

The COVID-19 vaccines and menstrual disorders

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Abstract. – OBJECTIVE: The COVID-19 vaccination has been linked to numerous reports of menstrual disorders as potential side effects. However, menstrual cycle results after vaccination were not collected throughout clinical trials. According to other research, COVID-19 vaccination and menstrual disorders have no discernible connection, and menstrual disorders are temporary.

SUBJECTS AND METHODS: We asked questions about menstruation disturbances following the first and second doses of the COVID-19 vaccine in a population-based cohort of adult Saudi women to determine whether the vaccination is linked to menstrual cycle irregularities.

RESULTS: According to the results, 63.9% of women experienced variations in their menstrual cycle either after the first or second dose. Such results show that COVID-19 vaccination impacts women's menstrual cycles. However, there is no need for concern because the alterations are relatively minor, and the menstrual cycle usually returns to normal within two months. Additionally, there are no obvious distinctions between the various vaccine types or body mass.

CONCLUSIONS: Our findings support and explain the self-reports of menstrual cycle variations. We have discussed reasons for these problems that describe the mechanism of the relationship between them and the immune response. Such reasons will help prevent hormonal imbalances and the influence of therapies and immunizations on the reproductive system.

Key Words:

Menstrual disturbance, SARS-CoV-2, Vaccine, Period, COVID-19.

been linked to vaccination against the human papillomavirus (HPV), suggesting that if there is a connection, it is the immunological response to vaccination². Menstrual irregularities after the first dose in a study³ involving roughly 4,000 women, aged 18 to 30, reverted to normal by about two months after the first dose. There was a little increase in menstrual disturbances following dose two compared to dose one. According to some studies⁴, brief hormonal abnormalities associated with sex brought on by ovarian function suppression are followed by a swift return to normalcy. A survey of 3,959 Americans that used the app "Natural Cycles" concluded that (COVID-19) immunization is linked to a slight change in cycle length but not menses length⁵. Besides, the inactivated influenza vaccination has been shown in a clinical investigation to lower progesterone levels. These instances demonstrate that vaccinations affect menstrual symptoms, whether directly or indirectly. The process is still poorly understood and may have a temporary impact⁶. Nonetheless, the link between immunizations and menstruation issues has not been conclusively shown. As a result, we asked adults in a population-based cohort about menstrual abnormalities. The primary objective of our study was to determine whether the vaccine affects the menstrual cycle, relate the occurrence of the disturbance to body mass index (BMI), and examine the type of dose administered. We also gathered data on whether there was a connection between menstruation disorders and the COVID-19 vaccination.

Introduction

Vaccination against COVID-19 protects against the potentially serious consequences of the COVID-19 pandemic. The UK Medicine and Healthcare Products Regulatory Agency (MHRA)'s Yellow Card Surveillance system received more than 36,000 reports of menstrual abnormalities following vaccinations¹. Reports were not limited to a specific type of vaccine, whether an mRNA vaccine or a COVID-19 adenovirus vaccine. Menstrual alterations have also

Subjects and Methods

This study collected data from published articles exploring the link between vaccinations and menstrual cycles and the mechanisms through which the immune response can cause menstrual cycle disorders. We conducted a study by polling Saudi women on whether or not the vaccine altered their menstrual cycles and, if so, how. From the 21st of February to the 10th of March 2022, Saudi women between the

Table I. Characterize of 216 women aged 18-45 taking part in the Saudi adult study.

	N	% (n= 216)
Age		
< 22	121	56.0%
> 23	95	44.0%
BMI category		
Underweight or normal weight	131	60.6%
Overweight	52	24.1%
Obese	33	15.3%
Type of vaccine, first dose		
Pfizer/BioNTech	181	83.8%
Oxford/AstraZeneca	32	14.8%
Moderna	3	1.4%
Type of vaccine, second dose		
Pfizer/BioNTech	166	76.9%
Oxford/AstraZeneca	35	16.2%
Moderna	15	6.9%

ages of 18 and 45 who had received two doses of the COVID-19 vaccine were randomly asked to participate in an online survey. And the survey link they were given allowed them to submit only one answer by email (Without appearing) to protect participants' anonymity. Participants ages, heights, and weights were collected first, followed by measurements of their body mass index. A second question focused on the vaccines they had received. After receiving their first dose of a vaccine, women who received either 1) Pfizer/BioNTech, 2) Moderna, or 3) Oxford/AstraZeneca were asked if they had experienced any menstrual abnormalities. There are eight possible menstrual changes: 1) longer interval between menstruations, 2) missed period, 3) shorter interval between menstruations, 4) more heavy bleeding than usual, 5) less bleeding than usual, 6) stronger pain during menstruation, 7) less pain during menstruation, 7) prolonged menstruation, 8) short menstruation. And how long did the changes take? 1) one cycle, 2) two cycles, 3) three or more. Subsequently, they were asked the same list of questions about their menstrual cycle after the second vaccine dose³.

Statistical Analysis

All findings, shown in mean Slandered Error format, were analyzed using SPSS 25 (IBM Corp., Armonk, NY, USA) (SE). Chi-square tests were used to determine the statistical significance between the groups. If *p* was 0.05, then the difference was statistically significant.

