

## The Association Between COVID-19 Pfizer Vaccine and The Reported Post-Vaccination Menstrual Changes in Citizen and Resident Women in KSA: Results of Riyadh Survey Study

Ezat A. Mersal<sup>1,2</sup>, Ahmed A. Morsi<sup>3</sup>, Alaa M. Hassanein<sup>2,4</sup>, Aryaf Alshammri<sup>5</sup>, Abeer Alshammari<sup>5</sup>, Nourah Alkahmous<sup>5</sup>, Fatimah Alhuwayji<sup>5</sup>, Riham G Elfawal<sup>6,7</sup>

<sup>1</sup>Biochemistry Department, Faculty of Science, Assiut University, Assiut, Egypt

<sup>2</sup>Department of Basic Medical Sciences, Vision College of Medicine, Riyadh, KSA

<sup>3</sup>Histology and Cell Biology Department, Faculty of Medicine, Fayoum University, Fayoum, Egypt

<sup>4</sup>Department of Public Health and Community Medicine, Faculty of Medicine, Assiut University, Assiut, Egypt

<sup>5</sup>Students at Vision College of Medicine, Riyadh, KSA

<sup>6</sup>Clinical Pathology Department, Faculty of Medicine, Alexandria University, Alexandria, Egypt

<sup>7</sup>Department of Clinical Sciences, Vision College of Medicine, Riyadh, KSA

**Corresponding author:** Dr Ahmed A. Morsi, Email: [aaa21@fayoum.edu.eg](mailto:aaa21@fayoum.edu.eg), [ahmed\\_sagr4@yahoo.com](mailto:ahmed_sagr4@yahoo.com), **ORCID:** 0000-0001-7911-0795

### ABSTRACT

**Background:** Pfizer vaccine has been approved for use in Saudi Arabia. Although the vaccine efficacy has been frequently addressed, little knowledge is available regarding the real-world post-vaccination menstrual disturbances.

**Objective:** The aim was to evaluate the possible association between Pfizer vaccine and the post-vaccination menstrual irregularities among Saudi citizen and resident women.

**Subjects and methods:** A self-administered validated questionnaire was used to obtain the data. It was distributed all over Riyadh City, KSA through social media and 731 females responded to the survey. **Results:** Overall, 50.9% of the participants reported a menstrual change after vaccination, in particular, those who received the 2 doses. There was a significant and positive correlation between the number of doses and the experience of menstrual changes being associated with the 2 dosed women. In details, 60.5% mentioned a menstrual delay, 30.4% reported early onset, and 9.1% mentioned a menstrual change other than in the date. 43.3% reported a decrease in the amount of menstrual flow, 34.9% mentioned an increase. 62.4% declared an increase in the severity of pain while 11% reported a decrease. Interestingly, only 60.8% of the respondents mentioned the persistence of the menstrual changes each following cycle. However, the changes were positively correlated with the age and negatively associated with the marital status being less in married.

**Conclusion:** It was concluded that the post-vaccination menstrual changes might be related to the age, marital status, and those receiving 2 doses and these changes could be related to the immune response frequently associated with vaccines.

**Keywords:** COVID19 immunization, Cross-sectional study, Fertile females, Menstrual irregularities, Side effects, Vaccine reactogenicity

### INTRODUCTION

The outbreak of the 2019-novel coronavirus (SARS-CoV-2) that causes severe respiratory infection (COVID-19) has been declared a pandemic by the World Health Organization (WHO) <sup>(1)</sup>. WHO first learned about this new virus on December 31, 2019, after case reports of viral pneumonia in Wuhan, People's Republic of China <sup>(2)</sup>. Clinical research and tests have demonstrated that licensed vaccines are effective in controlling the disease. However, the current vaccines should be evaluated against the emerging variants of SARS-CoV-2 <sup>(3)</sup>. There are a variety of vaccines that have been approved for use; Pfizer-BioNTech, AstraZeneca, and Moderna <sup>(4)</sup>. In Kingdom of Saudi Arabia, the Saudi Food and Drug Authority (SFDA) has announced the approval of the registration of Pfizer-BioNTech COVID-19 Vaccine since December 10, 2020 <sup>(5)</sup>.

