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Changes In the Menstrual Cycle Among the Covid-19 Vaccinated Women in The Eastern Province of Saudi Arabia: A Cross-Sectional Survey, 2022

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ABSTRACT

Background: There is growing concerns that COVID-19 vaccination causes disruption to menstrual cycle. The study has showed that several women required gynecological visits claiming menstrual irregularities or abnormal uterine bleeding after the first and second doses of vaccination (regardless of the type of vaccine used).

Objective: This study was conducted in the eastern province of Saudi Arabia to assess the effect of Covid-19 vaccination on the menstrual cycle of the women.

Material and methods: It was a cross-sectional prospective study that was conducted by survey the post Covid-19 vaccinated women in the eastern province of Saudi Arabia. The sample size was calculated using a Fisher's formula which was 344 women who have been vaccinated by Covid-19 vaccination.

Results: A total of 343 women participated in this study. The mean age of the participants was 30.16 ± 18.20 years. More than forty two percent of the participants had one time Covid-19 infection while 5% was twice infected with Covid-19 virus. The vast majority of the participants (91.3%) were immuned by 2 vaccines. More than sixty percent (60.3%) of the participants were suffering from one and other menstruation irregularities after Covid-19 vaccination. 14% of them were suffering from the menstruation frequency longer than 35 days while 10.2% of them were suffering from the menstruation frequency shorter than 25 days.

Conclusion: Coronavirus disease 2019 (COVID-19) vaccination is associated with change in menstrual cycle length, heavy menstruation and painful menstruation. Female with the age group of 15- 24 years were 2 times more likely to develop menstruation cycle change.

Keywords: Covid-19 infection, Covid-19 vaccination, Menstrual cycle.

INTRODUCTION

Coronavirus disease (COVID-19) an infectious disease caused by the SARS-CoV-2 virus, which emerged in Wuhan(China) and spread around the world as the epidemic of the century, has already infected more than 52 million people with more than 6 million deaths. More than 121 million people are already vaccinated by different types of COVID-19 vaccine thorough the world till date [1].

Covid-19 vaccines have proved to be effective counteracting the spread of Sars-Cov-2 infection among the general population reducing significantly both morbidity and mortality. However, the side effects of Covid-19 vaccination have been reported by various researches which are causing concern among the general population. Mild body ache, fever and fatigue has been reported as possible side effect of Covid-19 vaccination. But there is growing concerns that COVID-19 vaccination is also causing disruption to menstrual cycle especially among women suffering from PCOS [2].

The study showed that several women required gynecological visits claiming menstrual irregularities or abnormal uterine bleeding after the first and second doses of vaccination (regardless the type of vaccine used). The researchers don't yet understand exactly how vaccines could cause period changes [2]. However there are many hypotheses supporting the changes in the menstrual cycle by COVID-19 vaccination. **Emma *et al.*** [3] explains one possible reason might be that the uterus lining itself also contains the same chemical messengers, cytokines, that regulate inflammation; and if these are affected by immunization some women might notice some changes in bleeding. The second reason she explained that some women may had taken NSAIDs to help deal with vaccine after-effects like fever or aches and pains, so these too may make a small difference in menstrual flow.

So, COVID 19 vaccination impact may be linked to the immune system affecting the hormones driving the menstrual cycle. COVID -19 vaccines affected menstruation cycle in different ways. **Edelman *et al.*** [4] found that the length of the menstrual cycle (the time between periods) temporarily increased by an average of less than one day in people who received a dose of the COVID-19 vaccine, compared to unvaccinated people. However, the vaccination was not associated with a change in the number of days of bleeding. However, researchers have found among the COVID 19 infected women a range of menstrual changes such as menstrual volume change (25%), menstrual cycle change (28%) and prolonged cycle (19%) [5].

Very few studies have been done in the whole gulf regions including Saudi Arabia on the effect of Covid-19 vaccination on the menstrual cycle of the women. To the best of knowledge this was the first of its kind of study in Eastern province of Saudi Arabia.

MATERIALS AND METHODS

It was a cross-sectional prospective study in which data were collected during the 2 months' time by survey for the women in eastern province of Saudi Arabia. Women

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who underwent first dose or complete cycle of covid-19 vaccine, regardless of the type of vaccine used were the study population.

Exclusion criteria: Women undergoing any kind of hormonal therapy, including combined oral contraceptives, oral/vaginal progestin, intrauterine devices, GnRH-analogues, aromatase inhibitors, hormonal replacement therapy in menopause; surgical menopause (hysterectomy and/or bilateral oophorectomy) and breastfeeding were excluded from the study.

