

Changes in Women's Menstruation Cycle After COVID-19 Vaccination and Infection

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Abstract: Since the COVID-19 case was discovered, Indonesia has been one of the affected nations and found various COVID-19 infection and immunization risks. Most females are in the menstrual cycle following COVID-19 infection, regardless of the number of days between cycles, blood quantity, or menses duration. This study examines the changes in menstruation post-COVID-19 infection and vaccination. This study used a cross-sectional observational study with an online questionnaire. The 758 female respondents in Yogyakarta were divided into two groups: 532 females who received vaccination and never have been infected with COVID-19 (Group A) and 226 females with a history of being infected with COVID-19 and vaccination (Group B). The data was analyzed using SPSS 26. The results found that most respondents aged 17-25 (90.24%) were students (80.87%). Both two groups had acne on Pre-menstrual syndrome (28.16%), 5-8 days of menstrual duration (73.75%), <30 days of menstruation duration length (57%), and the regular menstruation volume (63.19%) after COVID-19 vaccination. The comparative analysis of menstruation changes in two groups ($p>0.05$), including menstrual duration (0.771), menstrual duration length (0.609), and menstrual volume (0.476) after COVID-19 vaccination. In conclusion, there was no significant difference in menstrual change between Group A and Group B. After vaccination, healthcare professionals can promote post-COVID-19 immunization counseling and services to women who experience an abnormal menstrual cycle.

Keywords: COVID-19; COVID-19 vaccination; menstrual change

INTRODUCTION

Since the first time the World Health Organization (WHO) declared COVID-19 infection a world pandemic, Indonesia has been one of the countries affected both from the health and economic sectors.¹ The vaccination policies have a significant impact on reducing COVID-19 infection. Thus, the vaccine recipients often feel the side effects such as soreness, headache, fever, chills, joint pain, and nauseous. Participants who received their most recent immunization mentioned one or more adverse effects, such as fever and soreness, redness, and swelling at the injection site. After receiving the COVID-19 vaccination, the respondents also drank adequate water and took painkillers or fever-reducers if they were exhausted and had headaches, muscle aches, chills, fever, and nausea.² Many women around the world have been complaining of irregularities in their menstrual bleeding after receiving COVID vaccines; some women reported severe menstrual bleeding (menorrhagia), others reported bleeding before their periods are due or bleeding frequently (metrorrhagia/polymenorrhagia), and still others had postmenopausal bleeding.^{3,4} There

are also reports regarding the side effects on women regarding their menstrual cycle. Although it is uncertain, this vaccination may impact the menstrual cycle.⁵ Edelman et al. (2022) stated that with both the first and second vaccine doses, vaccinated individuals had an adjusted increase in menstrual cycle length of less than one day compared to the unvaccinated group.⁶ In a small Saudi-Arabian web-based evaluation of COVID-19 vaccine adverse effects, menstrual disturbances were documented in this open text area, and a negligible proportion of respondents reported an atypical menstrual cycle (delayed/increased bleeding or discomfort).⁷ In a UK survey of nearly 5,000 vaccinated women, 20% reported eight periods of incontinence following vaccinations.⁸ 42% of women with regular menstrual cycles reported heavier periods after vaccination, while 44% reported no change.⁹

There were 50-60% of reproductive-age women who received the first COVID-19 vaccine, regardless of vaccine type, reported menstrual cycle irregularities.¹⁰ Human papillomavirus (HPV) research has reported menstrual alterations, which have also been linked to changes in the menstrual cycle.¹¹ Another study with 505 Lebanese women found that after vaccination, more women experienced either heavy or light bleeding, then fewer women reported having regular cycles. Post-vaccination cycle irregularity was linked to worsening Pre-Menstrual Syndrome (PMS) symptoms.¹²

After the COVID-19 infection, menstrual changes were 35.7% greater than after vaccination.; 17.4% of participants experienced a delayed cycle, 14% experienced a shortened cycle, 7.4% experienced heavier bleeding, 5.8% experienced lighter bleeding, 2.5% experienced a shorter period, and 4.1% experienced a more extended period.¹³ Najjar et al. (2022) found that following COVID-19 infection, nearly half of the female participants' menstrual cycles changed, either in the number of days between cycles, the amount of blood, or the length of the menses.¹⁴ Studies in Arab demonstrated that more than 35% of the vaccinated women reported changes in the duration of their menstrual cycles, and 18.7% of women with a history of SARS-CoV-2 infection reported Menstrual changes.¹⁵