The Pfizer-BioNTech COVID-19 vaccine, BNT162b2, is a lipid nanoparticle (LNP) that encapsulates nucleoside-modified mRNA that encodes the SARS-CoV-2 full-length spike (S) protein, and it is

the most widely used RNA vaccine. It was proven to induce both cellular and humoral immunities with better response than BNT162b1. Severe allergic reactions including anaphylaxis have been recorded to be the only contraindication <sup>(6,7)</sup>. The second vaccine developed by RNA technology is mRNA-1273. It is an LNP-encapsulated mRNA vaccine with no safety concerns were raised, aside from temporal local and systemic reactions <sup>(8)</sup>.

Recently, COVID-19 vaccines have been distributed on a wide scale worldwide. Despite their protective efficacy has been frequently addressed, little data is available regarding the real-world post-vaccination experiences outside the clinical trial conditions, in particular Pfizer mRNA vaccine on females' menstruation. So, the current study strived to investigate whether the Pfizer vaccine is associated with post-vaccination menstrual changes in a sample of 16-40 years citizen and resident women in Riyadh city, using a cross-sectional survey-based study. Precise information about the expectation after vaccination will help us

educate the public and minimize the vaccine hesitancy among the fertile women.

**MATERIAL AND METHODS**

*Study design*

A cross-sectional questionnaire-based observational study was conducted over a period of one week from 27 September to 4 October 2021 and included questions related to the post-vaccination menstrual changes experienced in fertile females (16-40 years old) in Riyadh City, KSA. Initially, the Saudi Ministry of Health was targeting to vaccinate 70% of the population (approximately, 28 million) <sup>(9)</sup>, so a calculated sample size of 385 was sufficient to represent a population of 30 million. It was determined within ±0.05 for a population of 30 million with a 95% confidence level. The sample size was then increased by 10%-15% to account for missing data. The current study included female participants who were given either single or double doses of Pfizer vaccine in Saudi Arabia. We have excluded all male participants, those who were less than 16 or older than 40 years, who objected to participate, those not vaccinated against COVID-19, or who had been given a vaccine other than Pfizer-BioNTech.

A self-administrated questionnaire was online disseminated for the attention of those women who received the vaccine through commonly used social media platforms in KSA. It was designed in both Arabic and English languages using Google Forms. The calculated sample size was 385 at confidence level 95 % and 731 responses were obtained (189.9%). The questionnaire items were formulated based on the research objectives and reviewed by gynecological and biostatistics experts. For validity of the questionnaire, face to face validation was done. Also, a pilot study of 50 participants was performed to develop, revise and validate the questionnaire. Furthermore, a biostatistician’s view-points were considered during questionnaire preparation. The questionnaire included a total of 12 items and was divided into sections; the first section included 3 items related to demographic data. The second section included 9 items and it evaluated the status of the menstrual cycle after COVID-19 Pfizer vaccine.

**Ethical considerations:**

**A front page for informed consent was included in the questionnaire and an opening sentence showed that they were completely free whether to participate or not in the study. The participants were provided the option to choose whether to participate by clicking on their answer in the relevant box. After that, the participants were directed, if agreed, to different sections with various questions. The participants were given no motivation of any kind**

**and the data collected was kept secret. All ethical issues regarding the distribution of the survey, getting the responses, and data analysis were followed, and fulfilled the scientific merits, and the ethical standard of health research. 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 and was approved by the institutional review board (IRB) committee at King Saud University (Code #: E-20-5623).**

*Statistical analysis*

All research data were managed in excel sheet and were analyzed by using SPSS software, version 24 (IBM SPSS Statistics for Windows, Armonk, NY, USA). Data were presented as frequency and percentage. Multivariate logistic regression models using Pearson’s correlation was used to find the association between variables. P-value less than 0.05 was considered statistically significant.

**RESULTS**

*Sociodemographic data (Table 1)*

About sixty-eighty percent of the respondents were single females. The majority of the participating females were 20-29 years old (44%). In addition, the results showed that most of the females received two doses of vaccination (90.3%).

