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Posted Date: 6 December 2024

doi: 10.20944/preprints202412.0531.v1

Keywords: Menstrual cycle; Reproductive Tract Signaling; menorrhea; post-COVID-19 vaccination



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Article

Frequent Menstrual Disturbance Post-COVID-19 Vaccination in Otherwise Healthy Young Women of Reproductive Age Imply Stress and Vaccine Stimulations

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Abstract: The mechanism of menstrual-disturbance post-COVID-19 vaccination is subtle. Although direct interactions with molecular vaccines *per se* is reported, albeit the indirect stimulants, factors, patient demographics involved are not clear. Stress and uterine dysbiosis are largely overlooked despite the similar neurochemicals to that in the gut-brain-axis. Thus, more surveillance on women's responses post-vaccination are needed. We aimed to survey the increasing trends in women's menstrual disturbance post-pandemic vaccination for frequency, potential factors, patients' demographics, and vaccine types involved using a self-administered web-based online public questionnaire sent to different regions of Saudi Arabia. We collected data on 1372 women who developed menstrual irregularity after vaccination and used statistical analysis to examine and identify associated factors. In 1372 females; 61.1% ($n=838$) aged 19-29 years, 94.2% ($n=1292$) Saudi citizens, 66.4% ($n=911$) graduates, 70% ($n=965$) were single, and only 15% ($n=205$) had chronic diseases. About 96.5% ($n=1285$) of 97% ($n=1332$) had two doses, mostly Pfizer's first and second doses (82% and 78, respectively) while ~3.5% ($n=47$) had one. No acute COVID infection appeared. The majority (77%; $n=1057$) reported no issues pre-vaccination except 23% ($n=315$) of whom 43% ($n=135$) reported worsening issues post-vaccination. However, 47.2% ($n=629$) complained only post-vaccination particularly after dose-2 (59% ($n=370$)). These were mostly multiple simultaneously occurring issue in 75% ($n=471$) on cycle-timing disruptions the rest were low frequencies of decreased blood, missed periods, increased blood volume, pain, or increased bleeding. Potential reasons were fear, stress, mental health, and/or emotional problems in 51% ($n=674$), while 53% ($n=701$) were worried about the pandemic. Although proportional differences between age-groups were significant ($P=0.05$), the relative frequency was highest in ages 30-39 (51%). Significant proportional differences in groups of (Pfizer, Moderna, Oxford, Don't know) occurred in outcomes post first (0.047) and second (0.049) doses. However, relative frequencies of outcomes were higher in Pfizer and Moderna. Logistic regression revealed postgraduate [OR=2.11 (0.98-4.72), $P=0.015$] employment [OR=2.18 (0.95-4.86), $P=0.049$] and Pfizer vaccine [OR=2.09 (0.96-4.10), $P=0.029$] two doses [OR=3.21 (1.23-5.21), $P=0.030$] as significant predictors. Mental health and emotional factors such as fear, worries, and emotional problems that triggered stress were also associated [OR=1.78 (0.76-3.21), $P=0.033$]. However, all other variables were not associated with menorrhea disturbances. Thus, menstrual disturbance was significantly associated with vaccinations. Fear, stress, mental health, worries about the pandemic, and/or emotional problems were the major reasons reported. Apart from direct viral interactions, these findings are consistent with the emerging evidence on indirect stress- and microbiome-induced stimulations. This is plausible in the absence of significant factors related to old-age, chronic diseases, and lifestyle-behaviors. These findings have significant implications in women's health, gender-based

interpretation, and vaccine improvement strategies. Future vertical studies on cortisol response and the consequence of uterine-dysbiosis in manipulating immune-response is warranted.

Keywords: menstrual cycle; reproductive tract signaling; menorrhea; post-COVID-19 vaccination

1. Introduction

The aftermath of the most devastating COVID-19 pandemic has brought about several gaps in our understanding of viral-host pathogen interactions. In a short time, the virus spread worldwide, dramatically disrupting what is known about the viral transmission dynamics. However, the massive vaccination campaign efforts of a total of 13.6 billion vaccine doses administered globally brought down the pandemic (WHO coronavirus COVID-19 vaccination data, available online at <https://covid19.who.int/> accessed February 27, 2024) [1]. This was the most rapid and extensive concerted campaign by companies with state-of-the-art mRNA and DNA products, including Pfizer Biontech, Moderna, and AstraZeneca. Nevertheless, as with all vaccines, increased cases of immune reactions such as mucocutaneous or major bleeding have been reported. Prothrombotic syndrome (PS) is one of the most prominent adverse effects. This has been explained by different names such as vaccine-induced immune thrombotic thrombocytopenia (VITT), thrombosis with thrombocytopenia syndrome (TTS), and vaccine-induced prothrombotic immune thrombocytopenia [2]. Although a risk of these reactions has been observed, complaints of menstrual disturbances have been reported, particularly in this region.

