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COVID-19 vaccinations and menstrual cycle changes in Egyptian females

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***Abstract*---**Background: To date, a number of clinical studies have investigated the impact of different COVID-19 vaccines on menses, while the results have been varied and inconsistent. Bearing in mind the strong relationship between regular normal menses and the general health of females, it is judicious to accomplish menstrual health research in the context of the COVID-19 pandemic and vaccination. Objective: To determine if there are any possible menstrual irregularities following the first and second doses (at least) of the COVID-19 vaccine and correlate it to the type of vaccine administered, and evaluate how long these effects will last. Subjects and methods: This study was a prospective observational study that included 347 questionnaires fulfilled by females who attended to receive COVID-19 vaccine at Menoufia University and Behera health directorate during the period of study from January 2022 till February 2023. Data were collected in two parts from cases who received any past doses; first part is past history about the

previous doses, then prospective follow up for 3 months after the current second or booster dose. Results: Among a total of 347 adult females who received one or more COVID-19 vaccine doses, 44.96% developed at least one menstrual change after any COVID vaccination dose. Regarding the menstrual cycle changes among the vaccinated women, pain was the most commonly reported symptom in 21.3% of participants. 16.7% of women after receiving the 1st dose, 15.3% of women after receiving both 1st and 2nd doses reported menstrual irregularities. Menstrual changes emerged in 56.4% directly post vaccination and 33.3% of cases that developed post-COVID-19 menstrual changes showed symptoms for one cycle only, 10.3% for 2 to 3 months. The most commonly used vaccines in the present study were Sinopharm or Sinovac (43.7%) followed by Pfizer vaccine (27.6%), AstraZeneca (14.4%), Moderna (7.5%), and Johnson and Johnson (6.9%). Conclusion: Menstrual changes were mild and transients and mostly didn't affect the quality of life of the vaccinated females.

***Keywords*---**COVID-19, Menstrual Cycle, COVID-19 vaccines.

Introduction

Since the launch of the coronavirus disease 2019 (COVID-19) in December 2019, it has disturbed almost every aspect of lives worldwide with not only remarkable morbidity and mortality, but also crucial social, educational as well as economic challenges [1].

Throughout history, vaccination performed as the most worthwhile way to shield against spreading of notable infectious diseases and was the major way to produce immunity for the whole community [2].

A multitude of vaccine platforms against COVID-19 have been manufactured worldwide and can be alienated into 3 main categories. The first group comprises mRNA-based vaccines, i.e. Pfizer-BioNTech and Moderna. The second one is inactivated whole virus vaccines like Sinopharm/BIBP-CorV and Sinovac Biotec. In addition, the third group represents the recombinant adenoviral vector vaccines (as Janssen; Johnson & Johnson and Oxford-AstraZeneca) [3].

By January 2021, Egypt initiated COVID-19 vaccination tracking the worldwide policy to prioritize geriatric people next to healthcare personnel. Afterward, the vaccine became accessible for the entire citizens for free [4].

There is no doubt that the menstruation pattern is a fundamental sign of reproductive wellbeing. Alteration of a woman's normal menstrual cycle causing menstrual disorders, as painful menstrual cramps, peri-menstrual mood disorders, and heavy menstrual bleeding, represents familiar gynecological complains [5].

There's a consensus that aberrant menstrual cycles has been concomitant with hazardous ailments such as increased risk of breast and ovarian cancers, subfertility, premature menopause, cardiovascular disease, chronic renal failure, and diabetes mellitus. Moreover, it may have a noteworthy impact on the female quality of life [6].

COVID-19 vaccination is broadly deemed as safe, and there is no proof that it has an influence on fertility in the analysis of laboratory models, clinical trials, or observational analyses [7].

The UK's Medicines and Healthcare Products Regulatory Agency (MHRA) and incorporate fever, sore arm, fatigue, and myalgia listed common COVID-19 vaccination side effects. But, the list didn't include period's changes and unpredicted vaginal bleeding is not listed also. Despite that, primary care or reproductive health clinicians had reported that some females have complained from these menstrual events shortly after vaccination [8].

There were around 50 000 reports by September 2021 about occurrence of menstrual cycle deviations that were reported to the MHRA, even though, none was proven to be due to vaccine effect [5]. Since that, there has been public concern about the possible causal relationship between COVID-19 vaccination and changes in menstrual cycles [9].

COVID-19 vaccines on menses, while the results have been varied and inconsistent. Bearing in mind the strong relationship between regular normal menses and the general health of females, it is judicious to accomplish menstrual health research in the context of the COVID-19 pandemic and vaccination. Therefore, this study aimed to determine if there are any possible menstrual irregularities following the first and second doses (at least) of the COVID-19 vaccine and correlate it to the type of vaccine administered, and evaluate how long these effects will last.

Subjects and Methods

This study was a prospective observational study of menstrual cycle. 400 females were recruited to the current study and 53 females of them were dropped out. So, data were collected from 347 filled questionnaires from females who attended to receive Covid-19 vaccine at Menoufia University and Behera health directorate and the data were collected during the period of study from January 2022 till February 2023. 53 females of them were dropped out through the study and 347 females completed the study. Data were collected prospectively from cases who came to receive the first dose by follow up for 3 months after the first dose then 3 more months after the second dose. Data were collected in two parts from cases who received any past doses; first part is past history about the previous doses, then prospective follow up for 3 months after the current second or booster dose

Sample size justification:

Based on review of past literature [10] who found that menstrual disturbances were generally common after receiving COVID-19 vaccines regardless the

vaccination type or dose and they reported that there was a significant increase in menstrual disturbances after vaccination, particularly heavier bleeding than usual, longer menses duration and short interval between menstruations .The risk of heavy bleeding following the second dose was 65.7%. The least sample size was calculated using Statistics and Sample size pro program version 6 and it was 347 participants. The power of study was 80% and confidence level was 95%.