**Table-1:** Sociodemographic data

<i>Sociodemo graphic Data</i>	731 Total Females	
	No	%
<i>Social state</i>		
Single	494	67.6%
Married	218	29.8%
Divorced	15	2.1%
Widow	4	0.5%
<i>Age</i>		
16-19	209	28.6%
20-29	322	44.1%
30-39	86	11.8%
40	114	15.6%
<i>Does of Pfizer vaccine</i>		
One dose	71	9.7%
Two dose	660	90.3%

**Changes in menstrual cycle (Table 2)**

The current findings indicated that 50.9% of the participants noticed menstrual changes after receiving Pfizer vaccines. Most of them (60.5%) noticed a delay in the date of the menstrual onset. The reported delay was 15 days in 50.2% of those who reported a menstrual

delay (225 participants). On the other hand, 30.4 % noticed more frequent cycles (i.e. came early than usual). Of those reporting frequent cycles, 40.7 % had 6-10 days earlier cycles. The rest of the participants (9.1 %) reported regular menstrual dates with no change. Moreover, of those who observed menstrual changes

(372 participants, 50.9%) 43.3% noticed that amount of bleeding had decreased. Regarding the changes in the severity of pain, 62.4% complained of increased pain. Furthermore 60.8% of the participants who told a menstrual change confirmed the repetition of these changes in all cycles after receiving the vaccine.

**Table 2:** Normal pattern of the menstrual cycle and the post-vaccination menstrual changes

<i>Survey statement</i>	<b>731 Total Female</b>	
	No	%
<b><i>Duration of menstruation?</i></b>		
Less than 5 days	106	14.5%
From 6 to 8 days	542	74.1%
From 9 to 10 days	73	10.0%
More than 10 days	10	1.4%
<b><i>Duration of the cycle?</i></b>		
Less than 25 days	337	46.1%
Between 25 to 45 days	371	50.8%
More than 45	23	3.1%
<b><i>Did you notice any changes in your menstrual cycle after receiving vaccine?</i></b>		
Yes	372	50.9%
No	359	49.1%
<b><i>Did you notice any changes in the date of your menstrual cycle after receiving vaccine?</i></b>		
No change	34	9.1%
Early	113	30.4%
Delay	225	60.5%
<b><i>If it delayed how long?</i></b>		
7 days	53	23.5%
15 days	113	50.2%
21 days	10	4.4%
30 days or more	49	21.7%
<b><i>If it is early how long it takes?</i></b>		
1 to 5 days earlier	44	38.94%
6 to 10 earlier	46	40.71%
11to 15 days earlier	17	15.04%
16 to 21 days earlier	2	1.77%
more than 21 days	4	3.54%
<b><i>Did you notice any changes in the amount of bleeding?</i></b>		
No change	81	21.8%
Decrease	161	43.3%
Increase	130	34.9%
<b><i>Did you notice any changes of the severity of the pain?</i></b>		
no change	99	26.6%
yes increase	232	62.4%
yes decrease	41	11.0%
<b><i>Are these changes repeated in all cycles after receiving the vaccine till time of survey?</i></b>		
no change	1	0.3
no	145	39.0
yes	226	60.8

**Regression analysis (Table 3):**

There was a significant and positive correlation between the number of vaccine doses and the menstrual changes experienced by the vaccinated participants, which means that the menstrual changes were noted in those women who received 2 doses of the vaccine. In more details, there was a significant negative correlation between the number of doses and the period of menstrual delay, which means a less delay in the onset of menstrual in those receiving the 2 doses.

When correlating the age of the participating females, the menstrual changes were associated with

elderly than those young aged indicating a positive correlation. On the other hand, the correlation was negative and significant with the delay in the onset of menstruation indicating that younger women experienced a delay in the onset of menses than those old aged. Parallel, the correlation was positive and significant with the early onset of menstruation indicating that older women experienced an early menses so, frequent cycles.

Regarding the marital status, in terms of the periods of delay and early onset menses, there were a significant negative and significant positive association with age.

