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Research Article

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Abnormal uterine bleeding after receiving COVID-19 vaccine among female in Saudi Arabia

Abstract

Introduction: The Coronavirus disease 2019 (COVID-19) vaccine has been approved by the United States Food and Drug Administration as safe and effective against the virus. In addition to the vaccine known adverse effects, a lot of women worldwide have experienced abnormal uterine bleeding (AUB) after receiving the COVID-19 vaccine. This study aimed to figure out the relationship between AUB and the COVID-19 vaccine and to compare the effects of different vaccine types on AUB.

Methods: An e-questionnaire-based cross-sectional study conducted between December 2021 to February 2022. The targeted population of the study was all COVID-19 vaccinated female in Saudi Arabia. A total of 1912 respondents participated in the survey, only 1533 were eligible for inclusion in the study. The collected data were analyzed using descriptive statistical methods via Statistical Packages for Social Sciences version 26.

Result: Out of 1533 participants, 998 (64.4%) reported AUB in relation to the COVID-19 vaccine. The mean age of the participants was 31.2±8.4 years, and more than half of them (59.4%) were married. Majority had received the Pfizer-BioNTech vaccine in their three shots (77.1%), (78%), and (92.1%), respectively. The incidence of AUB was (82.7%) mainly in form of menorrhagia (38.3%) in the first shot and (88.8%) after the second dose also in the form of menorrhagia (39.1%). Only 3.8% of women had the third dose, the incidence of AUB was 65.8%, mainly in the form of oligomenorrhea (21.1%). Regarding different types of the vaccine in three doses, the Chi-square test (p=0.239), (p=0.200) and Fischer exact test (p=0.265) were statistically significant showing no difference in AUB with different COVID-19 vaccines.

Conclusion: The majority of participants had AUB as a result of receiving the COVID-19 vaccine. Furthermore, there was no difference in the incidence of AUB between the Pfizer-BioNTech vaccination and the AstraZeneca Oxford vaccine for the two vaccine types investigated in the study.

Keywords: Coronavirus disease-19, COVID-19 vaccine, Pfizer-BioNTech vaccine, AstraZeneca Oxford vaccine, abnormal uterine bleeding, Saudi Arabia

Volume 13 Issue 4 - 2022

Zainab A Jeddo,[1] Ali M Hibshi,[2] Amal Yaseen Zaman,[3] Sarah Talal Kashkari,[1] Mernan Mohamed Mahrous,[1] Taif Jameel Tharwat,[1] Hiba Zain Barri,[1] Nora Tarq Alreefi[1]

[1]Medical College, Taibah University, Medina, Saudi Arabia
[2]Obstetrics & gynecology, King Salman bin Abdulaziz Medical City, Medina, Saudi Arabia
[3]Obstetrics & gynecology, Taibah University, Medina, Saudi Arabia

Correspondence: Zainab A Jeddo, Medical College, Taibah University, 6670 -Al Fath Dit. Near sultana road-442312, Medina, Saudi Arabia, Tel +966597615915, Email zzz.jeddo@hotmail.com

Received: July 25, 2022 | **Published:** August 08, 2022

Abbreviations: COVID-19, Coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome Coronavirus 2; WHO, World Health Organization; FDA, food and drug administration; VITT, vaccine-induced thrombosis and thrombocytopenia; AUB, abnormal uterine bleeding; SD, standard deviation

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a newly discovered coronavirus with the genetic sequence severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) has declared COVID-19 a global pandemic according to its devastating effects within a short time of its detection in December 2019. Meanwhile, urgent measures are being taken around the world to prevent the epidemic from spreading. Until today, there have been around 6,288,525 deaths worldwide.[1]

A huge effort was taken worldwide to face the COVID-19 pandemic and to reduce the likelihood of infection transmission. The Saudi Ministry of Health published health regulations and guidelines to raising public awareness about COVID-19, securing the border, and applying quarantine.[2]