Despite the success of COVID-19 vaccines, some studies have been undertaken to gauge public opinion on the COVID-19 vaccine induced menstrual disturbances in different geographies. In Columbia, in a total of 950 women aged 18–41 years with normal cycles, in nearly 50% of those met the criteria, significant number reported influence and/or alterations in their menstrual cycle [3]. Similarly, in a total of 14,153 vaccinated Spanish women (mean age 31.5 ± 9.3 years old), 11,017 (78%) reported menstrual changes, mostly in older ages [4]. A more profound change was reported among 3972 Young Norwegian women aged 18–30, with 36.7 % cycle disturbance; however, heavier bleeding than usual was reported in 95 % both after the first and second vaccine doses, which did not differ in the vaccine brand[5]. In the USA, among 545 premenopausal non-pregnant women who received a COVID-19 vaccine, 25% reported predominantly temporary changes in the menstrual cycle[6]. Furthermore, among 455 Iranian women aged 15–55 years, the prevalence of menstrual disturbances was higher in those with latency and heavy bleeding than in those with other disorders after vaccination. However, while %50 had no complaints, there was increased risk after vaccination, even in menopausal women (>10%)[7]. In Pakistan, 953 among a total of the 953 students, with a mean age of 20.67 ± 1.56 years, over half ($n = 512$, 53.7%) experienced menstrual cycle abnormalities post-vaccination who also developed anxiety significantly ($P = 0.000$)[8]. Among 4,170 administered, side effects were reported in 85.6% of BNT162b2 and 96.05% of ChAdOx1 vaccines, which were more severe in the former vaccine. However, ChAdOx1 vaccines reported mild, moderate, severe, and critical side effects in 30.13, 28.62, 29.73, and 1.53%, respectively. In contrast, most were mild side effects among the majority of BNT162b2 vaccinees (63.92%)[9].

Although global human genetic population structure is diverse, the universality of the reactions against common vaccine component(s) implies the need for further post-vaccine studies on components. A recent review of key safety outcomes with the Moderna vaccine included the common effects, association with menstrual cycle, 10-fold higher risk of myocarditis and pericarditis in young males 18–29 and increased titers of anti-polyethylene glycol antibodies. While these were temporary but serious, the Moderna expert opinion suggested that large-scale epidemiological studies with longer follow-up periods are required for the surveillance of rare safety outcomes[10]. While both vaccines are efficient and safe, reactions were reported to be less frequent with the Pfizer/BioNTech vaccine than with the Moderna COVID-19 vaccine. However, the latter vaccine is easier to transport and store because it is less temperature sensitive[11]. The universality of vaccine reactions is evident

in the vaccine comparisons. Comparisons of T cell, B cell memory, and antibody responses to Moderna mRNA-1273, Pfizer/BioNTech BNT162b2, Janssen Ad26.COV2.S, and Novavax NVX-CoV2373 were performed for six months. One hundred % of individual produced memory CD4⁺ T cells, with cTfh and CD4-CTL highly represented after mRNA or NVX-CoV2373 vaccination. mRNA vaccines and Ad26.COV2.S induced comparable CD8⁺ T cell frequencies, which were detectable only in 60-67% of subjects at six months. While substantial antibody decline was observed in mRNA vaccines, memory T and B cells were comparatively stable. A unique feature of Ad26.COV2.S (JJ) immunization is the high frequency of the CXCR3⁺ memory B cells. These findings imply relevant molecular mimicry in other microbial-pathogen interactions, which is an important confounding factor[12]. In this regard, the mRNA vaccine performed well and implied minimal reactions over whole-virus vaccines across vaccination phases[13].