According to previous study the prevalence of menstrual changes post vaccination among the menstruating women was 66% [7]. The sample size was calculated using a Fisher's formula by cited by **Mugenda & Mugenda [8];** $n = Z^2pq/e^2$ where n = the desired sample size = the estimated proportion of the target population, assumption of 66% of post vaccinated women who may be suffering from menstruation changes documented by **Muhaidat *et al.*[7]**, q=1-p, e= desired level of precision (0.05),n= $(1.96)^2(0.66)(0.34)/0.05^2$= 344 sample of women needed who have been vaccinated by Covid-19 vaccination. The sampling was done randomly by selecting every second eligible woman attending the Outpatient Department of Obstetrics and Gynaecology till the sample size was achieved. The data were collected in the data collection form specially designed for this study. Section 1 consisted of the demographic characteristics of the study subjects (such as age, education, marital status, any co-morbid condition). Section 2 contained the information on the menstrual cycle, Covid-19 infection status, Covid-19 vaccination status, type of Covid-19 vaccine administered and menstruation cycle changes. Variables regarding menstrual cycle abnormalities were defined as follow.

Frequency of the menstrual cycle: Time frame: 30 days after the administration of the first and second doses of vaccine.
In women of reproductive age, any frequency shorter than 25 days or longer than 36 days was defined as abnormal.

Quantity of the menstrual cycle: Time frame: 30 days after the administration of the first and second doses of vaccine.
In women of reproductive age, any quantity less than 30 ml or more than 80 ml will be defined as abnormal.

Duration of the menstrual cycle: Time Frame: 30 days after the administration of the first and second doses of vaccine. In women of reproductive age, any duration shorter than 3 days or longer than 7 days will be defined as abnormal.

Ethical consent:

An approval of the study was obtained from King Faisal University, (Saudi Arabia) Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study before distributing questionnaires and an objective of the research was clarified to them. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The data were entered and analyzed using the statistical package for social sciences, version 21 (SPSS, Chicago, IL, USA). Descriptive statistics were presented using counts, proportions (%), mean ± standard deviation whenever appropriate. The comparison study was done by using multivariate analysis/binary logistic regression. A p-value cut off point of 0.05 at 95% CI was used to determine statistical significance.

RESULTS

A total of 343 participants filled the questionnaires completely making the response rate to hundred percent. The mean age of the participants was 30.16 ± 18.20 years (Range 15-54 years). Majority of the participants (56.6%) were married while 41.1% were unmarried and 2.3% divorced. Almost three fourth of the participants (73.4%) were postgraduate followed by graduate (16.6%). 7% were secondary educated while 1.7% and 1.2 % were primary educated and uneducated respectively. The vast majority of the participants (77.8%) did not have any associated systemic diseases while 7.5%, 6.1%, 5.6% and 3.5% of the participants were suffering from Type 2 diabetes, hypothyroidism, types 2 diabetes mellitus and hypertension and hypertension respectively. More than 42% of the participants had one time Covid-19 infection while a minority of 5% was twice infected with Covid-19 virus.

The majority of the participants (52.5%) were never infected by the Covid-19 infection. The vast majority of the participants (91.3%) were immune by 2 vaccines while the rest were immune by single vaccination. More than 63% of the participants had taken Pfizer only vaccine followed by 22.4% who took both Pfizer and Oxford. Almost 7% of the participants were vaccinated by Pfizer and Moderna while 5.8%, 1.2% and 1.5% of the participants took combination of Pfizer plus Oxford plus Moderna, Oxford plus Moderna and oxford only respectively. Table (1) showed the socio demographic characteristics and Covid-19 infection and vaccination status of the participants.

Table (1): The socio demographic characteristics and Covid-19 infection and vaccination status of the participants

Variables	No.	Percentage
Age (Years)		
30.16 years ± Std. Dev. 18.20 years (Range 15-54 years)		
Age group		
15-24 years	111	32.4
25- 34 years	149	43,4
35-44 years	26	7.6
45-54 year	57	16.6
Marital status		
Unmarried	141	41.1
Married	194	56.6
Divorced	8	2.3
Educational qualification		
Illiterate	4	1.2
Primary educated	6	1.7
Secondary educated	24	7.0
Graduate	57	16.6
Post graduate	252	73.5
Associated chronic disease		
No disease	266	77.6
Type 2 diabetes	25	7.3
Hypertension	12	3.5
Type 2 Diabetes and hypertension	19	5.6
Hypothyroidism	21	6.1
Menstrual Cycle before Covid-19 infection or Covid-19 vaccination	294	85.7
Regular	49	14.3
Irregular		
Covid-19 infection status		
Never infected	180	52.5
First time infected	146	42.6
Second time infected	17	5.0
Vaccination status		
Immune by one dose	30	8.7
Immune by 2 doses	313	91.3
Name of the vaccine taken		
Pfizer only	217	63.3
Pfizer+ Oxford	77	22.4
Pfizer + Moderna	20	6.8
Oxford+ Moderna	4	1.2
Oxford only	5	1.5
Pfizer + Oxford + Moderna	20	5.8