Study participants:

Females aged ≥ 18 & < 45 years old with body mass index (BMI) < 35 kg/m2, regular cycles, normal pre-vaccination menstrual cycle lengths (average 21–35 days) duration (2-7 days) and amount (≦ 80 ml. average 8 full napkins per cycle {1 napkins = 10cc blood}) who came to administer any type of COVID-19 vaccine were included in our survey.

Excluded cases from the study were those who were less than 18 years old or ≥ 45 years old, menopause, peri-menopausal or with body mass index ≥ 35 kg/m^2. Also cases who gave history to irregular menstrual cycles or abnormal uterine bleeding were excluded. It was the same regarding to women who were taking any hormonal contraceptive methods or IUCDs. In addition, pregnant & lactating women at vaccination time were also excluded from this study.

Methodology

Approval of ethical committee was obtained from quality education assurance unit, Menoufia university faculty of medicine, Egypt. Informed consent was taken from all participants before participation in this study. The nature and aim of this work were fully discussed to all women who agreed to participate in the study. The elected participants were subjected to thorough history taking complete general and abdominal examination.

The study used a questionnaire that was developed in English and then translated into Arabic to ensure comprehensibility and content validity by translating expert. The questionnaire consisted of 27 detailed self-report questions covering five integral domains: The first section included sector to complete demographic data including name, age, residence, phone number & marital status (5 questions).The second section contained questions about previous COVID-19 infection, the severity of the symptoms of the infection and any occurrence menstrual abnormalities during the COVID-19 infection (3 questions). The third category inquired about the type of vaccine received, the number of doses, and occurrence of any COVID-19 vaccination side effects (3 questions). The fourth category encompassed questions about menstrual abnormalities after vaccination, the duration of symptoms, their relationship to the dose, and their impact on life (6 questions). The fifth category consisted of an open-ended question about the change in the menstrual cycle between baseline and following vaccination (10 questions).

Study Outcomes

The primary outcome of this study was the relation between COVID-19 vaccine administration, type and doses with the occurrence, type and duration of menstrual changes.

Statistical analysis

Statistical analyses of data were carried out by means of SPSS version 23. Shapiro –Wilks test was utilized to assess normal distribution of variables. Numerical data were expressed as mean ± standard deviation or median and range. Categorical data were summarized as percentages. The significance for the difference between groups was determined by using two-tailed Student's t test. Also, Qualitative variables were assessed via chi-squared x^2test. The probability (P) values of ≤0.05 were reflected as being statistically significant.

Results

Among total of 347 adult females who received one or more COVID-19 vaccine doses, 44.96% developed at least one menstrual change after any COVID vaccination dose (Figure 1).

Regarding the menstrual cycle changes among the vaccinated women, Pain was the most commonly reported symptom in 74 (21.3%) of participants. Almost 10.1% of the participants complained of inter-menstrual bleeding and the same percentage of them (10.1%) experienced increase of menstrual amount (Table 1). 9.8% of the whole cases were suffering from longer cycle than usual, while the amount of menstrual bleeding decreased in 31 (8.9%) cases. 8.6% of cases were suffering from shorter cycle than usual.

Menstrual irregularities were reported by 16.7% of women after receiving the 1st dose, 15.3% of women after receiving both 1st and 2nd doses, 5.5% of women after receiving the 2nd dose only, 3.5% of women after receiving all 3 doses, 2.3% of women after receiving both 2nd and 3rd dose, 1.2% of women after receiving the 3rd dose only, and 0.6% of women after receiving both 1st and 3rd doses (Figure 2).

Moreover, it was detected that 88 out of 156 (56.4%) of cases who developed menstrual changes post-COVID-19 vaccination showed symptoms directly post vaccination. A further 33.3% developed symptoms in less than 1 month following vaccination.1.3% of cases developed symptoms 1-2 month following vaccination. The remaining 9% of cases developed symptoms after > 2 month following vaccination.

Also, 96 out of 156 (61.5%) of cases who developed menstrual changes post-COVID-19 vaccination showed symptoms for one cycle only, 34.6% (n=54) for 2 to 3 month, and the remaining 6 cases (3.9%) of cases developed symptoms for more than 3 month following vaccination (Table 1).

About 42.9% of the participants with post-COVID-19 vaccination menstrual changes were worried regarding long-term and persistent effects, while other 42.9

% not worried and considered these changes temporary and the remaining 14.1% didn't care and asking about these symptoms only raised their attention about those changes (Table 1).

The most commonly used vaccines in the present study were Sinopharm or Sinovac (43.7%) followed by Pfizer vaccine (27.6%), AstraZeneca (14.4%), Moderna (7.5%), and Johnson and Johnson (6.9%). Out of the studied women, 52 (14.9%) took only one dose, 228 (65.5%) had received two vaccination doses. Moreover, 68 women (19.5%) had received three vaccination doses (Table 2).

The main reported general side effects post COVID-19 vaccination were fever, fatigue, headache, nausea, arm ache. Among the vaccinated women, 136 women (39.2%) reported mild side effects, 6.1% (n=21) reported moderate side effects, and the others 54.8% (n=190) reported no side effects (Table 2).