There is ample evidence regarding the relationship between “microbial endocrinology-dysbiosis and menstrual cycle disturbance. Similar to the lower female reproductive tract (FRT), signatures of biomass microbiota exists in the upper FRT [14–18] that influence signal transductions through mental health stimulations. In this context, the association between psychological stress and menstrual cycle has been well established. Specifically, lifestyle changes during the COVID-19 pandemic affected the patterns and symptoms of the menstrual cycle in women[17–23]. Similarly, there are several reports on the link between mental health stressors and neurogastrointestinal issues such as irritable bowel diseases and irritable bowel syndromes where the exact neurochemicals are involved in eliciting gut-brain axis mis-signalling [24–26]. Thus, it is plausible that, similar to the gut and other body microbiome compositions, concerted signaling in upper FRT could results in an inflammatory cascade that manipulates cycle signalling. It is increasingly becoming evident that the array of signals during menstruation is subject to much more complex internal and external senses that regulate the timed patterns of the menstrual cycle. However, there is a paucity of high-quality data regarding the nature of host-viral(or viral components) interactions on reproductive system in women at different geographies owing to the normal local genetic variations in the structure and balance of microbial signatures and the nature of stressors. Since the region has one of the most fascinating stable population structures and a stable microbiome composition, we aimed to study the factors and patterns of disruptive menorrhoea post-COVID-19 vaccination.

2. Materials and Methods

2.1. Study Design

This study was a cross-sectional design and used a web-based online public questionnaire sent to different regions of Saudi Arabia. A gap was considered from the time of vaccine administration (December 17, 2020) until the expected significant antibody titer was obtained (Apr to Dec 2021). All responses were recorded after this period including second dose from Jul 2021.

2.2. Sample Size and Sampling Procedure

The sample was a self-administered, non-probability sample of Saudi Arabian social media users. The web-based data collection tool was designed using Google Forms and distributed via social media applications, mainly WhatsApp and Twitter. The invitation letters were sent via WhatsApp groups and posted on Twitter community groups. The invitation letter explained the aim of the study and the approximate time required to complete the questionnaire. Participants were asked to distribute the survey on their social networks. A total of 1467 participants were initially screened from responses; responses before the critical gap period were not considered, and those who had signs of pregnancy or other serious issues made up the actual number 1372.

2.3. Data Collection Tool and Interpretations of Patients' Responses

The questionnaire comprised of four domains: consent forms, demographic information, health status, and covid-19 vaccine related questions. The questionnaire was prepared in English and was translated into Arabic. Language validity was undertaken by retranslating the Arabic version of the

questionnaire into English to ensure that the original meaning of the questions was preserved (back translation). This was done by the authors, who are bilingual speakers of both English and Arabic.

The structure of the questionnaire was designed to obtain detailed information around vaccination and evaluate the patients’ responses to identify stress conditions. However, this being a surveillance study, specific clinical and biomarker assessment of patients for stress condition was out of the scope of this study. Assessment of stress conditions was more accurately estimated by the psychiatric and obgyn specialists coauthors using the “self-reports”. They based this on important triangulated domains vital to the stress including the presence of environmental stressors, respondents psychological and biological reactions to stressors, and the length of time over which the stressor or stress response occurred. Patients’ response to the physical (pandemic/vaccination environmental) stressors and psychological stressors as a response to intense overall fear and emotional problems were accounted for. This included collection of data on different types of mental health problems that are likely to trigger stress and the consequences on menorrhea such as anxiety, fear, emotional problems, and worries.

2.4. Ethics Approval

Ethics approval was provided by the Research Ethics Standing Committee of the University of Hail #UOH 2021-631. All participants were asked to provide consent before participating in the study.

2.5. Statistical Analysis

The updated Statistical Package for Social Sciences software (IBM SPSS; Version 24 SPSS version 23.0, for Windows (SPSS, Inc., Chicago, IL, USA]) was used for data analysis. Descriptive and stratified analyses were conducted, and absolute numbers, proportions, and graphical distributions are presented. We conducted Chi square statistical tests and showed *p*-values, where appropriate (*p*-value <0.05, considered statistically significant). In addition, we have carried out a multivariate logistic regression analysis to identify the risk factors associated with menorrhea disturbances in females.

3. Results

We examined responses of 1372 females who mostly comprised the following groups: 61% (*n*=838) were aged 19-29 years, 94% (*n* = 1292) were Saudi citizens, 66.4% (*n*=911) were graduates, 70%(*n*=965) were single, and only 15%(205) had chronic diseases, mostly in the respiratory system (*n*=33/205;16%). Most of the respondents (30%) were from the eastern region of KSA, while similar frequencies, i.e., 22.8% (*n*=305), 22.7% (*n*=303), and 21.6%(*n*=289), were from Northern, Central, and Western regions of KSA, respectively, and only 5.4% (*n*=73) from southern region. Of the respondents, 15% had chronic diseases, and 14% had taken some form of medication. The detailed characteristics are shown in Table 1.