In light of the fact that everyone understands the importance of vaccinations, which act as a simple, safe, and effective immunization process against diseases, pushing the body to resist certain infections and boosting the immune system by training it to generate antibodies. Since of COVID-19's quick and simple dissemination, as well as the rising number of infected and fatality cases around the world, WHO has urged clinical trials to evaluate the vaccine against COVID-19 infection. The significance of this vaccination is that it allows the body produces a protective immune response that prevents or controls infection.[3] As a result, the importance of COVID-19 vaccinations in augmenting individual preventive measures to face the pandemic has become vital, and vaccination coverage is considered critical for maintaining effective public health measures.[4]

The COVID-19 vaccine has been licensed by the United States Food and Drug Administration (FDA) as safe and effective against the virus, depending on the vaccination type.[5] On December 10, 2020, the COVID-19 vaccination received its first approval in Saudi Arabia. Pfizer-BioNTech and AstraZeneca Oxford were approved first, followed by the Moderna COVID-19 vaccine.[6] Both the Pfizer-BioNTech and Moderna COVID-19 vaccines are messenger RNA (mRNA) vaccines based on relatively new technology, and the results showed high efficacy in preventing symptomatic disease.[7]

However, significant adverse effects such as Vaccine-Induced Thrombosis and Thrombocytopenia (VITT) have been documented.[8] Soreness at the injection site, swelling, fever, headache, and muscle pain are all possible side effects. Nausea, vomiting, and lymphadenopathy are a few of the less prevalent symptoms.[9] In a survey done by Chrissie

Giles in May 2021, 4000 women reported abnormal uterine bleeding (AUB) after getting the COVID-19 vaccine.[10]

AUB is a term that describes variations in menstruation caused by an increase in volume, duration, or frequency.[11] AUB describes a range of symptoms, such as heavy menstrual bleeding (bleeding that exceeds the 95th centile of the general population), inter-menstrual bleeding, and a combination of both heavy and prolonged menstrual bleeding.[12] AUB has great importance because it's quite common and it has an adverse impact on quality of life. It negatively affects physical, emotional, sexual, and professional aspects of women's lives.[11] An organized approach to determining the etiology using the International Federation of Gynecology and Obstetrics (FIGO) PALM-COEIN (Polyp, Adenomyosis, Leiomyoma, Malignancy (and hyperplasia), Coagulopathy, Ovulatory disorders, Endometrial, Iatrogenic, and Not otherwise classified) classification system will facilitate accurate diagnosis and inform treatment options.[13]

While a lot of women worldwide have experienced AUB after receiving COVID-19 vaccine, it is important to mention that this side effect made a hesitancy among young women by false claims that COVID-19 vaccination could affect their chances of future pregnancy.[14] The relation between vaccines and menstrual cycle abnormalities was first studied in 1913, when a medical doctor at the Presbyterian Hospital, New York, concluded that there was a striking relationship between the prophylactic typhoid vaccine and menstrual disturbances among one hundred cases. These disturbances disappeared within 6 months of the vaccine, suggesting that any such vaccine side-effect was temporary.[15] Also, similar results were associated with different types of vaccines.[15,16] Now it's worth to be mentioned that this problem is making a big concern between women, and it need to be studied more widely.[14] To the best of our knowledge, there has been no assessment of AUB disturbances following COVID-19 vaccination in Saudi Arabia. Therefore, this study aimed to figure out the relationship between AUB and COVID-19 vaccine.

Study objectives:

1) The prevalence of AUB post-receiving the COVID-19 vaccine.
2) To compare the effects of Pfizer-BioNTech vaccine and AstraZeneca Oxford vaccine on AUB.

Material and methods

Ethical consideration

The study protocol and instruments were revised by the King Salman bin Abdulaziz Medical City Institutional Review Board (IRB), Madinah. Ethical approval was obtained on December 2, 2021 (IRB log No. 21-001). An electronic informed consent was obtained from each participant. The study followed Helsinki Declaration in all stages.

Study design

A descriptive cross-sectional study was conducted between December 2021 to February 2022 to evaluate the prevalence of AUB post-receiving COVID-19 vaccination and figure out the relationship between different vaccines and AUB among females in Saudi Arabia.

