Author Gate

Journal of Medicine and Health Studies

Shaqra University

Original Article

Pharmacovigilance surveillance of menstrual cycle irregularities following primary and booster doses of COVID-19 vaccine among Saudi females: A large cross-sectional analysis

Abdullah Alanazi

Department of Clinical Pharmacy, College of Pharmacy, Jouf University, Sakaka, Saudi Arabia

CORRESPONDING AUTHOR

Abdullah Salah Alanazi
Department of Clinical Pharmacy, College of Pharmacy, Jouf University, Sakaka 72388, Saudi Arabia
Email: asdalananzi@ju.edu.sa

https://orcid.org/0000-0002-8120-4018

Received: 22 Oct 2023
Accepted: 27 Nov 2023
Published: 30 Dec 2023

DOI
10.37881/jmahs.223

ABSTRACT

Background: Several qualitative and anecdotal studies uncovered cycle irregularities in females following COVID-19 vaccination. However, research on the incidence and pattern of cycle irregularities among Saudi females is scarce. This study sought to check the frequency, pattern, and risk factors associated with menstrual irregularities following primary and booster doses of the COVID-19 vaccine.

Methods: A web-based and cross-sectional study (March to June 2022) was conducted in Saudi Arabia. The data collected from participants consist of demographics characteristics, menstruation experience, and vaccination status. The data was analyzed using R Statistical Software.

Results: Of 538 participants included in this study, suspected cycle irregularities were prevalent in 47.6%, 44.6% and 41.1% of females after the first, second and booster doses of COVID-19 vaccine. Delayed menses (20.8%, 21%), less bleeding (9.5%, 11.3%) and too much bleeding (7.2% and 7.4%) were frequently reported cycle irregularities after the first and second doses of vaccines, respectively. However, irregular periods (variable pattern) were frequently (12.8%) reported following the booster dose.

Conclusion: Our analysis showed a high proportion of menstrual cycle irregularities among Pfizer and AstraZeneca vaccinees. The incidence of adverse reactions exhibited a correlation with specific demographic factors, prompting the imperative for additional inquiries to elucidate a causative association.

Keywords: COVID-19; Menstrual Cycle; Pfizer-BioNTech; Oxford-AstraZeneca; Pharmacovigilance.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has taken the world by storm over the past few years, affecting every aspect of human life.[1-3] Vaccination studies have been initiated in addition to non-drug preventive measures to reduce cases and deaths that occurred due to the COVID-19 pandemic.[4,5] Various COVID-19 vaccines were developed and approved after identifying the virus as a response, including Moderna's mRNA and Pfizer-BioNTech's for emergency use in the US in 2020.[6,7] Research studies reported that an average vaccination level of 80 doses per inhabitant is required to reduce the number of confirmed cases and deaths. Moreover, the recent emergence of Omicron further necessitates

prevention efforts and vaccination to protect against COVID-19. However, the Vaccine Adverse Event Reporting System tracked the potential side effects of vaccines owing to the rapid worldwide use of vaccines by the Centers for Disease Control and Prevention (CDC).[8]

Various vaccine-related side effects were reported, ranging from mild symptoms, including headache, fever, chills, fatigue, arm pain, anaphylaxis, and thrombosis.[9-12] These side effects affect physical and psychological health and the quality of life. Moreover, COVID-19 vaccination resulted in several menstrual abnormalities, including pain, bleeding, and increased cycle length reported in a recent study.[13]

Irregular menstrual cycles lead to metabolic disorders, including diabetes mellitus and dyslipidemia.[14] Women are at higher risk of death before the age of 70 due to longer menstrual cycles or irregular cycles.[15] For this reason, the American Academy of Pediatrics recommended adding the menstrual cycle as a vital sign of adolescent females in light of the prevalence of menstrual abnormalities.[16] Menstrual irregularity was the top reason for women to apply to gynecologists, varying between 5% and 34%.[17,18] A total of 51435 suspected reactions had been reported after all three COVID-19 vaccines in the UK Yellow Card up to 24 August 2022 relating to various menstrual disorders.[19] Menstrual irregularities may occur in vaccinated women regardless of the type of vaccine.[20] For this reason, monitoring of adverse effects after vaccination and continuous attention to the effects of COVID-19 exposure on women's health is mandatory.[21] Hence, it is an important women's health imperative to clarify the association between COVID-19 vaccination and menstrual irregularities. To address this issue, we evaluated the frequency, pattern, and predisposing factors of menstrual irregularities following primary and booster doses of the COVID-19 vaccine.

MATERIALS AND METHODS

Ethical Approval

The Local Committee on Bioethics (LCBE) approved the study at Jouf University (Reference No. 2-05-44). A brief explanation about the study was given to all the participants, and online consent was taken from each of them before filling out the questionnaire. All data were subjected to anonymization before analysis.

Sample Size Estimation

The sample size was calculated using an online software, OpenEpi (version 3.01). The software uses a proportional formula to calculate the sample size by keeping the population size as one million. The expected frequency was set at 50% with a 95 % confidence interval, yielding a sample size of 381. The formula is: n = (DEFF*Np[1-p]) / (d2/Z21-α/2*[N-1]+p*[1-p]) [22]

Study Design, Setting, and Population

A cross-sectional survey was distributed to the adult female population of Saudi Arabia from March to June 2022. The study included only those participants who are 18 or more than 18 years old, residents of Saudi Arabia, received at least two doses of the COVID-19 vaccine and given consent to participate.