Table 1. Baseline characteristics of patients.

Characteristics (<i>n</i> =1372)		Frequency	Percent
Age (years)	<18	216	15.7
	19-29	838	61.1
	30-39	175	12.8
	40-50	143	10.4
Nationality	Non-Saudi	80	5.8
	Saudi	1292	94.2
Region	Central Region	303	22.1
	Eastern Region	402	29.3
	Southern area	73	5.3
	Northern area	305	22.2
	Western Region	289	21.1

Educational	No primary education	7	0.5
	Elementary or Intermediate	70	5.1
	Secondary	331	24.1
	Graduate	911	66.4
	Postgraduate	53	3.9
Employment status	Employed	182	13.3
	House wife	306	22.3
	Retired	25	1.8
Social status	Married	407	29.7
	Single	965	70.3
Chronic diseases	No	1167	85.1
	Yes	205	14.9
Type of Chronic diseases (n=205)	Cardiovascular disease	3	1.5
	Blood diseases	28	13.7
	Diabetes	15	7.3
	Hypertension	20	9.8
	Kidney disease	2	1.0
	Respiratory system diseases	33	16.1
	Rheumatic diseases	10	4.9
	Liver diseases	1	.5
	Other diseases	60	29.3
	Multiple diseases	33	16.1
Medications	No	1177	85.8
	Yes	195	14.2
Type of medications used (n=195)	Anti-hypertensive medications	24	12.3
	Insulin	22	11.3
	Cardiovascular medications	4	2.1
	Salbutamol	11	5.6
	Other medications	107	54.9
	Multiple medications	27	13.8

Table 2 shows whether the respondents had SARS-CoV-2 viral infection, the vaccination detail types of vaccines taken, or if they were infected with the virus despite vaccination. Most of the respondents were not infected with acute COVID-19 syndromes (77%) with SARS-CoV-2 before vaccination except 314(23%) who had with similar common but aggravated symptoms. About 96.5% (n=1285) of the 97% (n=1332) vaccinated reported taking two doses of the COVID-19 vaccine while only approximately 3.5% (n=47) took only one dose. No acute COVID syndromes were reported except for the reactions and side effects. The overwhelming majority had taken Pfizer's first and second doses of COVID-19 vaccine (82% and 78, respectively) and the other two vaccines were taken by low percentages of respondents. Figure 1 and Table 2 illustrate this information.

Table 2. Participant responses to Covid-19 and its vaccine-related questions.

		N	%
Infected with SARS-CoV-2	No	1058	77.1
	Yes	314	22.9
Received COVID-19 vaccine	No	40	2.9
	Yes	1332	97.1
Doses taken (n=1332)	One dose	47	3.5
	Two doses	1285	96.5
First dose taken (n=1332)	Pfizer	1091	81.9
	Oxford	209	15.7