**Table-3:** The correlation between the number of Pfizer vaccine doses received, social status, and age and other variables in the study

		Did you notice any changes in your menstrual cycle after receiving vaccine?	Changes in the date of a menstrual cycle after receiving the vaccine?	The period of delay in menstruation	The period of early menstruation	changes in the amount of bleeding	changes of the severity of the pain	Are these changes repeated in all cycles after receiving the vaccine?
How many Pfizer doses you complete?	Pearson Correlation	0.038	-0.023	-0.130	0.018	-0.049	0.032	0.007
	Significance	0.003	0.660	0.012	0.725	0.347	0.532	0.895
	N	372	372	372	372	372	372	372
Social Status (Widow, Divorced, Single, Married)	Pearson Correlation	-0.016	-0.116*	-0.141**	0.135	0.080	-0.006	-0.003
	Significance	0.6	0.025	0.006	0.009	0.124	0.901	0.955
	N	372	372	372	372	372	372	372
Age	Pearson Correlation	0.041	-0.109	-0.115	0.274	0.015	-0.076	0.003
	Significance	0.228	0.036	0.027	0.000	0.770	0.146	0.960
	N	372	372	372	372	372	372	372

“\*” $\alpha = 0.05$  for 95% confidence interval“\*\*\*” $\alpha = 0.01$  for 99% confidence interval.

## DISCUSSION

Despite the approval and availability of the vaccine for all citizens and residents in Saudi Arabia, there is a variation in people's hesitancy to receive the vaccine. This could be explained by the fact that the vaccine was developed in a short time with no sufficient studies, when compared to the previously developed vaccines. Another reason could be attributed to the usage of a newly arising methods, mRNA-based technology<sup>(10,11)</sup>. These two reasons may raise the concern among some women about potential post-vaccination menstrual disturbances so, the current study has investigated the correlation between COVID-19 Pfizer vaccine and the post-vaccination menstrual changes among citizen and resident females in Riyadh city. 731 females responded to the survey, which was unique and representative to the female receiving Pfizer vaccine in Riyadh City, KSA (calculated sample size was 385). The study showed the viewpoints of the females regarding the changes of their menstrual cycles after receiving the Pfizer vaccine.

The results revealed that about half of the participants (50.9%) have experienced menstrual changes after receiving Pfizer vaccines, while 49.1% have no changes. The results showed that the vast majority of them (60.5%) noticed a delay in the date of their menstrual onset, while (30.4%) reported frequent cycles (came early). Regarding the amount of menstrual flow and the severity of menstrual pain, 34.9%, 62.4% mentioned an increase in both variables meanwhile, 43.3%, (11%) reported a decrease, respectively. There was a positive and significant correlation between the number of vaccine doses and the occurrence of menstrual changes indicating that the menstrual changes were commonly associated with those females receiving 2 doses. Similarly, **Polack et al.**<sup>(12)</sup> and **Menni et al.**<sup>(13)</sup> reported systemic changes more in the 2-dose-recipients than the one-dosed. Also, the 2-dose vaccination was positively associated with the severity of pain while, negatively linked to the amount of bleeding.

Overall, it has been reported that both mRNA and adenovirus vectored covid-19 vaccines were associated with post-vaccination menstrual changes<sup>(14)</sup> suggesting that, if there is a possible causal relationship, it is likely to be due to an immune response to the vaccination rather than a particular vaccine component. Likewise, Human Papilloma Virus (HPV) vaccine has been reported to transiently cause menstrual changes<sup>(15)</sup>, so it would have been impractical to be surprised if COVID-19 vaccines do so. **Karagiannis and Harsoulis**<sup>(16)</sup> suggested a significant impact of the immune stimulation on the

female hormones driving the menstrual cycle. Hence, **Monin et al.**<sup>(17)</sup> explained such post-vaccination immune reaction. The immune cells participate in the cyclic building up and breaking down of the uterine endometrium that happens during the female periods. Vaccines enhance the body cells to produce cytokines and interferons that stimulate immune cells, including those in the uterus causing earlier or more vigorous bleeding than usual.