Development and Validation of the Study Instrument

A comprehensive literature search was conducted to identify the menstrual cycle irregularities associated with COVID-19 vaccines.[13,23-25] After the literature review, a study instrument was developed to collect participant data in Google form. The questionnaire was initially created in English and then independently translated into Arabic by three separate authors. A second translation of the Arabic version into English was undertaken to ensure that the questions' original meaning was not altered (forward and backward translation). The study instrument was validated by a team of experts from the pharmacy and health colleges of Jouf University, Saudi Arabia, and a pilot study was performed to check

the reliability. The pilot study data reported a Cronbach alpha value of 0.812, which shows good consistency among the data.

The validated study instrument, having three sections, was used to collect the data. In Section I, demographic characteristics such as age, body mass index (BMI), monthly income, marital status, number of children, smoking history, disease history, medication used (particularly corticosteroids, oral contraceptive pills, and hormone replacement therapy), presence of facial hairs and acne, and the history of miscarriage. Section II inquired about the participants' vaccination status, i.e., the type of vaccines received for their first, second, and booster dose from a list of COVID-19 vaccinations approved in Saudi Arabia. Section III consisted of items related to cycle irregularities. The participants were asked whether they experienced any menstrual cycle problems following either dose of COVID-19 vaccines. If participants reported having cycle irregularities, the menstrual cycle problems were further categorized into delayed menses, early menses, less bleeding, too much bleeding, skipped menses, and irregular periods. The term irregular periods refers to a type of menstrual cycle problem in which participants experience a variable pattern.

Data Collection

The study data was collected through Google form by distributed among the target population through convenient sampling. The survey was sent to potential participants through social media applications, including Twitter, Facebook, WhatsApp, and WeChat. The responses were collected for a specified study time, and data was downloaded in Microsoft Excel. The data was cleaned based on inclusion/exclusion criteria, and to maintain confidentiality, data was numerically coded for further analysis in R Statistical Software (Version 4.0.2).

Statistical analysis

The numbers and relative percentages (%) were calculated for categorical variables, and mean ± standard deviation (SD) was calculated for continuous variables. The chi-square test or Fisher's Exact test assessed the proportion differences between age groups, vaccine types, and associated menstrual cycle problems after the three doses. We fit a logistic regression model to explore the relationship between cycle irregularities and different factors. Predictors included age categories, vaccine type, smoking history, and comorbidities. Alpha level = 0.05 was considered significant through the analysis.

RESULTS

Participants characteristics

This study included 538 participants and most of them had aged less than 55 years. The mean age of the study participants was 36.2 ± 11.1 years. More than half of respondents were married (65.1%) and had children (62.7%). The majority of the responses (68.2%) were from the capital city (Riyadh) of Saudi Arabia. The demographics of study participants are described in Table 1.

The most common comorbid condition was seasonal allergy (15.8%) followed by hyperlipidaemia (14.5%) and polycystic ovarian syndrome (PCOS) (9.3%). Only 2.4% of respondents had uterine polyps and fibroids. About 14% of participants were using oral contraceptive pills (OCPs), and 5.8% reported the use of corticosteroids. Hirsutism (facial hairs) was present in one-third (33.1%) of the study population, while acne was prevalent in one-fourth (24.5%) of participants. Approximately, one-fourth (25.1%) of the study population indicated a history of miscarriage.

Table 1: Demographic characteristics of participants based on age categories.

Parameters	Total (N=538)	< 35 (N=253)	35-54 (N=255)	≥55 (N=30)
Age (years), mean ± SD	36.3±11.1	26.5±4.8	43.3±5.1	59.8±5.3
BMI				
Underweight (<18.5)	17 (3.2)	13 (5.2)	4 (0.7)	-
Normal (18.5 to 24.9)	192 (35.8)	130 (51.6)	58 (10.8)	4 (13.3)
Overweight (25 to 29.9)	191 (35.6)	62 (24.6)	113 (21.0)	16 (53.3)
Obese (≥ 30)	137 (25.5)	47 (18.7)	80 (14.9)	10 (33.3)
Marital Status				
Single	144 (26.8)	124 (49.0)	20 (7.8)	-
Married	350 (65.1)	112 (44.3)	212 (83.1)	26 (86.7)
Divorced	33 (6.1)	11 (4.3)	18 (7.1)	4 (13.3)
Widow	11 (2.0)	6 (2.4)	5 (1.9)	
Having Children	333 (62.7)	99 (39.3)	211 (84.7)	23 (76.7)
Area of Residency				
Rural resident	42 (7.8)	33 (13.0)	9 (3.5)	-
Urban resident	496 (92.2)	220 (86.9)	246 (96.5)	30 (100.0)
Region				
Al-Bahah	4 (0.7)	4 (1.6)	-	-
Al-Jawf	78 (14.5)	71 (28.1)	7 (2.7)	-
Al-Qassim	16 (2.9)	10 (3.9)	6 (2.4)	-
Aseer	6 (1.1)	4 (1.6)	2 (0.8)	-
Eastern region	17 (3.2)	8 (3.2)	8 (3.1)	1 (3.3)
Hail	12 (2.2)	8 (3.2)	4 (1.6)	-
Jazan	4 (0.7)	3 (1.2)	1 (0.4)	-
Mecca	21 (3.9)	9 (3.6)	10 (3.9)	2 (6.7)
Madina	2 (0.2)	-	1 (0.4)	-
Najran	4 (0.7)	4 (1.6)	-	-
Riyadh	367 (68.2)	128 (50.6)	212 (83.1)	27 (90.0)
Tabouk	3 (0.6)	1 (0.4)	2 (0.8)	-
Southern boarders	5 (0.9)	3 (1.2)	2 (0.8)	-
Monthly household income				
< 10,000 SR	237 (44.1)	142 (56.1)	87 (34.1)	8 (26.7)
10,000-15,000 SR	145 (26.9)	73 (28.9)	59 (23.1)	13 (43.3)
15,000-20,000 SR	92 (17.1)	23 (9.1)	62 (24.3)	7 (23.3)
> 20,000 SR	64 (11.9)	15 (5.9)	47 (18.4)	2 (6.7)
History of smoking				
Never	508 (94.4)	241 (95.3)	237 (92.9)	30 (100.0)
Current	18 (3.3)	5 (1.9)	13 (5.1)	--
Former	12 (2.2)	7 (2.8)	5 (1.9)	
Comorbidities				
Have a disease	134 (24.9)	30 (11.9)	81 (31.8)	23 (76.7)
Hypertension	48 (8.9)	13 (5.1)	23 (9.0)	12 (40.0)
Diabetes Mellitus	50 (9.3)	12 (4.7)	25 (9.8)	13 (43.3)
Hyperlipidaemia	78 (14.5)	9 (3.6)	54 (21.2)	15 (50.0)
Asthma or COPD	23 (4.3)	10 (3.9)	12 (4.7)	1 (3.3)
Chronic Kidney Disease	7 (1.3)	4 (1.6)	3 (1.2)	-
PCOS	52 (9.7)	29 (11.5)	23 (9.0)	-
Hypothyroidism	50 (9.3)	9 (3.6)	36 (14.1)	5 (16.7)
Hyperthyroidism	8 (1.5)	5 (1.9)	3 (1.2)	-
Cardiovascular Disease	7 (1.3)	4 (1.6)	3 (1.2)	-
Endometriosis	5 (0.9)	2 (0.8)	2 (0.8)	1 (3.3)