Table (1): Menstrual cycle changes after COVID-19 vaccination

Type of menstrual cycle changes	All participants N=347	Post-COVID-19 vaccination menstrual changes		Test	P-Value
		No (N = 191)	Yes (N=156)		
Type of menstrual cycle changes					
No change	191(55%)	191(100%)	0(0%)	x^2=115.16	<0.001
More pain	74(21.3%)	0 (0%)	74(47.4%)	x^2=347.000	<0.001
Decrease of menstrual length	30(8.6%)	0 (0%)	30(19.2%)	x^2=115.162	<0.001
Increase of menstrual length	34(9.8%)	0 (0%)	34(21.8%)	x^2=40.207	<0.001
Decrease of menstrual amount	31 (8.9%)	0 (0%)	31(19.9%)	x^2=46.150	<0.001
Increase of menstrual amount	35(10.1%)	0 (0%)	35(22.4%)	x^2=41.679	<0.001
Intermenstrual bleeding	35(10.1%)	0 (0%)	35(22.4%)	x^2=47.660	<0.001
Onset of symptoms following the vaccination					
No time **Less than 1 month** **1-2 months** **> 2 months**	279(80.4%) 52(15%) 2(0.6%) 14(4%)	191(100%) 0(0%) 0(0%) 0(0%)	88(56.4%) 52(33.3%) 2(1.3%) 14(9%)	Fisher's exact=120.928	<0.001
Duration of symptoms following the vaccination					
No **One month** **2-3 months** **> 3 months**	191(55%) 96(27.7%) 54(15.7%) 6(1.7%)	191(100%) 0(0%) 0(0%) 0(0%)	0(0%) 96 (61.5%) 54(34.6%) 16(3.9%)	Fisher's exact=120.928	<0.001
Participants' feelings regarding post-COVID-19 vaccination menstrual irregularities					
• **No** • **Not worried as the changes are temporary** • **Afraid of long term, persistent effects** • **Don't care**	191 (55%) 67(19.3%) 67(19.3%) 22(6.3%)	91(100%) 0(0%) 0(0%) 0(0%)	0 (0%) 67(42.9%) 67(42.9%) 22(14.1%)	Fisher's exact=347.0	<0.001

Regarding cases who received Sinopharm or Sinovac, the most frequent menstrual side effect was menstruation- associated pain that was reported by 23.68% of cases who received that vaccine. This was the case in Pfizer Vaccine as

pain was reported by 22.9% of cases who received that vaccine. In case of AstraZeneca vaccine, pain, increase of menstrual amount, intermenstrual bleeding were all the most frequently reported effects by 16%. Pain, decrease of menstrual length & intermenstrual bleeding were all the most repeatedly reported by 11.5% who received Moderna vaccine. In addition, the most frequent menstrual complain after Johnson and Johnson vaccine were pain and intermenstrual bleeding that were equally reported by 20.8% of cases (Table 3).

The mean age of the participants was 29.67±6.27 years. It was 30.07±6.61 years among cases that developed menstrual cycle changes post-COVID-19 vaccination compared to 29.35±5.98 years in Group 2 with no statistically significant difference detected among both studied groups (P=0.285). Most cases in both group belonged to the age range 25-34 years (55.6% of the cases).

The percentages of women lived in rural areas and those lived in urban areas were 51%, and 49% respectively (P=0.758) (Table 4). Approximately half of cases (47.3%) in the present study were married. The current study showed no statistically significant difference between both studied groups regarding marital status (P=0.758).

Also, classification of participants by BMI is illustrated at table (4). In the current study, there was no statistically significant difference between cases who developed menstrual changes post-COVID-19 vaccination and those who didn't develop menstrual cycle changes regarding BMI (kg/m2) (P=0.790), as the mean BMI was 23.58±3.5 kg/m^2 in the first group compared to 23.68±3.32 kg/m^2 in the second one.

Regarding past COVID infection prior vaccination, our results revealed that 235 women (67.7%) were previously infected with COVID-19 while the remaining percentage (32.3%) reported that they never infected with the novel virus, the majority of the infected cases had mild infection (61.7%), 82 out of 235 infected cases (34.9%) had moderate infection while 2.1% had severe infection. Additionally, 1.3% of infected cases admitted to critical care after infection (Table 4).

Regarding relation between previous self- reported COVID 19 infection severity and types and severity of Post-COVID-19 vaccination menstrual changes, our results revealed that most cases that either hadn't or presented with different COVID infection severity had no menstrual changes. Yet, menstrual pain was the most common menstrual change as it was presented in 26(23.2%), 28(19.3%), 13(15.9%), 5(100%),& 2(66.7%) who either hadn't or presented with mild, moderate, severe & also cases whose condition necessitated admission to critical care COVID-19 infection respectively (Table 5).