Menstruation irregularities among the participants:

60.3% of the participants were suffering from one and other menstruation irregularities after Covid-19 vaccination. 14% of them were suffering from the menstruation frequency longer than 35 days while 10.2% of them were suffering from the menstruation frequency shorter than 25 days. Almost 15% of the participants complained about the heavy bleeding and 9.6% of the participants had light bleeding for less period of time. The participants who had painful bleeding constituted 11.7% of the studied population (Table 2).

Table (2): Menstruation irregularities post Covid-19 vaccination

Variables	No.	Percentage
Normal Menstruation	136	39.7
Frequency shorter than 25 days	35 (16.9)	10.2
Frequency longer than 35 days	48(23.19)	14.0
Heavy bleeding	51(24.64)	14.9
Light bleeding for less period days	33(15.94)	9.6
Painful period	40 (19.32)	11.7

Association of menstrual irregularities with sociodemographic characteristics and Covid-19-vaccination and Covid-19 infection:

Table (3) showed the details of the association of menstrual irregularities with sociodemographic characteristics and Covid-19 vaccination and Covid-19 infection. The menstrual cycle irregularities were significantly more among the participants with the age group of 15-24 years as compared to those with age group of 25-34 years, 35-44 years and those of > 45 years of age (68.96% Vs. 62.41% vs. 65.33% vs. 45.61% , P=0.007). The menstrual irregularities were found more among the unmarried participants than those who were married and those who were divorced but it was not statistically significant (65.95% vs. 51.81% vs.62.5%, P=0.215). The menstrual change was more common among the primary educated participants as compared to uneducated, secondary, graduate and post graduate educated participants but it was also not statistically significant (100% vs.75% vs.50% vs.68.0% vs. 60%, P=0.310). The menstrual change was significantly more among the participants suffering from hypothyroidism as compared to those who were not suffering from any chronic disease, those suffering from type 2 diabetes, from hypertension and from both type 2 diabetes and hypertension (80.95% vs. 60.15% vs.40.0% vs.66.56% vs.63.16%, P=0.041). The participants with regular period pre-Covid-19 vaccination were suffering more from the menstruation changes as compared to those with already irregular period (pre-vaccination) but it was not statistically significant (60.40 vs. 59.18%, P=0.486). The menstrual change among the participants with one Covid-19 infection was significantly more as compared to those with two times infection and without infection (67.59% vs.47% vs. 58.11%, P= 0.05). There was no significant difference in the menstruation cycle changes among the participants with two doses vaccination and 3 doses vaccination (60% vs. 60.38%, P=0.567). Similarly there was no significant difference in the menstrual cycle changes among the participants with respect to the different types of Covid-19 vaccination (P=0.315).

Table (3): The association of menstrual irregularities with sociodemographic characteristics and Covid-19 vaccination and Covid-19 infection