Pelvic inflammation	4 (0.7)	3 (1.2)	1 (0.4)	-
Osteoporosis	19 (3.5)	4 (1.6)	10 (3.9)	5 (16.7)
Osteoarthritis	43 (7.8)	9 (3.6)	24 (9.4)	10 (33.3)
Seasonal Allergy	101 (18.8)	40 (15.8)	55 (21.6)	6 (20.0)
Other diseases	37 (6.9)	15 (5.9)	2 (6.7)	20 (7.8)
Cancer	8 (1.5)	4 (1.6)	3 (1.2)	1 (3.3)
Uterine cancer	4 (0.7)	3 (1.2)	1 (0.4)	-
Cervical cancer	4 (0.7)	3 (1.2)	1 (0.4)	-
Uterine polyps or fibroids	13 (2.4)	3 (1.2)	7 (2.7)	3 (10.0)
Use of hormones and steroids				
Using OCPs	75 (13.9)	40 (15.8)	34 (13.3)	1 (3.3)
Using corticosteroid	31 (5.8)	17 (6.7)	13 (5.1)	1 (3.3)
Using HRT	31 (5.8)	16 (6.3)	14 (5.5)	1 (3.3)
Symptoms of hyperandrogenism				
Facial hairs	178 (33.1)	111 (43.9)	62 (24.3)	5 (16.7)
Acne	132 (24.5)	95 (37.5)	37 (14.5)	-
History of miscarriage				
No	309 (57.4)	138 (54.5)	150 (58.8)	21 (70.0)
Yes	135 (25.1)	32 (12.6)	94 (36.9)	9 (30.0)
Not married	94 (17.4)	83 (32.8)	11 (4.3)	-

Data presented as n (%) unless otherwise specified

Type of vaccines administered among study participants

Pfizer-BioNTech was received by most of the participants as first (75.8%), second (74.5%) and booster dose (65.2%). The second most frequently administered vaccine was Oxford-AstraZeneca. It is important to note that vaccine use was equally distributed across various age categories (Table 2).

Table 2: Vaccine types for the three doses among age groups

Parameters	Total (N=538)	< 35 (N=253)	35-54 (N=255)	>55 (N=30)	[a]*P*
Dose 1					
Janssen (Johnson & Johnson)	5 (0.9)	3 (1.2)	2 (0.8)	-	0.307
Moderna	18 (3.3)	13 (5.1)	5 (1.9)	-	
Oxford-AstraZeneca	103 (19.3)	53 (20.9)	48 (18.8)	2 (6.7)	
Pfizer-BioNTech	408 (75.8)	182 (71.9)	198 (77.6)	28 (93.3)	
Dose 2					
Janssen (Johnson & Johnson)	13 (2.4)	11 (4.3)	2 (0.8)	-	0.095
Moderna	43 (7.9)	21 (8.3)	20 (7.8)	2 (6.7)	
Oxford-AstraZeneca	81 (15.1)	46 (18.2)	31 (12.2)	4 (13.3)	
Pfizer-BioNTech	401 (74.5)	175 (69.2)	202 (79.2)	24 (80.0)	
Dose 3					
Janssen (Johnson & Johnson)	13 (2.4)	10 (3.9)	3 (1.2)	-	0.195
Moderna	49 (9.1)	19 (7.5)	28 (10.9)	2 (6.7)	
Oxford-AstraZeneca	42 (7.8)	23 (9.1)	18 (7.1)	1 (3.3)	
Pfizer-BioNTech	351 (65.2)	155 (61.3)	174 (68.2)	22 (73.3)	
None	83 (15.4)	46 (18.2)	32 (12.5)	5 (16.7)	

[a]*P* value was based on Fisher's Exact test

Prevalence of cycle irregularities after the first, second, and booster dose

After the first dose of the COVID-19 vaccine, the prevalence of menstrual cycle problems was 47.6%, while it was 44.6% and 41.1% after the second and third/booster doses, respectively. Following the primary and booster doses, significantly higher rates of menstrual cycle problems were observed in women aged 35 to 54 years (Table 3).