Table (2): Vaccination status of the participants

Vaccine Type	All participants N=347	Post-COVID-19 vaccination menstrual changes		Test	P-Value
		No (N = 191)	Yes (N=156)		
Type of vaccine					
• Sinopharm or Sinovac	152(43.7%)	84(43.8%	68(43.6%)	x^2 7.747	0.101
• Pfizer	96(27.6%)	55(28.6%)	41(26.3%)		
• AstraZeneca	50(14.4%)	31(16.1%)	19(12.2%)		
• Moderna	26 (7.5%)	15(7.8%)	11(7.1%)		
• Johnson and Johnson (single dose vaccine)	24(6.9%)	7(3.6%)	17 (10.9%)		
Number of vaccine doses					
Dose 1 Dose 2 Dose 3	52(14.9%) 228(65.5%) 68(19.5%)	26(13.5%) 126(65.6%) 40(20.8%)	26(16.7%) 102(65.4%) 28(17.9%)	x2 0.930	0.628
Type & Severity of side effects of the vaccine					
Type of side effects: • Headache • Fatigue • Pain at the site of injection • Nausea • Fever	 133(38.2%) 129(37.2%) 76(21.9%) 37 (10.7%) 33(9.5%)	 45(23.6%) 71(37.2%) 43 (22.5%) 15(7.8%) 17(8.9%)	 88(56.4%) 58(37.2%) 33(21.1%) 22(14.1%) 16 (10.2%)	x2==7.747	0.101
Severity of side effects: • No • Mild • Moderate	 190(54.8%) 136(39.2%) 21(6.1%)	 97(50.8%) 83(43.5%) 11(5.8%)	 93(59.6%) 53(34%) 10(6.4%)	x2=3.252	0.197

Table (3): Menstrual Side Effects Reported From Each Received Vaccine

Vaccine type	Menstrual Side Effects		P-Value
	No	Yes	
Sinopharm /Sinovac vaccine (n=152):			
• No side effects at all	68(44.74%)	84(55.26%)	
• More pain	116(76.32%)	36(23.68%)	
• Decrease of menstrual length	138(90.8%)	14(9.2%)	
• Increase of menstrual length	139(91.4%)	13(8.6%)	
• Decrease of menstrual amount	136(89.47%)	16 (10.53%)	<0.001
• Increase of menstrual amount	145(95.4%)	7(4.6%)	
• Intermenstrual bleeding	142(93.42%)	10(6.58%)	
Pfizer Vaccine (n=96):			
• No side effects at all	41(42.7%)	55(57.3%)	
• More pain	74(77.1%)	22(22.9%)	
• Decrease of menstrual length	89(92.7%)	7(7.3%)	
• Increase of menstrual length	84(87.5%)	12(12.5%)	
• Decrease of menstrual amount	85(88.5%)	11 (11.5%)	<0.001
• Increase of menstrual amount	80(83.3%)	16(16.7%)	
• Intermenstrual bleeding	87(90.6%)	9(9.4%)	
AstraZeneca vaccine (n=50):			
• No side effects at all	19(38%)	31 (62%)	
• More pain	42(84%)	8(16%)	
• Decrease of menstrual length	46(92%)	4(8%)	
• Increase of menstrual length	47(94%)	3(6%)	<0.001
• Decrease of menstrual amount	48(96%)	2 (4%)	
• Increase of menstrual amount	42(84%)	8(16%)	
• Intermenstrual bleeding	42(84%)	8(16%)	
Moderna vaccine (n=26):			
• No side effects at all	11(42.3%)	15(57.7%)	
• More pain	23(88.5%)	3 (11.5%)	
• Decrease of menstrual length	24(92.3%)	2(7.7%)	
• Increase of menstrual length	23(88.5%)	3(11.5%)	<0.001
• Decrease of menstrual amount	25(96.2%)	1(3.8%)	
• Increase of menstrual amount	25(96.2%)	1(3.8%)	
• Intermenstrual bleeding	23(88.5%)	3(11.5%)	
Johnson and Johnson vaccine (n=24):			
• No side effects at all	17(70.8%)	7(29.2%)	
• More pain	19(79.6%)	5(20. 8%)	
• Decrease of menstrual length	21(87.5%)	3(12.5%)	
• Increase of menstrual length	21(87.5%)	3(12.5%)	<0.101
• Decrease of menstrual amount	23(95.8%)	1 (4.2%)	
• Increase of menstrual amount	21(87.5%)	3(12.5%)	
• Intermenstrual bleeding	19(79.6%	5(20. 8%)	

Table (4): Demographic data and prior COVID-19 infection history among COVID-19 vaccinated participants

	All participants N=347	Post-COVID-19 vaccination menstrual changes		Test	P-Value	S
		No (N =191)	Yes (N=156)			
Demographic Data						
Age (years)	29.67±6.27	29.35±5.98	30.07±6.61	t = -1.071	0.285	NS
18-24 years	67(19.3%)	36(18.8%)	31(19.9%)			
25-34 years	193(55.6%)	111(58.1%)	82(52.6%)	Fisher's exact=2.280	0.516	
35-44 years	83(23.9%)	43(22.5%)	40(25.6%)			
Residence						
Rural	177(51%)	96(50.3%)	81(51.9%)	x^2=0.095	0.758	NS
Urban	170(49%)	95(49.7%)	75(48.1%)			
Marital status						
Single	143(41.2%)	80(41.9%)	63(40.4%)	Fisher's exact=1.147	0.785	NS
Married	164(47.3%)	92(48.2%)	72(46.2%)			
Divorced	30(8.6%)	14(7.3%)	16(10.3%)			
Widow	10(2.9%)	5(2.6%)	5(3.2%)			
BMI (kg/m^2)	23.63±3.39	23.68±3.32	23.58±3.5			
Underweight	18(5.2%)	7(3.7%)	11(7.1%)	t =0.266	0.790	NS
Normal	105(30.3%)	54(28.3%)	51(32.7%)			
Overweight	141(40.6%)	84(44%)	57(36.5%)	x^2=3.329	0.189	
Obese	83(23.8%)	46(24%)	37(23.7%)			
Previous COVID-19 Infection						
No	112(32.3%)	58(30.4%)	54(34.6%)	x^2=0.709	0.400	NS
Yes	235(67.7%)	133(69.6%)	102(65.4%)			
Severity of COVID-19 symptoms						
Mild	145(61.7%)	85(63.9%)	60(58.8%)	Fisher's exact=1.389	0.760	NS
Moderate	82(34.9%)	44(33.1%)	38(37.3%)			
Severe	5(2.1%)	2(1.5%)	3(2.9%)			
Admitted to critical care	3(1.3%)	2(1.5%)	1(1%)			