While research on the COVID-19 vaccine and menstrual characteristics is limited, especially in Indonesia, studies already published briefly lengthened menstrual cycles,¹⁶⁻¹⁸ increased menstrual bleeding,^{7,19} prolonged menses durations, menstrual abnormalities, and breakthrough bleeding in people who had previously menstruated. Some studies have suggested that receiving the COVID-19 vaccine may result in menstrual irregularities.^{16,20} To alleviate concerns about the safety of these vaccines among menstruating females, this study was designed to assess menstrual change post-vaccination. We compare females who received vaccination and never have been infected with COVID-19 with a history of being infected with COVID-19 and vaccination. This study reported the impact of COVID-19 vaccinations on menstruation change, including pre-menstrual syndrome, menstrual pain, menstrual cycle, menstrual duration length, and menstrual volume of women of reproductive age, and recommended future avenues of study.

MATERIAL AND METHOD

Study Design

This study utilized a cross-sectional study to compare two groups of infected and non-infected COVID-19 respondents after receiving COVID-19 vaccination—this study was conducted in March - September 2022 in Yogyakarta, Indonesia. An online questionnaire was created using Google Forms and distributed over social media sites utilizing the snowball method to achieve a larger sample.

Participants

A total of 775 participants filled out the self-administered survey; the following inclusion criteria were eligible for the study: 1) Javanese women who already menstruated, 2) range age 10 - 45 years old, 3) have been infected with COVID-19, and 4) had two doses of COVID-19 vaccines. The exclusion criteria were 1) have been married and 2) have been pregnant, miscarriage, or giving birth.

The total respondents were 758 people who met the inclusion criteria, then divided into two groups. Group A was respondents who received two doses of the COVID-19 vaccine but had not been infected with COVID-19 (532 respondents). Group B was respondents who received two doses of the COVID-19 vaccine and have been infected with COVID-19 (226 respondents). All participants were informed that anonymity would be maintained. We ensured that all queries were understandable by defining the following terms: menstrual duration, period, volume, and irregular menstrual duration, as we were addressing a large population with diverse sociodemographic backgrounds.

Data Source Measures

The questionnaire consisted of forty questions organized into thirteen sections and required an average of 15 minutes. The survey consisted of the following sections: demographics (age, ethnicity, blood type, weight, height, education level, occupation, marital status, and pregnancy status), COVID-19 exposure and vaccination (previous infection with COVID-19, vaccine name, and adverse events following vaccination), hormonal background, and menstrual duration details.

The survey included six comparative binary questions (pre-vaccination versus post-vaccination). These queries were designed to detect alterations in menstrual duration, menstrual duration, and menstrual volume following vaccination. The final two sections investigated the participants' reproductive health and menstrual patterns. They thus included queries regarding menstrual duration, menstrual volume, change in menstrual duration, drug use, Pre-Menstrual Syndrome patterns, and Pre-Menstrual Syndrome pain scale.

The researchers arranged and wrote the questionnaire and conducted a validity and reliability test. A pilot study was inducted on 30 women before distributing the questionnaire. All participants were assured that everything was clear. The questionnaire also has been through a validity and reliability test using Statistical Package for the Social Sciences (SPSS) with the Kolmogorov-Smirnov test, and the significant result was 0.060 ($p > 0.05$). Therefore, the items in the questionnaire were reliable.

Statistical Analysis

The data was imported into Microsoft Excel and analyzed using the Statistical Package for the Social Sciences (SPSS) version 26. A p-value of 0.05 was used to determine statistical significance. Continuous variables were given as mean, standard deviation (SD) in descriptive statistics, and categorical variables were presented as numbers and percentages. The independent T-Test analysis was used to compare percentages of vaccination and infected responders between the two groups.

Ethical Considerations

This research was approved by the health research ethics committee of 'Aisyiyah Yogyakarta (Approval No. 2004/KEP-UNISA/III/2022) on March 24, 2022. The declaration of ethics applied until March 25, 2023.

RESULT

In this study on 758 Javanese females in Yogyakarta, Indonesia, we divided into 532 (70.18%) of Group A and 226 (29.82%) of Group B. Group A were respondents who received complete doses of the COVID-19 vaccine and were uninfected with COVID-19. At the same time, group B were respondents who received the COVID-19 vaccine and had been infected with COVID-19. In Table 1, most of the respondents were in the range age of 17 to 25 years old, both in group A (92.11%) and group B (85.84%), and 80.87% were students with senior high school education (70.05%). However, 0.79% of the aged 36 – 45 were unmarried, had never been pregnant, never miscarriage or given birth, in groups B (1.77%) and A (0.38%). Interestingly, 4.70% in group A used Moderna vaccines than Pfizer (4.51%). Meanwhile, in group B, 4.42% of respondents received the Pfizer vaccine than the Moderna vaccine (3.10%). In general, 77.04% of all respondents received the Sinovac vaccine in groups A (75%) and B (81.86%).