Table 3: Prevalence of Cycle Irregularities after primary and booster doses of COVID-19 vaccines

Parameters	Total (N=538)	< 35 (N=253)	35-54 (N=255)	≥55 (N=30)	[a]*P*
Change in Menstrual Cycle (Dose 1)					
Yes	256 (47.6)	113 (44.7)	141 (55.3)	2 (6.7)	0.001
No	282 (52.4)	140 (55.3)	114 (44.7)	28 (93.3)	
Change in Menstrual Cycle (Dose 2)					
Yes	240 (44.6)	109 (43.1)	128 (50.2)	3 (10.0)	0.001
No	298 (55.4)	144 (56.9)	127 (49.8)	27 (90.0)	
Change in Menstrual Cycle (Dose 3/Booster Dose)					
Yes	221 (41.1)	94 (37.2)	125 (49.0)	2 (6.7)	0.001
No	317 (58.9)	159 (62.8)	130 (50.9)	28 (93.3)	

[a]*P* value was based on Fisher's Exact test

Pattern of cycle irregularities after first, second, and booster dose

After the first dose, the most common cycle irregularities were delayed menstruation (20.8%), decreased bleeding (9.5%), and excessive bleeding (7.2%). Of participants with age > 55 years (n = 30), 93.3% experienced too much bleeding. After the second dose, a similar pattern of cycle irregularities was observed, with 21%, 11.3%, and 7.4% of study participants experiencing delayed menses, less bleeding, and excessive bleeding, respectively. Irregular period (variable cycle or pattern each month) was the most common cycle irregularity (12.8%) after the booster dose of COVID-19 vaccines followed by delayed menses (9.7%) and less bleeding (5.8%). It is important to note that 90% and 93.3% of women aged >55 years did not experience any cycle irregularities after the second and booster doses (Table 4).

Table 4: Pattern of Cycle Irregularities after primary and booster doses of COVID-19 vaccines

Parameters	Total (N=538)	< 35 (N=253)	35-54 (N=255)	≥55 (N=30)	[a]*P*
Dose 1					
Delayed Menses	112 (20.8)	52 (20.6)	60 (23.5)	-	0.001
Early Menses	27 (5.0)	10 (3.9)	17 (6.7)	-	
Less bleeding	51 (9.5)	22 (8.7)	27 (10.6)	2 (6.7)	
Too much bleeding	39 (7.2)	19 (7.5)	20 (7.8)	28 (93.3)	
Skipped Menses	2 (5.0)	10 (3.9)	17 (6.7)	-	
Irregular period	-	-	-	-	
No Cycle irregularities	282 (52.4)	140 (55.3)	114 (44.7)	-	
Dose 2					
Delayed Menses	113 (21.0)	49 (19.4)	64 (28.1)	-	0.002
Early Menses	26 (4.8)	13 (5.1)	11 (4.3)	2 (0.7)	
Less bleeding	61 (11.3)	27 (10.7)	33 (12.9)	1 (3.3)	
Too much bleeding	40 (7.4)	20 (7.9)	20 (7.8)	-	
Skipped Menses	-	-	-	-	
Irregular period	-	-	-	-	
No Cycle irregularities	298 (55.4)	144 (56.9)	127 (49.8)	27 (90.0)	

Dose 3					
Delayed Menses	52 (9.7)	25 (9.9)	27 (10.6)	-	0.001
Early Menses	14 (2.6)	6 (2.4)	8 (3.1)	-	
Less bleeding	31 (5.8)	17 (6.7)	13 (5.1)	1 (3.3)	
Too much bleeding	30 (5.6)	14 (5.5)	16 (6.3)	-	
Skipped Menses	25 (4.6)	4 (1.6)	21 (8.2)	-	
Irregular periods	69 (12.8)	28 (11.1)	40 (15.7)	1 (3.3)	
No Cycle irregularities	317 (58.9)	159 (62.8)	130 (50.9)	28 (93.3)	

[a]*P* value was based on Fisher's Exact test

Factors associated with cycle irregularities after primary and booster doses of COVID-19 vaccines

We fit a logistic regression model to examine the association between cycle irregularities and various factors. Age categories, type of vaccine, smoking history, oral contraceptives, miscarriage, hyperthyroidism, and comorbidities were considered independent variables during the analysis.

Factors associated with cycle irregularities after first dose

The odds of experiencing cycle irregularities after the first dose were 16.2 higher in females of < 35 years old age group (OR=16.2, 95% CI [4.4, 26.5], P < 0.001), and 22.9 higher in 35-54 years old females compared to 55-year-old age group (OR = 22.9, 95% CI [6.5, 41.8], P < 0.0.001). The odds for current smokers were 14.6 % higher than the odds for others (OR = 1.15, 95% CI [0.5,3.9], P = 0.56). Importantly, comorbidities increase the likelihood of experiencing cycle irregularities by 65% (OR = 1.65, 95% CI [1.1,2.6], P = 0.03). However, the use of OCPs (OR = 0.76, 95% CI [0.5,1.3] P = 0.288), miscarriage (OR = 1.12, 95% CI [0.9, 1.4], P = 0.358), and hyperthyroidism (OR = 0.47, 95% CI [0.1, 2.2], P = 0.354) were not found to be associated with cycle irregularities. Compared to the Janssen vaccine, all other types of vaccine had reduced odds of cycle irregularities after the first dose. Importantly, there was no evidence of increased odds of experiencing cycle irregularities related to the type of vaccine.