Study population

The target sample size of 385 participants was estimated using Surveymonkey.com with a 5% margin of error and a 95% confidence level. The actual sample size was increased to 1533 to better represent the population. The sample included all COVID-19 vaccinated females who are of childbearing age (14–45) as defined by the American College of Obstetricians and Gynecologists,[17] living nowadays in Saudi Arabia and having a regular cycle prior to vaccination. We exclude postmenopausal women, pregnant women, breastfeeding women, and women with irregular cycles e.g., oligomenorrhea.

Data collection and research tool

To ensure coverage of all regions of the kingdom, social media networks such as WhatsApp, Twitter, and Snapchat were utilized to invite participants via data collectors. The data collection took place from December 2021 to January 2022. Participation was optional and anonymous, and it was accomplished by the completion of a questionnaire. The invitation message included an explanation of the study's purpose, the primary investigator's contact information, and a live link to the survey (a Google form).

The study tool was a self-structured e-questionnaire (available in appendices) designed based on the literature review of menstrual irregularity and the COVID-19 vaccine. The questionnaire was divided into three sections: the first one contained six questions for obtaining informed consent and ensuring the respondent met inclusion criteria; the second section consisted of three questions for socio-demographic data; and the last one contained question about AUB in relation to the COVID-19 vaccines. There were eight questions for each vaccine dose. The questionnaire was translated into Arabic by expert physicians fluent in Arabic and English and another one revised it.

The questionnaire's validity and reliability were verified in a pilot study done by the researchers in an interview manner with 20 females chosen randomly from a patient list in an infertility clinic. These 20 females were not included in the study sample. In addition, two OB/GYN consultants one from King Salman bin Abdulaziz Medical City and the second one from Taibah university were reviewed the questionnaire and re-edited some AUB definitions that are attached in the 3rd section of the questionnaire.

Statistical analysis

Data entry and statistical analysis were performed using the Statistical Package for Social Sciences (SPSS), version 26. Descriptive analyses were used to examine all baseline characteristics of the participants. Categorical variables were described as frequency and percentage while numerical variables were described as arithmetic mean and standard deviation (SD). Finally, association and/or difference between the type of the COVID-19 vaccine and incidence of AUB were used Chi-square and Fischer exact test (for small frequencies) to inspect if there is a statistically significant were p-value <0.05 was utilized as a critical value for statistical significance between Pfizer-BioNTech and AstraZeneca Oxford vaccine in AUB rate.

Results

A total of 1912 females responded to the survey. However, only 1533 responders were eligible for inclusion in the study. As illustrated in Figure 1, out of 1533 participants, 988 (64.4%) reported AUB after receiving the COVID-19 vaccine.

Participants' demographic data

As detailed in Table 1, it presents the demographic characteristics of females who got AUB after receiving the COVID-19 vaccine. Out of 988 participants, their age ranged between 15 and 45 years, with a mean age of 31.2±8.4 years. More than half of them (59.4%)

were married and almost a quarter of them either lived in the Central (25.5%), Eastern (25.9%) or Western (26.1%) regions of the Kingdom of Saudi Arabia.

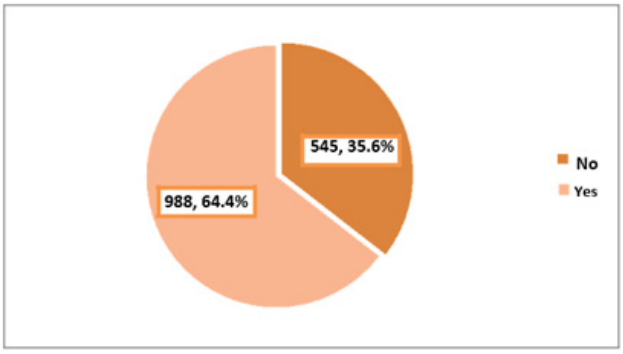

Figure 1 Prevalence of abnormal uterine bleeding among females received COVID-19 vaccine.