Table 1. Respondents Characteristic

Characteristics	Group A (n=532)		Group B (n=226)		Total (n=758)	
	Frequency	Percentage (%)	Frequency	Percentage (%)	Frequency	Percentage (%)
Age						
10 - 16	20	3.76	15	6.64	35	4.62
17 - 25	490	92.11	194	85.84	684	90.24
26 - 35	20	3.76	13	5.75	33	4.35
36 - 45	2	0.38	4	1.77	6	0.79
Education Level						
Junior high school	16	3.01	6	2.65	22	2.90
Senior high school	374	70.30	157	69.47	531	70.05
Undergraduate	134	25.19	62	27.43	196	25.86
Graduate	8	1.50	1	0.44	9	1.19
Occupation						
Student	434	81.58	179	79.20	613	80.87
Employed	74	13.91	37	16.37	111	14.64
Unemployed	24	4.51	10	4.42	34	4.49
Vaccine Type						
Pfizer	24	4.51	10	4.42	34	4.49
Moderna	25	4.70	7	3.10	32	4.22
Sinovac	399	75.00	185	81.86	584	77.04
Astra Zeneca	84	15.79	24	10.62	108	14.25

Note: Group A: Vaccinated and Uninfected
Group B: Vaccinated and Infected

After the COVID-19 vaccination, 38.13 % of respondents suffered more than one side effect, followed by Soreness (33.91%), fever (7.52 %), and headache (1.98%). Interestingly, 18.47% of responses had no effect after COVID-19 vaccination. On the other hand, most respondents experienced in their Pre-menstrual syndrome acne (28.16%) after COVID-19 vaccination. Subsequently, the respondents felt fatigued (22.30%) and headache (14.94%) as their Pre-Menstrual Syndrome after receiving the vaccine of COVID-19. However, 22.30% of respondents experienced symptoms in their gastrointestinal such as bloating and diarrhea (Figure 1).

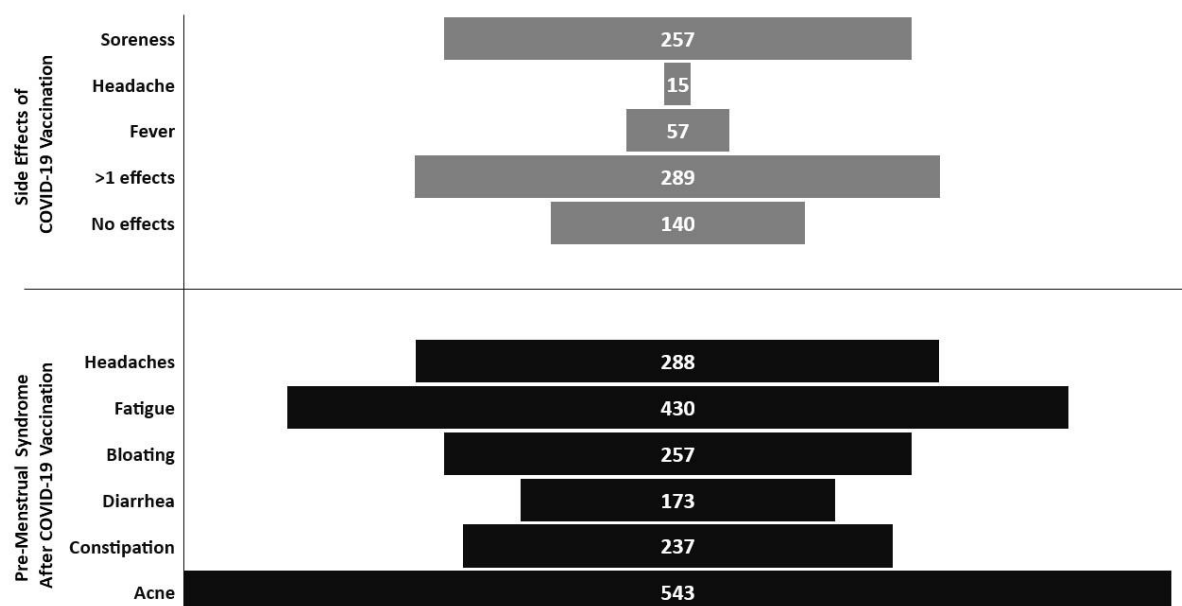


Figure 1. Effects After COVID-19 Vaccination and Pre-Menstrual Syndrome After COVID-19 Vaccination