Factors associated with cycle irregularities after second dose

The odds of experiencing cycle irregularities after the second dose for females under the age of 35 years old were 9.84 (OR = 9.84, 95%CI [3.2, 13.7], P < 0.001), and for females of 35-54 years old, the odds were 12.12 (OR=12.11, 95% CI [4.0, 52.8], P < 0.0001) times the odds for 55 years old. However, there is no evidence of increased odds in current smokers (OR = 0.81, 95% CI [0.30, 2.15], P = 0.676), or former smokers (OR = 0.23, 95%CI [0.03, 0.89], P = 0.046), and miscarriage history (OR= 1.11, 95% CI [0.87, 2.22], P= 0.388). However, comorbidities increase the odds of experiencing cycle irregularities by 56.9% than those who had no comorbid condition (OR = 1.57, 95% CI [1.00, 2.46], P= 0.067). There was a lack of evidence that those who received the Janssen vaccine had reduced odds compared to other types of vaccine (OR = 0.91, 95% CI [0.06, 2.22], P= 0.948).

Factors associated with cycle irregularities after booster dose

The odds of experiencing cycle irregularities after the booster dose were high in females under 35 years old (OR= 7.44, 95% CI [2.1, 49.1], P < 0.001), and females between 35 and 54 years old (OR = 14.1, 95%CI [3.9, 89.8], P < 0.0001). Moreover, the odds for participants who were current smokers were higher than the odds for former or non-smokers (OR = 1.26, 95% CI [0.4, 3.5], P = 0.651). Importantly, there were significantly higher odds of having cycle irregularities among females who had miscarriage (OR = 1.52, 95% CI [1.18, 1.96], P =0.001). Our analysis revealed that all vaccines increase the likelihood of experiencing cycle irregularities compared to those who did not receive a booster vaccine (Table 5).

Table 5: Odds ratio for vaccine types and cycle irregularities

Vaccine type	OR	95%CI Low-high	*P* value
None (No booster dose)	Reference		
Moderna	4.91	2.06 – 12.38	<0.001
Pfizer-BioNTech	5.52	2.83 – 11.85	<0.001
Oxford-AstraZeneca	14.24	5.70 – 38.39	<0.001
Janssen (Johnson & Johnson)	15.91	4.22 – 70.56	<0.001

DISCUSSION

This is the first study of its own kind evaluating menstrual cycle irregularities among recipients of primary and booster doses of COVID-19 vaccines in Saudi Arabia. Approximately one-third of study participants experienced cycle irregularities, including delayed menstruation, less bleeding, and excessive bleeding. Following the primary and booster doses of the COVID-19 vaccine, women between 35 and 54 years of age, smokers, and those with comorbid conditions had a greater likelihood of cycle irregularities. These findings suggest that COVID-19 vaccines may induce changes in the menstrual cycle in women of reproductive age.

Menstrual cycle irregularities were first reported through social media.[26] By January 2022, the UK Medicines and Healthcare Products Regulatory Agency's (MHRA) yellow card surveillance scheme received 48,488 reports on menstrual cycle changes following three doses of COVID-19 vaccination. From 1 September 2022 to 22 February 2023, a total of 182 suspected reactions related to menstrual disorders, including delayed periods, heavier than usual periods, and unexpected vaginal bleeding, were reported after administration of the bivalent COVID-19 vaccines or the COVID-19 vaccine Novavax. The analysis of these cases suggested a possible link between the Moderna and Pfizer vaccines and heavy menstrual bleeding. Heavy menstruation has been listed as a potential side effect of the Pfizer and Moderna vaccines in the product information, even though these events were typically mild and transient.[27] It is important to note that no conclusive evidence currently links COVID-19 vaccines with menstrual cycle changes.

Our study revealed that 47.6%, 44.6%, and 41% of women suspected menstrual cycle abnormalities after the first, second, and booster doses, respectively. These findings are in contrast with another online study evaluating the side effects among COVID-19 vaccinees in Saudi Arabia, where cycle irregularities were reported in only 18 (0.69%) and 7 (0.45%) cases following the administration of BNT162b2 and ChAdOx1, respectively.[28] Another study conducted on physicians and dentists from Saudi Arabia and Jordan examined the long-term adverse effects of COVID-19 vaccines and found cycle irregularities in 5% of females.[24] However, our study's proportions of suspected cycle irregularities are consistent with other investigations. A survey of fertile females (age: 16 to 40 years) residing in the capital city (Riyadh) of Saudi Arabia reported menstrual changes among 50.9% of participants after receiving the Pfizer vaccines.[29] Qashqari et al. reported a prevalence of lighter (14.6%) and heavier (14.5%) periods than usual after the first dose and lighter (20.8%) and heavier (17.1%) periods than normal after the second dose.[25] Alahmadi et al. conducted a study on Saudi females of reproductive age. They revealed the prevalence of cycle irregularities to be 45.9% and 42.8% following the first and second doses of the Pfizer and Oxford-AstraZeneca vaccines, respectively.[23] Our study showed a higher rate of suspected cycle irregularities after the first dose, and similar results were observed in a study by Alahmadi et al.[23]

A recent systematic review of 73 articles revealed that 50.05% of females who received the COVID-19 vaccines experienced menstrual issues.[30] In this systematic review, the overall rate of menstrual abnormalities ranged from 0.83% to 90.9%. Another systematic review and meta-analysis indicated an association between vaccination and menstruation changes with an odds ratio of 1.91.[31] A review of 16 studies has also reported that approximately one-quarter of women suffered from cycle irregularities following the COVID-19 vaccinations.[32] These results indicate significant disparities in the reported incidence of cycle irregularities, which is primarily attributable to differences in study design, population, methodology, type of vaccines, number of doses, and data collection period. However, these results indicate that cycle irregularities may occur following COVID-19 vaccinations, prompting health authorities to design and implement proactive measures to prevent vaccine refusal among females.