Table (5): Relationship between previous self- reported COVID 19 infection severity and types and severity of Post-COVID-19 vaccination menstrual changes

Previous self-reported COVID 19 infection					
Menstrual Side effects	**NO (N=112)**	**Mild Infection (N=145)**	**Moderate infection (N=82)**	**Severe Infection (N=5)**	**COVID 19 related Admitted to critical care (N=3)**
✦ **No change at all**	65(58%)	83(57.2%)	42(51.2%)	1(20%)	0(0%)
✦ **More pain**	26(23.2%)	28(19.3%)	13(15.9%)	5(100%)	2(66.7%)
✦ **Decrease menstrual length**	13(11.6%)	8(5.5%)	6(7.3%)	2(40%)	1(33.3%)
✦ **Increase menstrual length**	23(20.5%)	6(4.1%)	4(4.9%)	0(0%)	1(33.3%)
✦ **Decrease menstrual amount**	5(4.5%)	13(9%)	12(14.6%)	1(20%)	0(0%)
✦ **Increase menstrual amount**	9(8%)	16(11%)	6(7.3%)	2(40%)	2(66.7%)
✦ **Intermenstrual bleeding**	11(9.8%)	7(4.8%)	13(15.9%)	3(60%)	1(66.7%)

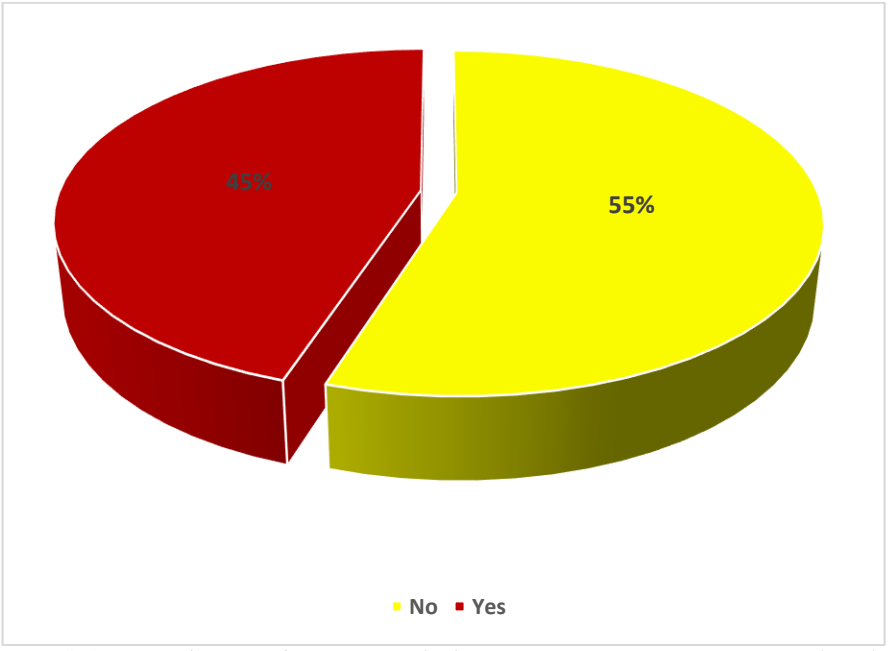

Figure (1): Prevalence of menstrual changes post-COVID-19 vaccination

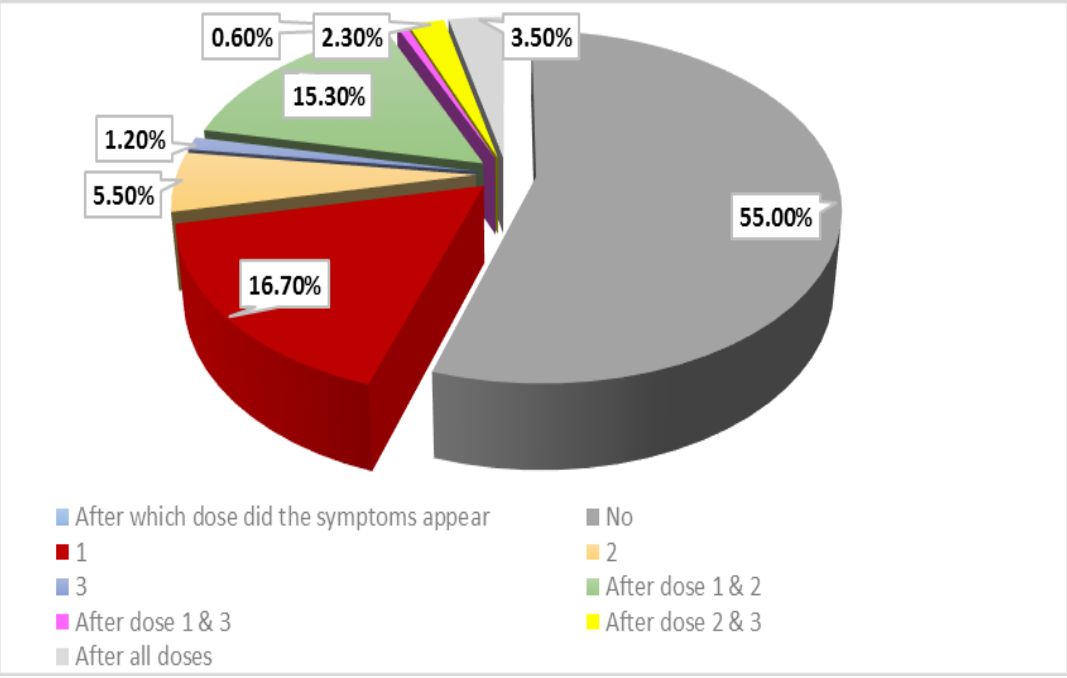

Figure (2): The relationship between doses received and menstrual irregularities appearance

Discussion

According to the prevalence of menstrual irregularities after COVID-19 vaccination in our research, 44.96% reported at least one menstrual change. *Alahmadi and his co-workers* [11] in Saudi Arabia in 2022 research reported a nearly similar percentage as menstrual cycle changes after one or both of the COVID-19 vaccines were observed among 46.7% of their participants.

A study conducted in the Middle East/North Africa (MENA) region among Palestine, Iraq, Lebanon, Al-Bahrain, Tunisia, Kuwait, Qatar, Turkey, Jordan, UAE, KSA, Egypt, Oman, Morocco, Sudan, and Syria on the effect of COVID-19 vaccine declared that 66.3% of females experienced menstrual aberrations after receiving COVID-19 vaccine [5].

We excluded any menstrual irregularity before vaccination to rule out any bias. However, menstrual irregularities were not excluded in other studies as *Muhaidat et al.,* [5] who reported that 24.9% of their participants had irregular menstrual cycles prior to vaccination.

Additional study conducted in Italy by *Laganà et al.,* [12] indicated that 50%–60% of contributors have given an account about occurrence of menstrual cycle irregularities next to receiving the first dose of COVID-19 vaccine. In a Norwegian cross-sectional survey; 39%–41% of women suffered some form of post-vaccination menstrual changes [10].

Regarding the menstrual cycle changes among the vaccinated women, pain was the most commonly reported symptom in 74 (21.3%) of participants. It was also the most frequently reported complain from every utilized vaccine separately. Almost 10.1% of the participants complained of inter-menstrual bleeding and the same percentage of them (10.1%) experienced increase of menstrual amount. 9.8% of the whole cases were suffering from longer cycle than usual, The amount of menstrual bleeding decreased in 31 (8.9%) cases, while 8.6% of them were suffering from shorter cycle than usual.