In Figure 2, the respondents also experienced other symptoms of Pre-Menstrual Syndrome, namely arthralgia and abdominal cramps. The respondents experienced arthralgia in their Pre-Menstrual Syndrome, with 283 respondents (37.33%) in Group A and 109 respondents (14.37%) in Group B. Respondents experiencing arthralgia gave the scale for the pain they felt. Most respondents, 106 (27.04%) of Group A and 55 (14.03%) of Group B, felt the pain on a scale 3. Another symptom was abdominal cramps during Pre-Menstrual Syndrome after the COVID-19 vaccination, with 553 respondents (72.95%). The scale of abdominal cramps included Group A, with the majority on Scale 3 and Group B on Scale 4. Interestingly, the respondents who had side effects after COVID-19 vaccination chose not to consume medicine (82.71%), both drugstore medicine (14.77%) and herbal medicine (2.90%), to relieve symptoms.

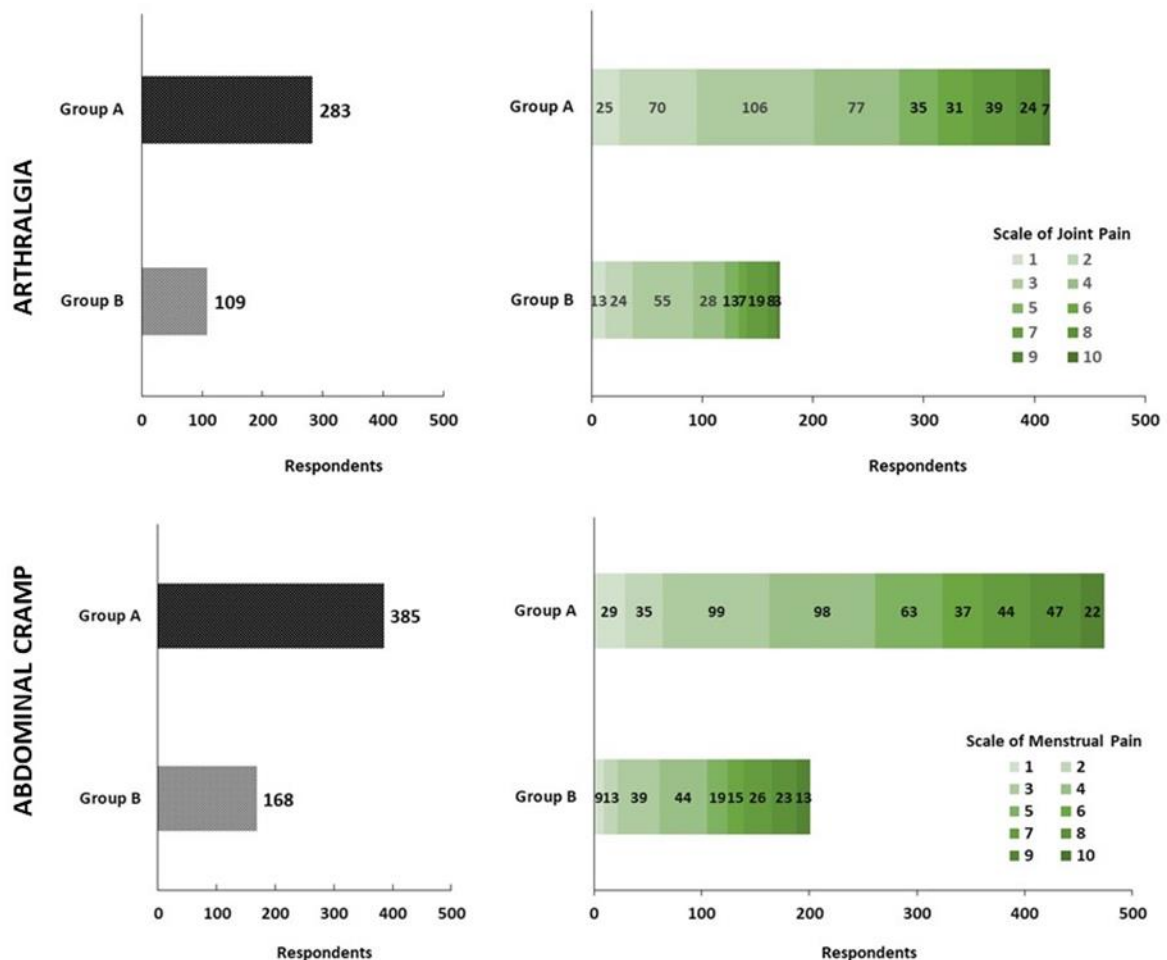


Figure 2. On the Left Side, The respondents experienced Arthralgia (Above) and Abdominal Cramps (Below) in their Pre-Menstrual Syndrome. On the Right Side (Green color), The Arthralgia Pain Scale (Above) and Abdominal Cramp Pain Scale (Below) during Pre-Menstrual Syndrome

Group A included respondents who received only the COVID-19 vaccine, and respondents in Group B received the COVID-19 vaccine and have been infected with COVID-19. The results revealed that most respondents had 5-8 days of menstrual duration in Group A and Group B before and after COVID-19 vaccination. Interestingly, 10.29% of the respondents had a menstrual period 8-14 days before the COVID-19 vaccination. After the COVID-19 vaccination, there was a change where 16.23% of respondents experienced a change in duration to <5 days. The COVID-19 vaccination changed the menstruation period, menstrual duration length, and menstruation volume (Figure 3).

In Figure 4, most respondents experienced their menstrual duration length for less than 30 days; 58.08% in Group A and 54.42% in Group B. Respondents stated they experienced a change in their menstrual volume; 82.52% of respondents in Group A and 88.05% of respondents in group B. 17.48% of respondents in Group A and 11.95% in Group B needed clarification on their change in menstrual volume. Unfortunately, this study did not have data on the duration length and menstrual volume before the COVID-19 vaccination.