Our study's most prevalent cycle irregularity was delayed menstruation after the first and second doses. These findings concurred with other studies conducted in the USA and UK reporting a delay in the next period following the COVID-19 vaccination.[33,34] These results also concord with the findings of studies conducted on the Saudi population.[25,29] Other common cycle irregularities reported in our study were less and too much bleeding after the first and second doses of COVID-19 vaccines. After the booster dose, irregular periods, i.e., a variable pattern of menstrual problems, were identified as the most common cycle irregularity. It is important to note that several women have reported an irregular menstrual cycle, irregular menstruation, or menstrual disorders, as opposed to providing specific information about the types of cycle problems. Zhang et al. observed similar outcomes while interpreting the Vaccine Adverse Event Reporting System (VAERS) data, in which the majority of females (34.63%) reported irregular menstruation and menstrual disorders (14.47%). Delayed menstruation was the second most common (19.42%) cycle irregularity in their study.[35] It is important to note that existing literature reported various menstrual problems, including menorrhagia, oligomenorrhea, and dysmenorrhea. These variations are linked with the socio-demographic features of the study participants.[30] Previous research also indicated that Pfizer-BioNTech accounted for the majority of cycle irregularity reports,[35] and this may be a possible explanation for the high prevalence of cycle irregularities in our study, as the majority of women received this vaccine as their first and second dose.

According to our findings, the incidence of cycle irregularities was significantly higher among women aged 35 to 54. These findings concur with those of a previous study that found a high prevalence of menstrual cycle changes among women aged 38 to 54.[23] Smoking was also found to be associated with cycle irregularities among recipients of the COVID-19 vaccine; these findings are consistent with the existing literature.[36,37] The relationship between smoking and menstrual cycle issues has been well-documented.[38] In this context, current female smokers should be counseled about the likelihood of cycle irregularities after receiving the COVID-19 vaccine. In addition, females with comorbid conditions should be prioritized for education and monitoring as a high-risk group for cycle irregularities. It is important to note that the type of vaccine was not found to be associated with the incidence of cycle irregularities in our study. Dar-Odeh et al. indicated menstrual changes can occur after receiving mRNA and adenovirus vector COVID-19 vaccines.[24] Edelman et al., demonstrated that changes in cycle length did not differ by the vaccine's mechanism of action.[34] Diverse studies have demonstrated a stronger association between the second dose and menstrual problems,[30]but our findings indicate a higher incidence after the first dose. Multiple other large-scale studies have also reported the high prevalence of cycle irregularities following the first dose.[39,40]There should be pre- and post-vaccination educational campaigns for women at high risk of developing cycle irregularities.

The exact mechanism by which COVID-19 vaccines cause cycle irregularities is unknown. However, vaccine-induced immune-mediated thrombocytopenia,[41] loss of endometrial hemostasis,[42] and

endocrine alterations[26] have been linked to cycle irregularities among vaccine recipients. Notably, these mechanisms are merely speculations based on the data of other vaccines, such as diphtheria-tetanus-acellular pertussis-acellular pertussis (DTaP), varicella, hepatitis A and B, measles-mumps-rubella (MMR), and even influenza, being previously linked to vaccine-induced thrombocytopenia leading to menstrual irregularities.[43] However, it is important to note that cycle irregularities after the COVID-19 vaccines can be associated with other predisposing factors such as age-related changes in menstruation, pre-menopause, PCOS, uterine polyps or fibroids, use of steroids and oral contraceptive pills, history of previous cycle irregularities and hormonal imbalances.[44-46] Psychological issues associated with the pandemic[47] and a history of COVID-19 infection[48] may also contribute to the menstrual cycle irregularities. Several co-variables must be considered to elucidate the precise mechanisms underlying vaccine-induced menstrual cycle irregularities. Moreover, observational and cross-sectional studies cannot establish a causal relationship between vaccine-related variables and the occurrence of cycle irregularities. Future research with a case-control design should consider these variables in order to establish a definitive connection between COVID-19 vaccines and menstrual problems. In addition, longitudinal studies will determine the long-term consequences of menstrual problems.

Study Limitations

This study's findings should be interpreted with few limitations. First, as a cross-sectional and self-reported study, it is possible that the results were affected by the participants' preconceived notions and misconceptions regarding vaccines. Second, the recall and selection biases can be disregarded in this study. Third, convenient sampling and greater participation from Saudi Arabia's capital city may limit the findings' applicability to the entire population. Fourth, we did not collect data on several crucial variables that may be associated with menstrual cycle problems, such as a history of cycle irregularities and COVID-19 infection. Fifth, this study did not evaluate the frequency, duration, or onset of cycle irregularities. Sixth, the participants may report menstrual problems that occurred after the first dose as occurring after the second and booster dose, leading to an overestimation of the prevalence of cycle irregularities after the second and booster dose. Seventh, this study lacks clinical diagnosis; as a result, cycle irregularities reported in this study should be regarded as suspected rather than confirmed. This study may not include women who do not use social media applications due to its web-based data collection methodology. Despite these limitations, the large analysis revealed important information regarding menstrual cycle problems and their risk factors among Saudi women who have received primary and booster doses of the COVID-19 vaccine.

