomavirus [23]. Such disturbances are likely ascribed to the inflammatory/immunological reaction ensuing from adjuvants in the vaccines, at least in some cases [24].

Although speculation, we may hypothesize that what we observed could be partly due to hormonal variation caused by potential pro-inflammatory and pro-coagulative changes. Indeed, some evidence suggests crosstalk between inflammatory homeostasis and menstrual cycle regulation, which may be slightly disturbed by temporary hormonal variation secondary to the inflammatory reaction induced by the vaccine.

Reproductive toxicity studies performed in mouse models with Comirnaty (Pfizer-BioNTech) [25], Spikevax (Moderna) [26], Vaxzevria (AstraZeneca) [27], and Janssen (Johnson & Johnson) [28] reveal no specific hazard for humans regarding fertility.

Although reported changes to the menstrual cycle after vaccination is temporary and self-limiting, the association between COVID-19 vaccination and irregularities in the menstrual cycle must be investigated in further studies.

The menstrual cycle is regulated by the hypothalamic-pituitary-ovarian (HPO) axis, which can be affected by daily life, environment, and health stressors [29]. Psychological stress may activate the corticotropin-releasing hormone from the nervous system, leading to increased cortisol and prolactin levels, resulting in changes in the pattern of menstrual bleeding [30]. Although we excluded those taking medications or who had specific psychological disorders, daily and occupational stress can also cause menstrual abnormalities. Therefore, a limitation of this study was that we could not have a control group and could not compare these cases with unvaccinated people, so our report only offered a description of what we observed without any possibility of inferring cause and effect. The other limitation of this study was that this questionnaire was self-administered. It was published

among the general population through social media, so it is possible that women who had menstrual cycle irregularities after the COVID-19 vaccination were more motivated to answer it than women who had not experienced it. We also could measure the amount of blood loss. We left this parameter as a subjective evaluation from the patient's perspective (more or less heavy than usual); however, we used exact ranges for the number of days of bleeding and the menstrual cycle length.

CONCLUSIONS

The results showed that about one-fifth of the women who received COVID-19 vaccines had menstrual cycle irregularities, regardless of the vaccine type. However, these problems were self-limiting and resolved within three months. However, it seems better for people with chronic or gynaecological diseases to consult a doctor before receiving the vaccine to reduce the chance of possible complications and drug interactions with the vaccine.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

K.A., A.H., M.M.: Conceptualization. K.A., S.S., M.M.: Data curation. All authors: Writing – original draft, writing – review & editing.

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Study registration

None.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

This manuscript was derived from project code No. 400000874 and was approved by the Ethics Committee of Kerman University of Medical Sciences, Iran (the code of ethics No. Kmu.ac.ir.1400.594). At the request of the ethics committee, the study was conducted following the Declaration of Helsinki and Ethics Publication on Committee (COPE). Unique codes were used for each participant to ensure information confidentiality.

Informed consent

Written informed consent was obtained to enter the study, and participants could easily withdraw from the study whenever they were willing.

Data sharing

Data are available under reasonable request to the corresponding author.

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