Results

From the 338 responses, 216 (63.9%) reported changes to their menstrual cycle after either dose and 122 (36.1%) reported no change after both doses. Among the women who had changed, those who received Pfizer/BioNTech had the highest rate in either the first or second dose, 83.8% and 76.9%, respectively (Table I). All the disturbance were documented, and their frequency was 78.7% (Table II). The results showed that 43.5% of women experienced longer intervals between menstruations, and 33.3% experienced stronger pain during menstruation. Similarly, Table III demonstrates that longer intervals were 45.8% and 37.5% stronger in pain during menstruation following the second vaccination dose.

Discussion

Table II shows that after the first dose, 50.9% of participants indicated that the effects of the vaccinations were still noticeable three months later. After the second dose, 47.2% of patients reported the same (Table III). After the first dose, we noticed no differences in the type of vaccine (Table IV). However, after taking the two doses, most of those with whom the changes continued for three months or more were the ones who received Pfizer/BioNTech (Table V). But this is not conclusive proof; more study is required. Table VI shows no clear correlation between body mass and health outcomes after the first dose. However, most people who are obese were affected after the second dose by about 93.93%, and there are statistically significant differences between the two groups (Table VII).

The Mechanical Relationship Between Immunity and Disorders in the Menstrual Cycle

Although the research is still grounded on similar principles, various studies have provided conflicting accounts of the nature of the effect.

Nuclear Factor-Kappa B (NF-κB)

NF-κB is a protein transcription factor that controls immune responses. The NF-kappa B signalling pathway coordinates cellular resistance to invading pathogens by bridging the gap between pathogenic signals and cellular danger signals⁷. SARS-CoV-2 has been shown to trigger an inflammatory immune response in human epithelial

cells by activating the nuclear factor κ B⁸. Menstruation is characterized by a return to the fundamental process of tissue breakdown and bleeding. Therefore, we find NF- κ B essential in this context as its presence provides degradative enzymes and MMP activators. In response to the loss of progesterone intercellularly within the endometrium, it is secreted when reactive oxygen species (ROS) increase due to decreased prostaglandin metabolism⁹. This could be read as an explanation for the resulting disorders, which include longer intervals between menstruations, more heavy bleeding than usual and prolonged menstruation.

Estrogen Hormone

When infected or vaccinated, estrogen E2 stimulates antibody production by B cells. It acts as an Immune-Stimulating Factor by suppressing the production of proinflammatory cytokines, thus preventing neutrophils and monocytes' migration into inflamed areas. Additionally, it stimulates CD4+ T-helper cell production of anti-inflamma-

tory cytokines and promotes immune tolerance¹⁰. Endometrial cell survival depends on estrogen, which affects distinct intracellular signalling pathways like MAPK, PI3K/AKT, and NF-kappa B, so a shift in estrogen activities after vaccination could account for menstrual irregularities. It exerts its effect on Endometrial cells through a rearranged immune response and chemokines¹¹. Oral ovulation-inducing agents for most cases of anovulatory patients, like d-chiro-inositol (DCI), are available, and they can help treat anovulation caused by estrogen imbalances. DCI induces ovulation because it inhibits aromatase, a key enzyme in estrogen production¹².

Angiotensin-Converting Enzyme 2 (ACE2) Receptor

When vaccinated with the (SARS-2-S) vaccine, a spike protein interacts with the human ACE2 receptor to access cells to initiate infection. Organs with high ACE2 expression may be more susceptible to damage¹³. Previous animal¹⁴

Table II. Disturbances after the first vaccine dose among women aged 18 to 45 years participating in the Saudi Adult Cohort, n=216.

		Count	Column N% (n= 216)	p-value
Disturbance occurrence	Yes	170	78.7%	.144
	No	46	21.3%	
Disturbance occurrence, BMI				
Shorter interval between menstruations	No	182	84.3%	
	Yes	34	15.7%	
Longer interval between menstruations	No	122	56.5%	
	Yes	94	43.5%	
Missed period	No	185	85.6%	
	Yes	31	14.4%	
Less pain during menstruation	No	199	92.1%	
	Yes	17	7.9%	
Stronger pain during menstruation	No	144	66.7%	
	Yes	72	33.3%	
More heavy bleeding than usual	No	162	75.0%	
	Yes	54	25.0%	
Less bleeding than usual	No	165	76.4%	
	Yes	51	23.6%	
Prolonged menstruation	No	211	97.7%	
	Yes	5	2.3%	
Short menstruation	No	214	99.1%	
	Yes	2	0.9%	
Disturbance duration		N	% (n=170)	
One cycle	25	11.6%		
Two cycles	35	16.2%		
Three or more	110	50.9%		
Disturbance duration, type of vaccine			.683	

This implies that Disturbance occurrence and BMI are independent, which means that there is no association between them. Disturbance duration and type of vaccine are also independent, which means that there is no association between them, since the p-values are higher than 0.05.

Table III. Disturbances after the second vaccine dose among women aged 18 to 45 years participating in the Saudi Adult Cohort, n=216.