CONCLUSION

This study proves that females subjected to primary and booster doses of COVID-19 vaccines may experience cycle irregularities. The most common menstrual cycle problems experienced by the study population included but were not limited to delayed menses, less bleeding, and too much bleeding. Age, presence of comorbidities, and active smoking were associated with the higher odds of cycle irregularities. To continue vaccination campaigns until the official end of the pandemic is declared, healthcare professionals and authorities must address the concerns of women of reproductive age regarding the relationship between COVID-19 vaccines and menstrual problems. In addition, future research should concentrate on the mechanism of vaccine-induced menstrual changes and the long-term outcomes on affected females.

Financial support and sponsorship
Nil

Conflict of Interest
The authors declare that there is no conflict of interest relevant to this article.

REFERENCES

1. Khan YH, Mallhi TH, Alotaibi NH, et al. Threat of COVID-19 Vaccine Hesitancy in Pakistan: The Need for Measures to Neutralize Misleading Narratives. *Am J Trop Med Hyg*. 2020;103(2):603-604.
2. Mallhi TH, Liaqat A, Abid A, et al. Multilevel Engagements of Pharmacists During the COVID-19 Pandemic: The Way Forward. *Front Public Health*. 2020;8:561924.
3. Salman M, Mustafa ZU, Raza MH, et al. Psychological Effects of COVID-19 Among Health Care Workers, and How They Are Coping: A Web-Based, Cross-Sectional Study During the First Wave of COVID-19 in Pakistan. *Disaster Med Public Health Prep*. 2022;17:e104.
4. Balbi C, Musone R, Menditto A, et al. Influence of menstrual factors and dietary habits on menstrual pain in adolescence age. *Eur J Obstet Gynecol Reprod Biol*. 2000;91(2):143-148.
5. Bruinvels G, Blagrove RC, Goldsmith E, Shaw L, Martin D, Piasecki J. How Lifestyle Changes during the COVID-19 Global Pandemic Affected the Pattern and Symptoms of the Menstrual Cycle. *Int J Environ Res Public Health*. 2022;19(20):13622.
6. Bok K, Sitar S, Graham BS, Mascola JR. Accelerated COVID-19 vaccine development: milestones, lessons, and prospects. *Immunity*. 2021;54(8):1636-1651.
7. Conte C, Sogni F, Affanni P, Veronesi L, Argentiero A, Esposito S. Vaccines against Coronaviruses: The State of the Art. *Vaccines (Basel)*. 2020;8(2):309.
8. Control, C.f.D. and Prevention, V-safe after vaccination health checker. Centers for Disease Control and Prevention. Retrieved November, 2021.
9. Barda N, Dagan N, Ben-Shlomo Y, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. *N Engl J Med*. 2021;385(12):1078-1090.
10. Locht C. Vaccines against COVID-19. *Anaesth Crit Care Pain Med*. 2020;39(6):703-705.
11. Shimabukuro TT, Cole M, Su JR. Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US-December 14, 2020-January 18, 2021. *JAMA*. 2021;325(11):1101-1102.
12. Heath PT, Galiza EP, Baxter DN, et al. Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine. *N Engl J Med*. 2021;385(13):1172-1183.
13. Alghamdi AN, Alotaibi MI, Alqahtani AS, Al Aboud D, Abdel-Moneim AS. BNT162b2 and ChAdOx1 SARS-CoV-2 Post-vaccination Side-Effects Among Saudi Vaccinees. *Front Med (Lausanne)*. 2021;8:760047.
14. Rostami Dovom M, Ramezani Tehrani F, Djalalinia S, Cheraghi L, Behboudi Gandavani S, Azizi F. Menstrual Cycle Irregularity and Metabolic Disorders: A Population-Based Prospective Study. *PLoS One*. 2016;11(12):e0168402.
15. Wang YX, Arvizu M, Rich-Edwards JW, et al. Menstrual cycle regularity and length across the reproductive lifespan and risk of premature mortality: prospective cohort study. *BMJ*. 2020;371:m3464.
16. American Academy of Pediatrics Committee on Adolescence; American College of Obstetricians and Gynecologists Committee on Adolescent Health Care, Diaz A, Laufer MR, Breech LL. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. *Pediatrics*. 2006;118(5):2245-2250.