Table 1 Demographic characteristics of females with AUB after up-taking of COVID-19 vaccine (n=988)

	Frequency	Percentage
Age (years)		
≤18	42	4.30%
19-30	442	44.70%
31-40	340	34.40%
>40	164	16.40%
Range	15-45	
Mean±SD	31.2 ± 8.4	
Marital status		
Single	372	37.70%
Married	587	59.40%
Divorced	24	2.40%
Widowed	5	0.50%
Living region		
Northern	68	6.90%
Southern	154	15.60%
Central	252	25.50%
Eastern	256	25.90%
Western	258	26.10%

SD, standard deviation

COVID-19 vaccination and AUB

According to the results shown in Table 2, regarding the first vaccination shot, majority of the females had received the Pfizer-BioNTech vaccine (77.1%) and the incidence of AUB was 82.7%, mainly in the form of menorrhagia (38.3%), oligomenorrhea (35.7%), and/or polymenorrhea (24.5%). As regards the second vaccination shot, the majority of those who had the first shot also had the second shot (97.4%). Among them, the incidence of AUB was 88.8%, mainly in the form of menorrhagia (39.1%), oligomenorrhea (34.1%), and/or intermenstrual bleeding (24.2%). Concerning the third dose, only 3.8% of women had the third dose, mainly the Pfizer-BioNTech vaccine (92.1%). Among them, the incidence of AUB was 65.8%, mainly in the form of oligomenorrhea (21.1%), menorrhagia (15.8%) and/or intermenstrual bleeding (15.8%).

Table 2 Abnormal uterine bleeding after up-taking the COVID-19 vaccine among the participants

	Frequency	Percentage
First vaccination shot		
Time since receiving (n=988)		
1-3 months	47	4.8
3-6 months	270	27.3
6-9 months	671	67.9
Type of the vaccine (n=988)		
Pfizer-BioNTech vaccine	762	77.1
AstraZeneca Oxford vaccine	226	22.9
History of any irregularity in period or abnormal uterine bleeding post first dose of vaccine		
No	181	17.3
Yes	817	82.7*
Menorrhagia	313	38.3
Metrorrhagia	100	12.2
Intermenstrual bleeding	114	14
Oligomenorrhea	292	35.7
Menometrorrhagia	91	11.1
Polymenorrhagia	200	24.5
Others	77	9.4
Second vaccination shot		
No	26	2.6
Yes	962	97.4
Time since receiving (n=962)		
1-3 months	210	21.8
3-6 months	609	63.3
6-9 months	143	14.9
Type of the vaccine (n=962)		
Pfizer-BioNTech vaccine	750	78
AstraZeneca Oxford vaccine	212	22
History of any irregularity in period or abnormal uterine bleeding post first dose of vaccine		
No	108	11.2
Yes	854	88.8*
Menorrhagia	334	39.1
Metrorrhagia	94	11
Intermenstrual bleeding	207	24.2
Oligomenorrhea	291	34.1
Menometrorrhagia	75	8.8
Polymenorrhagia	143	16.7
Others	56	6.6
Third vaccination shot		
No	950	96.2
Yes	38	3.8
Type of the vaccine (n=38)		
Pfizer-BioNTech vaccine	35	92.1
AstraZeneca Oxford vaccine	3	7.9
History of any irregularity in period or abnormal uterine bleeding post first dose of vaccine		
No	13	34.2
Yes	25	65.8*
Menorrhagia	6	15.8
Metrorrhagia	5	13.2
Intermenstrual bleeding	6	15.8

Table Continued...

	Frequency	Percentage
Oligomenorrhea	8	21.1
Menometrorrhagia	3	7.9
Polymenorrhagia	5	13.2
Others	2	5.3

SD, standard deviation

*Not mutually exclusive (i.e. the sum exceeded 100%)

Table 3 shown, among women presented with AUB, there was no statistically significant difference between Pfizer-BioNTech vaccine and AstraZeneca Oxford vaccine regarding the incidence of AUB at different vaccination shots.