Variables	No change in the menstrual cycle No. (%)	Change in the menstrual cycle No. (%)	P value
Age group			
15-24 years	40 (31.04)	71 (68.96)	
25- 34 years	56(37.59)	93(62.41)	0.007
35-44 years	9(34.67)	17 (65.33)	
45-54 year	31(54.39)	26 (45.61)	
Marital status			
Unmarried	48(34.05)	93 (65.95)	0.215
Married	84(48.19)	109(51.81)	
Divorced	3(37.5)	5(62.5)	
Educational qualification			
Illiterate	1 (25.0)	3 (75.0)	
Primary educated	0(0.0)	6 (100.0)	0.310
Secondary educated	12(50.0)	12 (50.0)	
Graduate	22(32.0)	35 (68.0)	
Post graduate	101(40.0)	152(60.0)	
Associated chronic disease			
No disease	106(39.85)	160 (60.15)	
Type 2 diabetes	15(60.0)	10 (40.0)	0.041
Hypertension	4(33.34)	8(66.66)	
Type 2 Diabetes and hypertension	7(36.34)	12(63.16)	
Hypothyroidism	4)19.04)	17(80.95)	
Menstrual Cycle before Covid-19 infection or Covid-19 vaccination			0.486
Regular	116 (19.6)	177 (80.4)	
Irregular	20(40.81)	29(59.18)	
Covid-19 infection status			
Never infected	47(32,440	98(67.56)	0.05
First time infected	9(53.0)	8(47.0)	
Second time infected	79(43.89)	101(56.11)	
Covid-19 vaccination status			
Immune by two doses	12(40.0)	18 (60.0)	0.567
Immune by booster dose (3 doses)	124(39.62)	189(60.38)	
Name of the vaccine taken			
Pfizer only	93(42.85)	124(57.15)	
Pfizer+ Oxford	24(31.17)	53(68.83)	
Pfizer + Moderna	10 (50.0)	10950.0)	0.315
Oxford+ Moderna	2 (50.0)	2(50.0)	
Oxford only	1(20.0)	4(80.0)	
Pfizer + Oxford + Moderna	6(30.0)	14(70.0)	

Multivariate analysis:

The multiple regression analysis has shown that females with the age group of 15- 24 years were 2 times more likely to develop menstruation cycle change (AOR = 2.0, 95% CI 1.65-4.76). The subjects with associated hypothyroidism were found to be 3.2 times more susceptible to the menstrual cycle change after Covid-19 vaccination (AOR=3.2, 95% CI 1.67-5.23).

DISCUSSION

The present study was conducted to assess the menstruation changes after Covid-19 vaccination among the women in the eastern province of Saudi Arabia. The study has found that more than sixty percent of the participants were suffering from one and other menstruation irregularities after Covid-19 vaccination. The majority of them were suffering from heavy bleeding (24.64%) followed by menstruation frequency longer than 35 days (23.19%), painful bleeding (19.32%), menstruation frequency shorter than 25 days (16.9%) and light bleeding for fewer periods (15.94%). In a Similar study **Lee *et al.*** [6] have reported that 56% of the women who took Covid-19 vaccination were having menstrual irregularities. In this study 42.1% of the total respondent reported heavier menstrual flow while 14.3% reported not heavier menstrual flow (characterized by a mix or higher or no change). One study that was conducted in the MENA

region has revealed that 66.3% of the participants reported changed menstrual symptoms post vaccination. Like the present study, vaccine type did not significantly influence the incidence of the abnormalities in menstruation (P=0.05) in this study also. The participants who had confirmed previous Covid-19 infection had a very similar percentage of menstrual dysfunction compared to people who did not have Covid-19 infection. The same result is found in the present study [7]. Study conducted on adult Lebanese post Covid-19 vaccinated women has also shown increased number of heavy bleeding or light bleeding ($p = 0.02$ and $p < 0.001$ respectively). The number of women having regular cycles decreased after taking the vaccine ($p < 0.001$) [9].

A large retrospective UK cohort analysis of menstrual cycle data has shown that Covid-19 vaccine was associated with a less than 1-day change in cycle length for both vaccine-dose cycles compared to pre-vaccine cycles (first dose 0.71 day-increase, 98.75% CI 0.47–0.94; second dose 0.91, 98.75% CI 0.63–1.19). Unvaccinated individuals showed non-significant change compared to three baseline cycles (cycle four 0.07, 98.75% CI −0.22 to 0.35; cycle five 0.12, 98.75% CI −0.15 to 0.39) [10].

However, a UK case-control study has reported menstrual cycle changes only among 20% of the post-vaccinated premenopausal women. A previous history of SARS-CoV-2 infection was found to be risk factors, while using estradiol-containing contraceptives was found to be a protective factor. The reported menstrual changes ranged from menstrual bleeding cessation to heavy menstrual bleeding [11]. A study conducted on Norwegian subjects has also reported menstrual irregularities among 39.4% of the participants after the Coviod-19 vaccination. The irregularities included heavy bleeding, unusually long-lasting or short menstruation, long intervals between menstruations and painful menstruation. However, the changes in the menstruation were found to be transient[12].

CONCLUSION

Coronavirus disease 2019 (COVID-19) vaccination is associated with changes in menstrual cycle (duration of the cycle, heavy menstruation and painful menstruation). Female with the age group of 15-24 years were 2 times more likely to develop menstruation cycle changes. The subjects with associated hypothyroidism were found to be 3.2 times more susceptible to the menstrual cycle changes after Covid-19 vaccination. However more studies especially case-control studies are required to confirm this association.

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