Muhaidat et al., [5] also reported that there was altered duration and length of the menstrual cycle was reported in vaccinated women, resulting in a significant difference between before and after vaccination. Although some participants in their study like ours reported a reduction in the duration of menstruation and length of menstrual cycle while others reported a prolongation. When they compared AstraZeneca, Sinopharm and Pfizer, differences in the incidence of menstrual abnormalities were statistically insignificant, 68.4%, 66.2%, 65.4%, respectively ($p > 0.05$).

Qashqari and his coworkers, [13] in a novel research in 2023 in Saudi Arabia, reported also that after receiving the first dose, cases' subsequent period was heavier than usual in 14.5% of their participants, later than usual in 27.7%, together with that the pain (cramps) were graver than usual in 26.5%. After the second dose, the next period was heavier than anticipated in 17.1%, later than routine in 24.7%, and cramps were worse in 26.8% signaling that menstrual troubles following vaccination considerably impacted the participating females' quality of life.

Alahmadi et al., [11] declared that changes in cycle length or duration, bleeding volume, or other cycle characteristics such as pain were the most common post-vaccination complaint, followed by heavier-than-usual cycles like our results. But, they found that Moderna is associated with the highest rate of menstrual cycle changes for the second dose with a statistically significant value. These differences could also be due to differences in the demographic profile or other characteristics of their recruited women.

In a study conducted by *Edelman et al. 2022* [14] in the U.S, correlation between COVID-19 vaccine and cycle length was found, but this change was for less than a day in cycle length for the two vaccine-dose cycles. They concluded that COVID-19 vaccination is related to a trivial change in cycle length not the duration of menses.

Consistent with our findings, *Khalil et al.,* [15] in Jordan also reported that other vaccination like human papillomavirus (HPV) vaccine has also been associated with menstrual changes. Undeniably, the menstrual cycle can be influenced by immune stimulation via various antigenic provocations rather than a specific vaccine component.

These menstrual deviations may be exemplified by that the vaccine may activate the immune system and the activated immune system might attack immune cells as well as inflammatory molecules in the uterus. To elucidate these postulates,

controlled studies are required [16]. Furthermore, some studies suggest that vaccination is less likely to disturb menstruation through ovarian hormone pathways, but more likely alongside the inflammatory pathways. Even now, the strict pathophysiological mechanisms are yet mysterious [17].

In our study, most menstrual irregularities appeared in 16.7% of women after receiving the 1st dose, 15.3% of women after receiving both 1st and 2nd dose, 5.5% of women after receiving the 2nd dose only. According to *Alahmadi et al.,* [11], both the first and second doses of the COVID-19 vaccine altered cycle length.