Table 3 Comparison of type of the COVID-19 vaccine and incidence of AUB among women who had bleeding

	Pfizer-BioNTech vaccine No. (%)	AstraZeneca Oxford vaccine No. (%)	p-value
First vaccination shot			
Abnormal uterine bleeding			
No	126 (16.5%)	45 (19.9%)	
Yes	636 (83.5%)	181 (80.1%)	0.239*
Second vaccination shot			
Abnormal uterine bleeding			
No	79 (10.5%)	29 (13.7%)	
Yes	671 (89.5%)	183 (86.3%)	0.200*
Third vaccination shot			
Abnormal uterine bleeding			
No	11 (31.4%)	2 (66.7%)	
Yes	24 (68.6%)	1 (33.3%)	0.265**

*Chi-square test

**Fischer exact test

Discussion

In this study, 998 females reported AUB in relation to the COVID-19 vaccine. Incidence of AUB was 82.7% after first dose, 88.8% after the second, and 65.8% after the third dose. In a similar study, among 2403 vaccinated females, 98.75% of them reported changes in their menstrual cycle. Compared with unvaccinated females COVID-19 vaccine was associated with a less than 1-day change in cycle length.[18]

Menstrual changes have been reported after both mRNA and adenovirus vectored COVID-19 vaccines. Also in the present study, there was no statistically significant difference between Pfizer-BioNTech vaccine and AstraZeneca Oxford vaccine regarding the incidence of AUB. Suggesting that if there is a connection, it is likely to be a result of the immune response to vaccination rather than a specific vaccine component.[19]

Menstrual cycle timing is regulated by the hypothalamic-pituitary-ovarian axis, which can be affected by life, environment, and health stressors.[20] It could be affected by many situations such as stress, weight gain, hormones, and during the pandemic, studies show that women have significantly higher stress, anxiety, and depression compared to men.[21] In fact, the vaccines activate the immune system, and the activated immune system might attack immune cells and inflammatory molecules which may cause changes in menstrual cycles.[22]

While mRNA vaccines create a robust immune response or stressor, it could temporarily affect the hypothalamic-pituitary-ovarian axis.[23] Similarly, vaccination against human papilloma virus has also been associated with menstrual changes.[16] The menstrual cycle can be affected by immune activation in response to various stimuli, including viral infection: in one study of menstruating women, around a quarter of those infected with SARS-CoV-2 experienced menstrual disruption.[24]

It is important to mention that most people who report a change to their period after vaccination find that it returns to normal the following cycle and, importantly, there is no evidence that COVID-19 vaccination adversely affects fertility.[13]

Our study is the first conducted in Saudi Arabia that spotlights the differences between approved vaccines in Saudi Arabia and their links to AUB. However, it has some limitations, as the data collection was via social media networks, which increased the risk of selection bias and could have some recall bias.

Conclusion

In conclusion, more than half of the participants (64.4%) experienced AUB influenced by COVID-19 vaccine taking. In Saudi Arabia, the Pfizer-BioNTech vaccine was administered in three doses to the vast majority of females. Additionally, increased cycle length and amount, or frequent cycles of fewer than 21 days, or less frequent periods of more than 35 days, are the most common menstrual irregularities observed. Furthermore, in a comparison between the Pfizer-BioNTech vaccine and the AstraZeneca Oxford vaccine regarding the incidence of AUB, there was no statistically significant difference between them. Morever, retrospective studies are required to identify further risk variables and predictors of AUB in relation to the COVID-19 vaccine. Finally, the imperative of women's health clinics in primary health care settings to activate counseling regarding menstrual irregularities before and after the COVID-19 pandemic is recommended.

Acknowledgments

We would like to thank all of the women who took part in this study and made it possible. Special thanks to Aseel AlMandeel, Ayah AlQattan, Hoida Sahl, Khuzama AlGhasham, Siba AlGaidy, and Zahra AlBarak for their assistance in data collection.

Funding

None.

Conflicts of interest

No conflict of interest exists.

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Citation: Jeddo ZA, Hibshi AM, Zaman AY, et al. Abnormal uterine bleeding after receiving COVID-19 vaccine among female in Saudi Arabia. *Obstet Gynecol Int J.* 2022;13(4):244–248. DOI: 10.15406/ogij.2022.13.00656