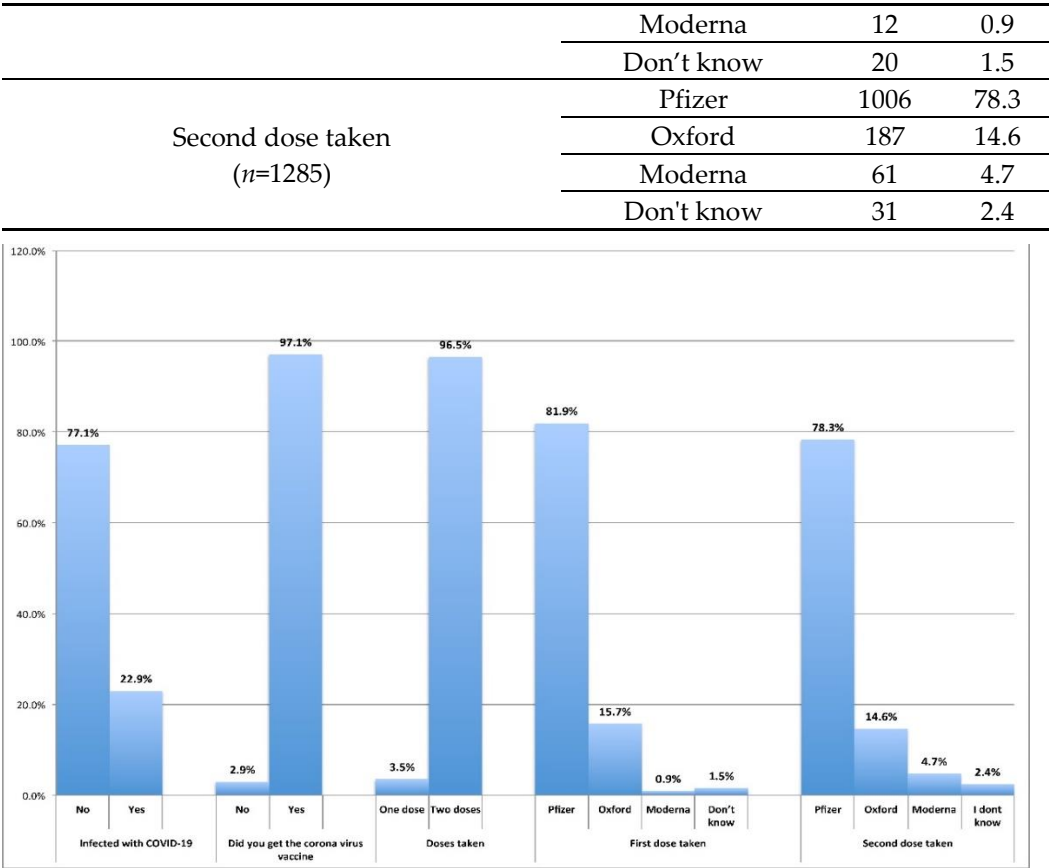


Figure 1. Respondents’ profiles on SARS-CoV-2 infection and COVID-19 vaccine doses.

The details of the major issues related to the COVID-19 vaccine administration are shown in Table 3 and Figure 2. The overwhelming majority (77%; $n=1057$) reported they experienced no menstrual problems before vaccination except 23% ($n=315$) who have had issues. Of the latter group, 43% ($n=135/315$) reported their menstrual problems worsened after vaccination. However, 47.2%($n=629$) of all respondents experienced specific menstrual problems only after taking the vaccine. Of these, 59% ($n=370$) reported the issues increased after the second dose and 41% ($n=259$) had them after the first dose. The majority (75%; $n=471$) reported occurrence of multiple issues together in their cycles. Independent occurrence of each issue was also surveyed; these were mostly irregularities in cycle times (8.4%; $n=53$), followed by approximately 2 to 4% either in decreased days or amount of blood, missed periods, increased blood volume, or increased bleeding days. More importantly, 51% ($n=674$) of the participants thought that the menstrual problems were due to fear, stress, and/or emotional problems. A similar percentage of respondents (53%; $n= 701$) indicated their worries about the pandemic were their reason [Table 3, Figure 2].

Table 3. Predominant menstrual problems related to the COVID-19 vaccinations.

		N	%
Suffered from any menstrual problems before taking the vaccine (<i>n</i> =1332)	No	1057	77.0
	Yes	315	23.0
Get worse after taking the vaccine (<i>n</i> =315 of respondents said Yes)	No	180	57.1
	Yes	135	42.9
Did you have any menstrual problems after taking the vaccine (<i>n</i> =1332)	No	703	52.8
	Yes	629	47.2
After the first dose		259	41.2

Time of menstrual problems (of <i>n</i> =629 who responded Yes to issues after vaccination)	After the second dose	370	58.8
Types of menstrual problems reported by participants (<i>n</i> =629)	Decrease the time between the two menstrual cycles	12	1.9
	Decrease amount of blood	18	2.9
	Increase amount of blood	23	3.7
	Decreased number of days of bleeding	7	1.1
	Increase in numbers of days of bleeding	12	1.9
	Irregular menstruation	53	8.4
	Missed periods after taking vaccine	26	4.1
	Severe pain than usual	7	1.1
Simultaneous multiple menstrual problems		471	74.9
Menstrual problems happened due to fear, worries, stress and or emotional problems (<i>n</i> =1332)	Yes	674	50.6
	No	658	49.4
Worried about pandemic (<i>n</i> =1332)	Yes	701	52.6
	No	631	47.4