		Count	Column N% (n= 216)	p-value	
Disturbance occurrence	Yes	176	81.5%	.017 *	
	No	40	18.5%		
Disturbance occurrence, BMI					
Shorter interval between menstruations	No	186	86.1%		
	Yes	30	13.9%		
Longer interval between menstruations	No	117	54.2%		
	Yes	99	45.8%		
Missed period	No	185	85.6%		
	Yes	31	14.4%		
Less pain during menstruation	No	206	95.4%		
	Yes	10	4.6%		
Stronger pain during menstruation	No	135	62.5%		
	Yes	81	37.5%		
More heavy bleeding than usual	No	170	78.7%		
	Yes	46	21.3%		
Less bleeding than usual	No	158	73.1%		
	Yes	58	26.9%		
Prolonged menstruation	No	209	96.8%		
	Yes	7	3.2%		
Short menstruation	No	213	98.6%		
	Yes	3	1.4%		
Disturbance duration		N	% (n=176)	.006**	
One cycle	33	15.3%			
Two cycles	41	19.0%			
Three or more	102	47.2%			
Disturbance duration, type of vaccine					

This implies that disturbance occurrence and BMI are not independent, which means that there is association between them. Disturbance duration and type of vaccine are also not independent, which means that there is association between them since the *p*-values are lower than 0.05. **p* < 0.05 significant; ***p* < 0.01 highly significant.

Table IV. Chi-Square Tests between Disturbance duration and type of vaccine first dose.

		Type of vaccine			Total
		Pfizer	Oxford	Moderna	
Disturbance duration	No changes	38	8	0	46
	One cycle	20	5	0	25
	Two cycles	30	5	0	35
	Three or more	93	14	3	110
Total		181	32	3	216
Pearson Chi-Square	Value	df	p-value		
	3.954	6	.683		

This implies that the disturbance duration and type of vaccine are independent, which means that there is no association between them since the *p*-values are higher than 0.05.

Table V. Chi-Square Tests between disturbance duration and type of vaccine second dose.

		Type of vaccine			
		Pfizer	Oxford	Moderna	Total
Disturbance duration	No changes	26	11	3	40
	One cycle	27	5	1	33
	Two cycles	29	4	8	41
	Three or more	35	15	3	102
Total		166	35	15	216
Pearson Chi-Square	Value	df	p-value		
	18,229	6	.006**		

This implies that the disturbance duration and type of vaccine are not independent, which means that there is association between them since the *p*-values are lower than 0.05. **p* < 0.05 significant; ***p* < 0.01 highly significant.

Table VI. Chi-Square Tests between disturbance occurrence after the first dose and BMI.

		BMI			Total
		Underweight or normal weight	Overweight	Obesity	
Disturbance	Yes	108	36	26	170
	No	23	16	7	46
Total		131	52	33	216
Pearson Chi-Square	Value	df	p-value		
	3.877	2	.144		

This implies that the disturbance duration and type of vaccine are not independent, which means that there is association between them since the *p*-values are lower than 0.05.

Table VII. Chi-Square Tests between disturbance occurrence after the second dose and BMI.

		BMI			Total
		Underweight or normal weight	Overweight	Obesity	
Disturbance	Yes	99	46	31	176
	No	32	6	2	40
Total		131	52	33	216
Pearson Chi-Square	Value	df	p-value		
	8.105	2	.017*		

This implies that the disturbance duration and type of vaccine are not independent, which means that there is association between them since the *p*-values are lower than 0.05. **p* < 0.05 significant.

research reported ACE2 expression in granulosa cells of the ovary. This suggests that a malfunction in regulating ovarian hormones may be at the root of menstrual cycle irregularities.

Conclusions

About half of the women in the survey (51.1%) experienced changes to their menstrual cycle after the first dose. Besides, about a third of the women in the study (36.9%) experienced no change in their cycle after either dose. These results are encouraging in a limited sense because we found no evidence of a clinically significant shift in the menstrual cycle at the population sample level. Our results concur and clarify the menstrual cycle shifts reported. Even when controlling factors like age, gender, and ethnicity, there are no discernible differences between the various vaccines. The mechanism of the connection between these disorders and the immune response has been discussed, which helps avoid hormonal imbalances and the impact on the reproductive system that can result from treatments and vaccinations. Additional study is urgently needed on this topic, which includes issues like the lengthening of transition periods and the inability to return to a regular menstrual cycle quickly.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contributions

Investigation, resources, methodology, validation, data curation, formal analysis, and writing-original draft preparation done by Alya Al-Furaydi. Resources, data curation, formal analysis done by Shouaa Alrobaish. Conceptualization, methodology, validation, writing, review and editing, visualization, supervision, and project administration, done by Noorah Al-Sowayan. All authors have read and agreed to the published version of the manuscript.

Informed Consent

A meeting took place with the volunteers and explained the experiment to them. We asked them to sign the informed consent form, and they were told that they could leave the experiment at any time they wanted.

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Ethics Approval

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Qassim University Committee for Scientific Research Ethics (protocol code: 21-4-24; date of approval: 22-1-2022).

Availability of Data and Materials

Data is contained within the article.

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