17. El-Shitany NA, Harakeh S, Badr-Eldin SM, et al. Minor to Moderate Side Effects of Pfizer-BioNTech COVID-19 Vaccine Among Saudi Residents: A Retrospective Cross-Sectional Study. *Int J Gen Med*. 2021;14:1389-1401.
18. Ergün N, SAKIZ H, COVID-19 Sürecinde Önleyici Davranışlar ile Yaşam Kalitesi Arasındaki İlişkinin İncelenmesi. Anemon Muş Alparslan Üniversitesi Sosyal Bilimler Dergisi. 2021;9(6):1679-1697.
19. Trogstad L, Juvet L, Feiring B, Blix K. Covid-19 vaccines and menstrual changes. *BMJ Med*. 2022;1(1):e000357.
20. Laganà AS, Veronesi G, Ghezzi F, et al. Evaluation of menstrual irregularities after COVID-19 vaccination: Results of the MECOVAC survey. *Open Med (Wars)*. 2022;17(1):475-484.
21. Sharp GC, Fraser A, Sawyer G, et al. The COVID-19 pandemic and the menstrual cycle: research gaps and opportunities. *Int J Epidemiol*. 2022;51(3):691-700.
22. Sullivan KM, Dean A, Soe MM. OpenEpi: a web-based epidemiologic and statistical calculator for public health. *Public Health Rep*. 2009;124(3):471-474.
23. Alahmadi AM, Aljohani AH, Fadhloun RA, Almohammadi AS, Alharbi DF, Alrefai LS. The Effect of the COVID-19 Vaccine on the Menstrual Cycle Among Reproductive-Aged Females in Saudi Arabia. *Cureus*. 2022;14(12):e32473.
24. Dar-Odeh N, Abu-Hammad O, Qasem F, et al. Long-term adverse events of three COVID-19 vaccines as reported by vaccinated physicians and dentists, a study from Jordan and Saudi Arabia. *Hum Vaccin Immunother*. 2022;18(1):2039017.
25. Qashqari FSI, Dahlawi M, Assaggaf HM, et al. Effect of the COVID-19 Vaccine on the Menstrual Cycle among Females in Saudi Arabia. *Ethiop J Health Sci*. 2022;32(6):1083-1092.
26. Trogstad L, Increased occurrence of menstrual disturbances in 18-to 30-year-old women after COVID-19 vaccination. Available at SSRN 3998180, 2022.
27. Coronavirus vaccine - summary of Yellow Card reporting. 2023 [cited 2023 March 29]; Available from: https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting.
28. Alghamdi AN, Alotaibi MI, Alqahtani AS, Al Aboud D, Abdel-Moneim AS. BNT162b2 and ChAdOx1 SARS-CoV-2 Post-vaccination Side-Effects Among Saudi Vaccinees. *Front Med (Lausanne)*. 2021;8:760047.
29. Morsi A, Mersal E, Hassanein A, Alshammri A, Alkahmous N, Alhuwayji F, Elfawal R, The Association Between COVID-19 Pfizer Vaccine and The Reported Post-Vaccination Menstrual Changesi Citizen and Resident Women in KSA: Results of Riyadh Survey Study. The Egyptian Journal of Hospital Medicine.2022.;87(1):1442-1448.
30. Nazir M, Asghar S, Rathore MA, et al. Menstrual abnormalities after COVID-19 vaccines: A systematic review. *Vacunas*. 2022;23:S77-S87.
31. Chao MJ, Menon C, Elgendi M. Effect of COVID-19 vaccination on the menstrual cycle [published correction appears in Front Med (Lausanne). 2023 Mar 02;10:1170876]. *Front Med (Lausanne)*. 2022;9:1065421.
32. Al Kadri HM, Al Sudairy AA, Alangari AS, Al Khateeb BF, El-Metwally AA. COVID-19 vaccination and menstrual disorders among women: Findings from a meta-analysis study. *J Infect Public Health*. 2023;16(5):697-704.
33. Alvergne A, Woon EV, Male V. Effect of COVID-19 vaccination on the timing and flow of menstrual periods in two cohorts. *Front Reprod Health*. 2022;4:952976.
34. Edelman A, Boniface ER, Benhar E, et al. Association Between Menstrual Cycle Length and Coronavirus Disease 2019 (COVID-19) Vaccination: A U.S. Cohort. *Obstet Gynecol*. 2022;139(4):481-489.
35. Zhang B, Yu X, Liu J, Liu J, Liu P. COVID-19 vaccine and menstrual conditions in female: data analysis of the Vaccine Adverse Event Reporting System (VAERS). *BMC Womens Health*. 2022;22(1):403.

36. Alvergne A, Kountourides G, Argentieri MA, et al. *COVID*-19 vaccination and menstrual cycle changes: A United Kingdom (UK) retrospective case-control study. MedRXiv.2021;2021-11.
37. Alvergne A, Kountourides G, Argentieri MA, et al. A retrospective case-control study on menstrual cycle changes following COVID-19 vaccination and disease. *iScience*. 2023;26(4):106401.
38. Sakai H, Ohashi K. Association of menstrual phase with smoking behavior, mood and menstrual phase-associated symptoms among young Japanese women smokers. *BMC Womens Health*. 2013;13:10.
39. Cheng Y, Li T, Zheng Y, et al. Self-Reported adverse events among Chinese healthcare workers immunized with COVID-19 vaccines composed of inactivated SARS-CoV-2. *Hum Vaccin Immunother*. 2022;18(5):2064134.
40. Muhaidat N, Alshrouf MA, Azzam MI, Karam AM, Al-Nazer MW, Al-Ani A. Menstrual Symptoms After COVID-19 Vaccine: A Cross-Sectional Investigation in the MENA Region. *Int J Womens Health*. 2022;14:395-404.
41. Hunter PR, Thrombosis after covid-19 vaccination. 2021, British Medical Journal Publishing Group.
42. Speiser DE, Bachmann MF. COVID-19: Mechanisms of Vaccination and Immunity. *Vaccines (Basel)*. 2020;8(3):404.
43. Perricone C, Ceccarelli F, Nesher G, et al. Immune thrombocytopenic purpura (ITP) associated with vaccinations: a review of reported cases. *Immunol Res*. 2014;60(2-3):226-235.
44. Kurdoğlu Z, Do the COVID-19 vaccines cause menstrual irregularities. Int J Womens Health Reprod Sci. 2021;9(3):158-159.
45. Demir O, Sal H, Comba C. Triangle of COVID, anxiety and menstrual cycle. *J Obstet Gynaecol*. 2021;41(8):1257-1261.
46. Foster C, Al-Zubeidi H. Menstrual Irregularities. *Pediatr Ann*. 2018;47(1):e23-e28.
47. Maurya P, Meher T, Muhammad T. Relationship between depressive symptoms and self-reported menstrual irregularities during adolescence: evidence from UDAYA, 2016. *BMC Public Health*. 2022;22(1):758.
48. Lebar V, Laganà AS, Chiantera V, Kunič T, Lukanović D. The Effect of COVID-19 on the Menstrual Cycle: A Systematic Review. *J Clin Med*. 2022;11(13):3800.