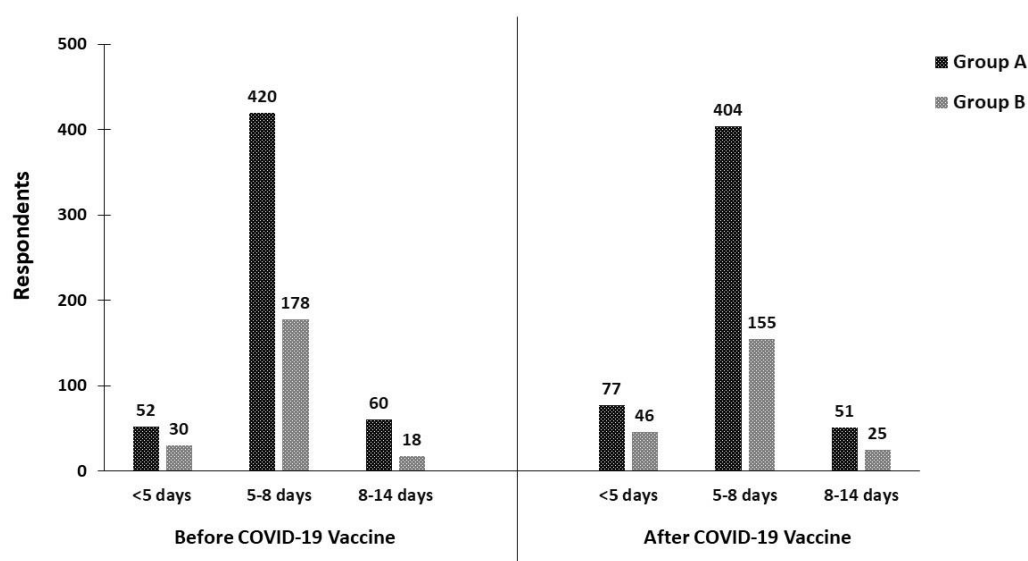


Figure 3. Menstrual Duration Before and After COVID-19 Vaccination

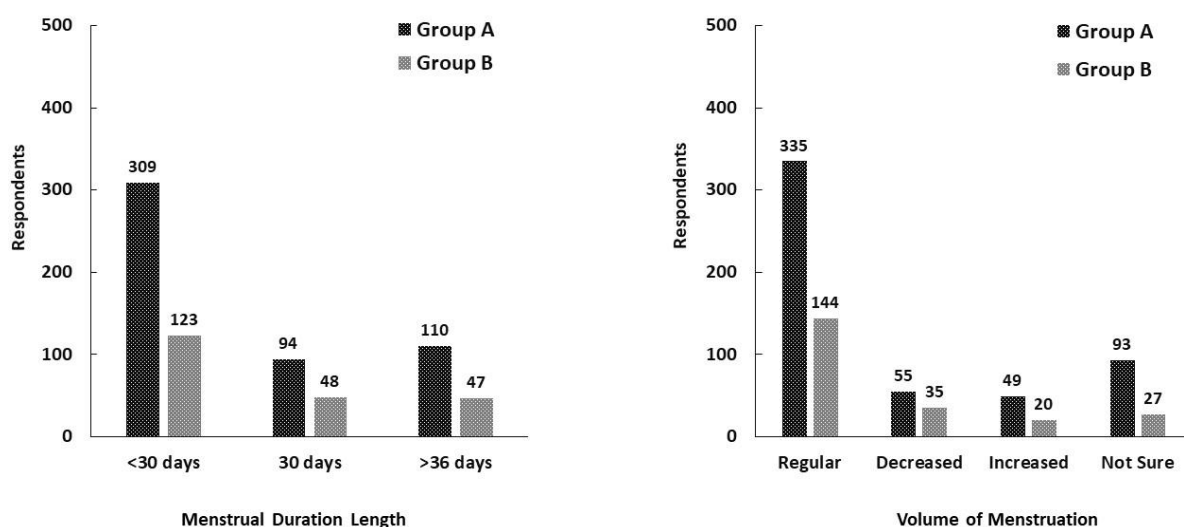


Figure 4. Menstrual Change after COVID-19 Vaccination

The comparative analysis using the independent-samples T Test in this research was divided into three categories: a comparison between females who received vaccination and never have been infected with COVID-19 (Group A) with a history of being infected with COVID-19 and vaccination (Group B) on menstrual change and followed the menstrual change. In Table 2, there is no significant difference between Group A and Group B on menstruation change, following the menstrual duration change $0.771 > 0.05$ ($p > 0.05$), the menstrual duration length $0.609 > 0.05$ ($p > 0.05$), and the menstrual volume $0.476 > 0.05$ ($p > 0.05$).

Table 2. Comparison between Group A and B on Menstrual Change

Variable	Menstrual Duration Change	Menstrual Duration Length	Menstrual Volume
Group A	0.771	0.609	0.476
Group B			

Source: SPSS 26, $P > 0.05$

DISCUSSION

Javanese female adults in this study aged 10 to 45 years old, unmarried, had never been pregnant, had never miscarriage, or had given birth. To get married, Indonesian women should be older than 20 years old. Age at first marriage, place of residence, wealth quintile, degree of education, and employment status all significantly affect each other statistically.²¹ Women aged 15-49 who reside in cities have a good economic status and are highly educated. They are more likely to marry or face the risk of experiencing the age of first marriage above 20 years.²¹ Socioeconomic situations, genetics, general health, dietary status, exercise, seasonality, and family size play a substantial effect in determining the reproductive health of women.^{22,23}

In this study, most of the respondents were in the range age 17-25 years old, both in Group A (92.11%) and Group B (85.84%) and 80.87% were students with senior high school education (70.05%). Menarche is the medical name for the first menstrual cycle that a female teenager experiences, which often begins with puberty. The average age of onset of menarche is 12.4, occurring between the ages of 10 to 16.²²⁻²⁵ In some women who go through menopause at 40 years old²⁶, the menstrual cycle is usually in the menopause phase, which occurs at 48.8 ± 51 years old.^{26,27} It also can vary according to their ethnicity.²⁸ Unlike men, females' reproductive systems exhibit regular cyclic alterations that, teleologically speaking, might be seen as periodic preparation for conception and fertilization.²⁹ The cycle is a menstrual cycle in primates and humans, and its most noticeable characteristic is the recurrent vaginal bleeding that comes with the shedding of uterine mucosa (menstruation). Although the cycle's duration is notoriously unpredictable, on average, it lasts 28 days between the beginning of one menstrual period and the beginning of the next. The days of the cycle are ordinarily designated by a number beginning with the first day of menstruation.²⁹ It starts at puberty, between the ages of 10 and 16, and concludes at menopause, which occurs on average at 51.^{22,24,25}