Moreover, post-COVID-19 menstrual changes emerged in most cases (56.4%) directly post vaccination. A further 33.3% developed symptoms in less than 1 month following vaccination. Also, 61.5% of cases who developed menstrual changes post-COVID-19 vaccination showed symptoms for one cycle only, 34.6% for 2 to 3 month. 42.9% of the participants with post-COVID-19 vaccination menstrual changes worried regarding long-term and persistent effects, while other 42.9 % not worried and considered these changes temporary and the remaining 14.1% didn't care and asking about these symptoms only raised their attention about those changes.

Muhaidat and his colleagues, [5] mentioned the same results; menstrual irregularities symptoms appeared after a week in 30.5%, and within a month in 86.8%. Furthermore, the majority (46.7%) of their participants had the symptoms after the first dose, while 32.4% after the second dose and 20.9% after both doses. Those symptoms were relieved in less than a month in 86.8% of their respondents. Lastly, 56.2% of their participants indicated that post-vaccine menstrual abnormalities had negatively impacted their quality of life.

In *Alahmadi et al.,* [11] study, 46.9% of participants experienced menstrual changes following one or both vaccines, a particularly high rate after the first dose of the COVID-19 vaccine. However, approximately 42.5% of menstrual changes in their sample were transient and disappeared within a month or less.

Further studies also informed analogous menstrual changes longer or shorter than usual cycles, heavier menses, unpredicted breakthrough bleeding in those using contraceptives, as well as dysmenorrhea. Those symptoms appeared more frequently following the second dose [10, 12, 19].

The most commonly used vaccines in the present study were Sinopharm or Sinovac (43.7%) followed by Pfizer vaccine (27.6%), AstraZeneca (14.4%), Moderna (7.5%), and Johnson and Johnson (6.9%). Out of the studied women, 52 (14.9%) took only one dose, 228 (65.5%) had received two vaccination doses. Moreover, 68 women (19.5%) had received three vaccination doses.

While the most common types of vaccine received in *Matar et al.,* [20] study in six Arab countries (Jordan, Syria, Palestine, Egypt, Libya and Sudan) were in order; Pfizer (27.2%), Sinopharm (24.7%) or Sinovac, and AstraZeneca (24.3%). *Muhaidat et al.,* [5] also reported that the majority of their participants received Pfizer-BioNTech, Sinopharm, and AstraZeneca (48.4%, 35.3%, and 13.4%, respectively), and the mainstream of their subjects (85.4%) received two doses.

Moreover, the most familiar vaccine used in *Khalil et al.,* [15] study was Pfizer followed by Astra Zeneca and Moderna. Jonson & Johnson was the least used vaccine. They also reported that almost all women had received the first vaccine dose, only one did not get vaccinated, 98% took the second dose and only 66% had received the third dose.

While in *Alahmadi et al.,* [11] study, Pfizer vaccine was the most commonly reported either for the first dose (75.8%) or second (74.3%), followed by Oxford-AstraZeneca (23% and 21.8% for the first and second dose, respectively) and the majority of their participants (76.5%) have received three vaccine doses against COVID-19.

What is supporting our finding about the higher reporting of using the Chinese vaccine is that there was discrepancy regarding the vaccine type distribution among countries even in Egypt the accessibility of diverse vaccine types varied along time and sectors all over the country. Moreover, people in Egypt preferred to use the whole killed vaccine due to the concept of lower adverse effects as mentioned in *Elareed et al.,* [21] in 2023 that collected data about the public opinion towards COVID-19 vaccination in Egypt and reported that 61.5% of their participants received the Chinese vaccine and the remaining 38.5% received AstraZeneca.

For patients received Sinopharm or Sinovac, the most frequent menstrual side effect was menstruation-associated pain that was reported by 23.68% of cases that received that vaccine. This was the case in Pfizer Vaccine as pain was reported by 22.9% of cases that received that vaccine. In case of AstraZeneca vaccine, pain, increase of menstrual amount, intermenstrual bleeding were all the most frequently reported effects by 16%. Pain, decrease of menstrual length and intermenstrual bleeding were all the most repeatedly reported by 11.5% who received Moderna vaccine. In addition, the most frequent menstrual complain after Johnson and Johnson vaccine were pain and intermenstrual bleeding that were equally reported by 20.8%of cases.

Matar et al., [20] delineated that vaccinated females with Moderna and Pfizer vaccines reported the highest mean pain score through menses than other vaccine types. Both vaccines also were allied to significantly higher number of bleeding days versus other vaccines. Higher percentage of menstrual irregularity was also reported in Johnson & Johnson, followed by Sinopharm, Moderna, and AstraZeneca ($p = 0.022$). Similarly, Johnson & Johnson was concomitant with a higher percentage of heavy bleeding then Pfizer, Sinopharm, AstraZeneca, and Moderna ($p = 0.003$). They explained that as mRNA vaccinations might instigate a robust immunological responsewhich can briefly interrupt the hypothalamic–pituitary-ovarian axis.

Menstrual changes have been recounted after getting nearly the entire vaccines brands or categories (either killed, mRNA or adenovirus-vectored), signifying that no special brand is clearly concomitant with menstrual changes. There is also some inter-individual variation in menstrual changes following COVID-19 vaccination that may be owed to individual or genetic factors that may influence the kind of variations that people experience [18].