On the other hand, the age of the participants was positively correlated with occurrence of menstrual changes indicating that the vaccine reactogenicity might increase with the increase in age, being more associated in the (20-29) age group than (16- 19) age group. In contrast, **Polack et al.**<sup>(12)</sup> demonstrated a systemic reactogenicity for the vaccine in younger than older vaccine recipients in clinical trials. This conflict might be attributed to the evaluation of a systemic event (fever, fatigue, headache...etc) rather than menstrual changes, like in our study. Parallel to the current finding, some authors<sup>(18)</sup> reported age-related changes in post-vaccination response based on the estrogen level. In regard to the marital status, there was a negative correlation with the occurrence of menstrual changes. These cyclic changes were noted more in widow and divorced than single and married, that might indicate a psychological background as an additional factor. This notion was supported by **Darabi et al.**<sup>(19)</sup> who declared menstrual irregularities associated with stress.

When correlating the age and marital status with the onset of menstruation (after vaccination), it was noted an early onset of menses with the increase in age groups as well as in married more than single females. Also, when correlating both parameters with the amount of bleeding and severity of pain, it was noted an increase in the amount of menstrual flow and a decrease in pain in the older and married females more than the single ones, which is, practically, a plausible speaking as the married female are usually older than single ones. Interestingly, the repetition of menstrual changes each cycle following the vaccination was positively correlated with number of doses of the vaccine and the age while, negatively correlated with marital status. This means that the older females and those received the 2 doses reported the persistence of the menstrual disturbances after vaccination. In contrast, the married women reported a repetition of these changes but not every following cycle. This conflict could be revealed by that all married females are not elder ones. The findings of current study may reassure those women who are worried about the new vaccine. Also, the demonstration of the fact that the

post-Pfizer vaccination menstrual changes is due to an immune response and have been previously reported in other vaccines such as flu and HPV will help us interfere with the false claims that COVID-19 Pfizer vaccine could affect their menstruation and decrease the chance of their future pregnancy. Noteworthy, that current study was performed at the time when the Saudi Arabia encouraged the population to take the second dose<sup>(20)</sup>, a limitation that was reflected on our study sample which included only 9.7% who received one dose and 90.3% received the 2 doses, in addition to the short interval between the 2 doses in Pfizer-BioNTech vaccine. It would be interesting to include a larger sample of respondents with one dose to evaluate their experience of menstrual changes compared to the 2-dosed. The second limitation was the inability to avoid the possible selection bias as online platforms were used to reach the participants. The third limitation was the use of self-reported symptoms without guidelines or diagnosis by a gynecologist. The respondents are unlikely to mention a change to their periods unless specifically asked. The outcomes were only simple symptoms and their impact on regular life and not a syndrome or disease. Thus, personal interpretation to questions is likely to be rather homogeneous despite the fact that the validity of the survey questions using self-reporting is unknown in those participants. So, information about changes in menstrual flow and other cyclic changes should be actively addressed in further clinical trials on covid-19 vaccines. The fourth limitation was the temporal relationship between vaccination and the post-vaccination menstrual changes and the inability to reach a causal relationship due to the cross-sectional nature of the study. For more accurate determination of the association between vaccination and the post-vaccination menstrual changes, further studies are needed.

Despite such limitations, the authors believe that the findings of the study are an enormous addition to the current knowledge on the safety of COVID 19 Pfizer vaccination in KSA. Informing the females about what to expect after vaccination regarding their menstrual cycle may provide the opportunity to educate the public, eradicate misinformation and reduce vaccine hesitancy, in particular, among fertile women.

## CONCLUSION

In this large-scale survey in Riyadh, KSA, the study demonstrated menstrual changes following Pfizer vaccine immunization mostly in the form of delay in the menstrual onset, in those who received

the 2 doses, and in older than younger recipients, and more in single than married ones. A correlation between the Pfizer vaccination and the post-vaccination menstrual alterations was reported in the current study and these changes could be related to the immune response often associated with vaccines and not related to any constituent or component of the vaccine and could be correlated with the observations of previously published study regarding HPV vaccine. Also, our findings could be used to inform the female people on the possibility of occurrence of menstrual changes based on their age, marital status and whether one or 2 doses received.