The pre-menstrual syndrome occurs in our respondents after receiving COVID-19 vaccination, with the typical symptoms being acne, fatigue, bloated stomach, constipation, diarrhea, and headaches. A specific category of headaches known as menstruation-related headaches (MRH) affects women and is brought on by a drop in estrogen levels throughout the menstrual cycle. Estrogen, which affects the serotonergic and glutamatergic circuits of the central nervous system (CNS), is primarily responsible for menstrual headaches³⁰. Our respondents experienced other symptoms, such as arthralgia and abdominal cramps. Ding et al. (2021) found dysmenorrhea history and menstrual duration phase between non-severe and severe COVID-19 women.³¹ Interestingly, mostly the respondents with pre-menstrual syndrome symptoms choose not to consume medicine from drugstores and herbal medicine to relieve symptoms. Hospitalized patients with COVID-19 are at risk for menstrual irregularity if given the corticosteroid dexamethasone. This medication is believed to work by increasing endometrial cortisol levels, which may affect the maturation of endometrial blood vessels and alter the menstrual cycle and blood loss.^{32,33}

This study discovered a strong link between age and post-vaccination change in the menstrual cycle. Since irregular and protracted cycles have been found to raise the risk of premature mortality, the menstrual cycle is a crucial sign of a woman's general health.³⁴ Regularity of the menstrual cycle, which is correlated with public health and fertility in women of reproductive age, is an essential physiological process.¹⁶ With five-day menses, the average menstrual cycle lasts between 26 and 35 days.³⁵ Regular menstrual cycles may occasionally have irregular or stress-related disruptions, which may cause a period to be missed or altered.³⁶ Besides, a woman's menstrual cycle may be impacted by her exposure to various variables. These include biological factors like body weight, age, ovarian conditions, and genetics, lifestyle factors like stress, shift work, exercise, dietary composition, and alcohol, life history factors like parity and age at menarche, environmental factors like air pollution and lifestyle factors like smoking, drugs, and alcohol.³⁷ A study in the United States on reproductive women (age 18-45) found menstrual and COVID-19-related stress.³¹

To control the menstrual cycle, circulating sex hormones act on the hypothalamic-pituitary-gonadal axis (HPG axis), which regulates the endometrium's discharge during menstruation.³⁸ Corticotropin-releasing hormone (CRH), a steroid hormone generated in reaction to stress, inflammation, and immunological processes, is also produced by the brain, pituitary, and cortisol.³⁸ In response to traumatic events, the release of CRH activates the receptors in female reproductive organs responsible for ovulation and the destruction of the corpus luteum.³⁸ When exposed to stressful events, the levels of the female sex hormones CRH and cortisol diminish, causing anomalies in menstruation.³⁸

Filfilan et al. (2023) stated that a substantial correlation exists between age and post-vaccination alterations in the menstrual cycle, with a high proportion of women in the 21 to 30 age group reporting these changes.³⁹ It was followed by previous studies revealing that alterations were noted by many women aged 21 to 30.²⁶ Our findings are comparable with those of Alghamdi et al. (2021), who documented menstruation

abnormalities in females of the same age range following the COVID-19 vaccination.⁷ Moreover, most Saudi girls of reproductive age who had completed secondary school experienced post-COVID-19 immunization anomalies in their menstrual cycle.⁷

Interestingly, our result found that most respondents experienced a change in duration to <5 days, with a menstrual cycle of <30 days, in groups A and B. The standard process in women's menstrual is 28 days with ± 7 days of menstrual. The normal phase of menstruation usually occurs between 2 -7 days.⁴⁰ The International Federation of Gynecology and Obstetrics considers a variation of fewer than eight days between a person's shortest and longest periods normal.⁴¹ Individual cycle lengths vary naturally.^{42,43} The degree of change we observed in our data after immunization fell well within this range of normal variation. Contrarily, COVID-19 infection may result in long-lasting impairment of menstrual function.^{31,44-48} The previous study reported that some women changed their menstrual durations since the pandemic began³¹ and after the COVID-19 vaccination.⁴⁹ It also can return to normal on its own.⁴⁹ About 10% of females had a cycle length change of 8 days or more that was clinically significant; this difference quickly subsided after two post-vaccination cycles.⁴⁹ A study on October 2020 – September 2021 conducted in the US reported that compared to those who weren't immunized, a subset of people who received both vaccine doses in a single cycle had an adjusted 2-day lengthening of their vaccination cycle.⁴⁹ This is in line with another study which stated that 77% of respondents experienced regular menstrual durations within three months after receiving the COVID-19 vaccination.³¹