Yet, *Morsi et al.,* [19] study in Saudi Arabia reported post-vaccination menstrual changes next to Pfizer vaccine only. As regard the main reported side effects post COVID-19 vaccination, they were fever, fatigue, headache, nausea, arm ache. Among the vaccinated women, 136 women (39.2%) reported mild side effects, 6.1% (n=21) reported moderate side effects, and the others 54.8% (n=190) reported no side effects, which was parallel to the FDA Fact Sheet for Recipients and Caregivers about the most common reported side effects.

Furthermore, our findings are consistent with other reports that were gathered from 152 locates worldwide (130 sites at USA, 1 at Argentina, 2 at Brazil, 4 at South Africa, 6 at Germany, and 9 at Turkey) and found that headaches were the furthermost familiar complaint subsequent to vaccination injection and that young persons were more probable to develop a fever following the second dose [22].

Muhaidat et al., [5] also reported that after receiving the COVID-19 vaccination, 78.3% reported side effects, including fever; fatigue, headache, nausea, and arm pain, which in 14.4% were described as severe. Whereas, *Elareed et al.,* [21] reported that approximately 69.7% of the vaccinated cases reported vaccine side effects with bony aches/fatigue represented the most common side effects in their study (86.7%) followed by severe pain in the site of injection (64.3%).

Similarly, injection site pain, headache, flu-like symptoms, fever, and fatigue were the most prevalent vaccination adverse effects reported by *Elgendy et al.,* [23] among Egyptian and Saudi Arabian citizens who were vaccinated with various COVID-19 vaccines.

There was no statistically significant difference in socio-demographic data, between cases who developed menstrual changes post-COVID-19 vaccination and those who didn't develop menstrual cycle changes according to age (P=0.285), BMI (P=0.791), residence (P=0.758) relationship status (P=0.785), with the mean age of our sample population was 29.67±6.27 years and the mean BMI was 23.63±3.39 kg/m^2. Most respondents were (47.3%) were married.

Nearer to our results, *Matar et al.,* [20] on studying the effect of COVID-19 vaccine on menstrual experience among females in six Arab countries reported a mean age 24.02±5.73 years of their sample and a mean BMI 23.56 ±4.79 kg/m^2. *Muhaidatet et al.,* [5] reported a mean age of cases was 34.32 (±8.53) years with 62.4% of their cases were married with no significant association between occurrence of menstrual irregularities between both groups and age and marital status, (p>0.05).

Alahmadi et al., [11] similar to our finding, reported that there was no statistically significant difference between cases who developed menstrual changes post-COVID-19 vaccination and those who didn't develop menstrual cycle changes according to BMI, residence (P=0.758), relationship status (P=0.785), however age was significantly different among both groups in their work as in the menstrual irregularity groups age was near the lower and higher age range.

Regarding past COVID infection prior vaccination our results revealed that 235 women (67.7%) were previously infected with Covid-19 with the majority of the infected cases had mild infection (61.7%).

Closer to our findings, *Matar et al.,* [20] in their large multi-nation research reported that merely 48.7% of their participants reported a COVID-19 infection history and virtually two thirds of them (72.6%) suffered from mild symptoms only. Also *Khalil et al.,* [12] study reported that roughly 40% of the participants had experienced COVID infection.

In contrary to our results, Alvergne *and his colleagues,* [9] in 2023 in the UK also reported that most of their COVID 19 vaccinated participants (76 %) didn't report any COVID 19 symptoms prior vaccination.

Regarding relation between previous self- reported COVID 19 infection severity and types and severity of Post-COVID-19 vaccination menstrual changes, our results revealed that menstrual pain was the most common menstrual change as it was presented in 26(23.2%), 28(19.3%), 13(15.9%), 5(100%),& 2(66.7%) who either hadn't or presented with mild, moderate , severe & also cases whose case necessitated admission to critical care COVID infection respectively.

The postulate that menstrual irregularities ensued thanks to COVID-19 pandemic stress rather than the vaccine itself also can be a point of doubt grounded on existing evidence. As, the unvaccinated group didn't complain from alterations in the menstrual cycle during the pandemic when they paralleled to the vaccinated counterparts. Nevertheless, the cumulative intense immune response after both SARS-COV-2 infection & the administration of COVID-19 vaccines can't be ruled out [3].

Literature also can't deny that prior severe COVID-19 infection gave rise to more frequent post-vaccination menstrual changes as well. These outcomes make allusion to a potential cumulative immune response owing to repeated antigen exposure along with the environmental factors by the pandemic itself, such as psychological distress and domestic workload [5, 9]. The findings of this study suggest that there is a possible link between menstrual cycle changes and receiving COVID-19 vaccine doses.

However, most literature in this point were in the form cross-sectional studies that were incapable of confirming causal relationship linking menstrual irregularities and COVID-19 vaccination due to lack of data from randomized-controlled clinical trials researching the COVID-19 vaccines effect on the menstrual cycle.

Conclusion

Approximately one half of the COVID19 vaccinated participants in our study developed at least one change in their menstrual pattern. Pain was the most commonly reported symptom followed by increase of menstrual amount and inter-menstrual bleeding and those changes were not varied according to the vaccine type in our study. Moreover, changes were mild and transients and mostly didn't

affect the quality of life of the vaccinated females. We were unable to report the relationship between menstrual irregularities and COVID-19 vaccination status due to the lack of data, but there is a possible link between menstrual changes before and after receiving COVID-19 vaccine doses.

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Conflict of interest: The authors declare that they have no conflicts of interest.

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