## Conflict of interest

The authors have no conflict of interest to declare.

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## Data availability statement

All data generated or analyzed in the current research are available.

## REFERENCES

1. **Rehman H, Mirza M, Ahmad M *et al.* (2020):** A putative prophylactic solution for COVID-19: Development of novel multiepitope vaccine candidate against SARS-COV-2 by comprehensive immunoinformatic and molecular modelling approach. *Biology (Basel)*, 9(9):296.
2. **Šehović A and Govender K (2021):** Addressing COVID-19 vulnerabilities: How do we achieve global health security in an inequitable world. <https://www.researchgate.net/profile/Kaymarlin-Govender/publicatio...>
3. **Abdel-Moneim A, Abdelwhab E and Memish Z (2021):** Insights into SARS-CoV-2 evolution, potential antivirals, and vaccines. *Virology*, 558:1–12.
4. **Voysey M, Clemens S, Madhi S *et al.* (2021):** Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*, 397(10269):99–111.
5. **Saudi Press Agency S (2020):** SFDA Approves Registration of Pfizer-BioNTech COVID-19 Vaccine . Available from: <https://www.spa.gov.sa/viewfullstory.php?lang=en&newsid=2166947>
6. **Walsh E, Frenck Jr R, Falsey A *et al.* (2020):** Safety and immunogenicity of two RNA- based Covid-19 vaccine candidates. *N Engl J Med.*, 383(25):2439–50.
7. **Jhaveri R (2021):** The COVID-19 mRNA Vaccines and the pandemic: Do they represent the beginning of the end or the end of the beginning? *Clin Ther.*, 43(3):549–56.
8. **Baden L, El Sahly H, Essink B *et al.* (2021):** Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med.* ,384(5):403–16.

9. **Alhazmi A, Alamer E, Daws D et al. (2021):** Evaluation of side effects associated with COVID-19 vaccines in Saudi Arabia. *Vaccines*, 9(6):674.
10. **Bono S, Faria de Moura Villela E, Siau C et al. (2021):** Factors affecting COVID-19 vaccine acceptance: An international survey among low-and middle-income countries. *Vaccines*, 9(5):515.
11. **Alfageeh E, Alshareef N, Angawi K et al. (2021):** Acceptability of a COVID-19 vaccine among the Saudi population. *Vaccines*, 9(3):226.
12. **Polack F, Thomas S, Kitchin N et al. (2020):** Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med.*, 383:2603-2615.
13. **Menni C, Klaser K, May A, Polidori L et al. (2021):** Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. *Lancet Infect Dis.*, 21(7):939-949.
14. **Medicine and Healthcare Products Regulatory Agency (2021):** Coronavirus vaccine—weekly summary of yellow card reporting [Internet]. Nature Publishing Group. Available from: <https://www.gov.uk/government/publications/coronavirus-covid-19-vaccineadverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting#annex-1-vaccine-analysis-print>
15. **Suzuki S and Hosono A (2018):** No association between HPV vaccine and reported post-vaccination symptoms in Japanese young women: results of the Nagoya study. *Papillomavirus Res.*,5:96–103.
16. **Karagiannis A and Harsoulis F (2005):** Gonadal dysfunction in systemic diseases. *Eur J Endocrinol.*,152(4):501–13.
17. **Monin L, Whettlock E, Male V (2020):** Immune responses in the human female reproductive tract. *Immunology*,160(2):106–15.
18. **Giefing-Kröll C, Berger P, Lepperdinger G and Grubeck-Loebenstien B (2015):** How sex and age affect immune responses, susceptibility to infections, and response to vaccination. *Aging Cell*, 14(3):309–21.
19. **Darabi R, Ghoreshi B, Dianaty S and Motevalli M (2021):** Stress and menstrual disorders among Iranian medical students: A cross-sectional study. *South East Asia J Med Sci.*,8–15.
20. **Saudi Gazette Report (2021):** Saudi Arabia starts giving second dose of vaccine for all age groups .Available from: <https://saudigazette.com.sa/article/608717>