There are no significant differences in women on menstrual duration change between the respondents who received COVID-19 vaccination and those who received COVID-19 vaccination and have been infected with COVID-19. These results are supported by the study by Bouchard et al. (2022), who stated that in 279 women as the respondents, there were no statistically significant differences in menstrual duration parameters between the pre-vaccine, vaccine, and post-vaccine cycles.⁵⁰ Studies on the 127 women who tested positive for COVID-19 showed changes in menstrual cycles to increasing premenstrual syndrome symptoms, infrequent menstruation, and irregular menstruation.⁵¹ The previous studies evaluated menstrual function and had a control group of women who had not received the COVID-19 vaccine discovered a minor, transient increase in menstrual cycle duration and a weak correlation between the vaccination and cycle irregularity.^{6,31,52,53}

In the menstrual volume, our respondents showed that 62.97% of Group A and 63.72% of Group B had their regular volume even after the COVID-19 vaccine. A cross-sectional study conducted in 2020 in China found that the COVID-19-infected woman had a change and that 20% of 177 women with COVID-19 had significantly reduced menstrual volume, and 19% had a protracted menstrual cycle.⁵⁰ A difference between a person's shortest and longest periods of less than eight days is regarded as normal by the International Federation of Gynecology and Obstetrics.³² Cycle lengths vary naturally between individuals. The amount of change we identified in our data following vaccination was well within this range of expected variance. On the other hand, COVID-19 infection may cause long-lasting menstrual function impairment.³² The virus is regarded as one of the reasons for menstrual abnormalities. Anti-Müllerian hormone levels were lower in post-COVID patients, a finding that the existence of ACE2 receptors in antral follicles may explain. Utilizing ACE2 receptors, SARS-CoV-2 can directly infiltrate ovarian follicles, reducing ovarian reserve and causing irregular menstruation. ACE2 receptors in the endometrium are involved in spiral artery vasoconstriction and uterine epithelial cell proliferation. Thus, SARS-CoV-2 and endometrial ACE2 receptors may combine to generate post-infection menstrual changes.^{48,54,55}

In contrast to those who had COVID-19 disease in 2020 and reported no change in menstrual cycles, 16% of a cohort who had the condition before vaccinations became available reported changes in menstrual cycles.⁵⁶ In two studies conducted when vaccinations were available, menstrual alterations were reported by 16% or 28% of menstruation patients with COVID-19, with changes linked to more severe disease.^{46,50} More than 30% of menstruation participants in a cohort of individuals with extended COVID reported experiencing some menstrual disorder.⁵⁷ Menstrual changes were linked to more severe COVID-19 symptoms in those who reported them.⁴⁶ Finally, while discussing worries regarding menstruation irregularities and immunization, it is important to remember that unvaccinated people are at high risk of morbidity and mortality from COVID-19.

When advising patients about vaccination, clinicians will find it easier if they have a better grasp of these associations, including whether one exists and the size and longevity of potential changes.⁵² Numerous confounding variables complicate research on this topic during such unprecedented circumstances as significant lifestyle changes, stress, immunization, and COVID-19 illness.³² It can be challenging to distinguish

between menstrual cycle fluctuations brought on by the pandemic's confounding characteristics and those induced by the exposure because these variables may significantly impact the research findings.⁵⁸ Clinicians find it difficult to make recommendations due to the broad range of potential causes of reproductive health disturbance in the COVID-19 era, the likely variation in impact by geographic location and socioeconomic status, and the lack of clinical practice guidance, longitudinal studies, or studies assessing potential interventions.

Our study has limitations, the limited variation of respondents who are only from the Yogyakarta area. It may need to be more generalizable to the Indonesian woman population. Second, we did not yet know whether these populations experience more significant changes in the menstrual cycle and length associated with COVID-19 vaccination because we do not have women who have been menstruated and have never been pregnant but have never been vaccinated (control group). Third, we did not have data about the history of COVID-19 infection and did not check the titer antibody in infected groups. Lastly, we did not check the women hormonal. The suggestion for other researchers who study a similar topic can broaden the research area and consider other factors, including lifestyle, life history, environmental, and biological factors.

CONCLUSION

In conclusion, the current evidence suggested that there was no significantly different between females who received vaccination and never have been infected with COVID-19 with a history of being infected with COVID-19 and vaccination on menstruation change, including pre-menstrual syndrome, menstrual pain, menstrual cycle, menstrual duration length, and menstrual volume post COVID-19 vaccination. Healthcare workers can promote post-COVID-19 immunization counseling and services to a woman that experiences an unusual menstrual period after vaccination.

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CONFLICT OF INTEREST

There is no conflict of interest in this study.

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