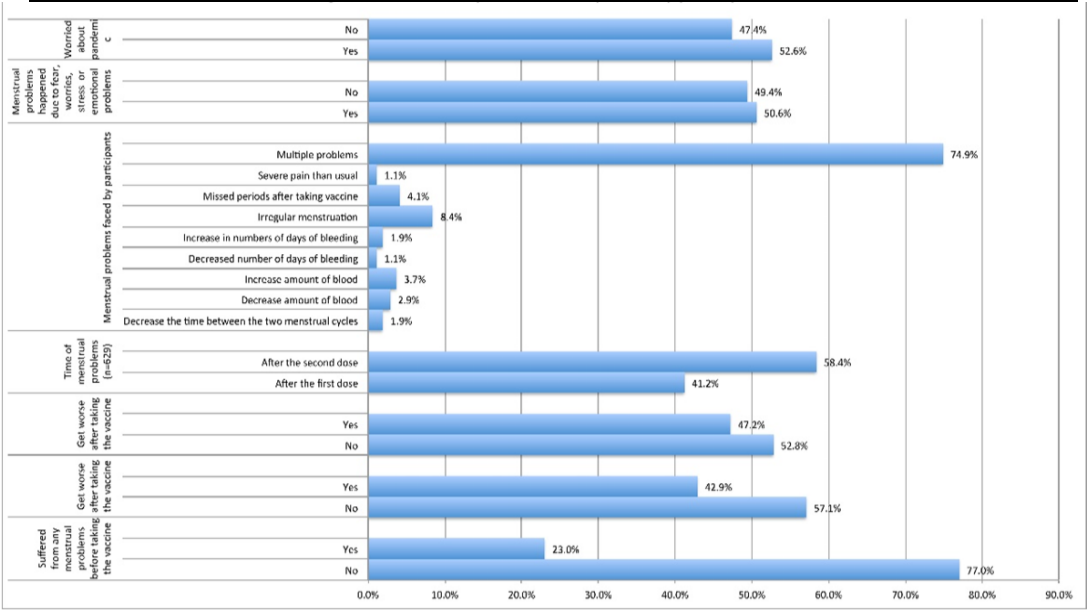


Figure 2. Different types of major menstrual problems related to COVID-19 vaccine in participants.

Analysis of the relationship between menstrual problems and age indicated that the difference in proportions between age groups was significant regarding outcomes (menstrual problems) ($P=0.05$). Although age groups had similar relative frequencies, it was higher in age group 30-39 (51%). No statistically significant differences were observed in menstrual problems between nationalities ($P=0.833$) or social status (P value $=0.592$). This study also found that menstrual problems after vaccination did not show any statistically significant association with the presence of chronic diseases ($P=0.592$) or those who took medications ($P=0.913$). Participants who received Moderna and Pfizer as the first doses reported more menstrual problems. However, the statistical analysis indicated that there were significant differences in proportions between the study groups (Pfizer, Moderna, Oxford, Don't know) regarding outcomes (menstrual problems) in the first (0.047) as well as in the second dose (0.049). Nevertheless, frequencies of mild menstrual problems were higher among females who received both doses of Pfizer and Moderna [Table 4, Figure 3].

Table 4. Relationship between menstrual problems after taking the vaccine with baseline characteristics.

		Menstrual problems after taking the vaccine*		<i>p</i> value
		*(<i>n</i>) for each character = (yes+no)		
		No	Yes	
Age	12-18	109	95	0.05
		53.4%	46.6%	
	19-29	439	380	
		53.6%	46.4%	
	30-39	85	88	
40-50	49.1%	50.9%		
	70	66		
		51.5%	48.5%	
	Non-Saudi	41	35	0.833
53.9%		46.1%		
Nationality	Saudi	662	594	
		52.7%	47.3%	
Social status	Married	214	183	0.592
		53.9%	46.1%	
	Single	489	446	
		52.3%	47.7%	
Chronic disease	No	593	542	0.351
		52.2%	47.8%	
	Yes	110	87	
		55.8%	44.2%	
Taking medication	No	605	540	0.913
		52.8%	47.2%	
	Yes	98	89	
		52.4%	47.6%	
First dose	Pfizer	561	530	0.047
	(<i>n</i> =1091)	51.4%	48.6%	
	Oxford	121	88	
	(<i>n</i> = 209)	57.9%	42.1%	
	Moderna	6	6	
	(<i>n</i> = 12)	50.0%	50.0%	
I don't know	15	5		
	(<i>n</i> = 20)	75.0%		25.0%
Second dose	Pfizer	515	491	0.049
		51.2%	48.8%	
	Oxford	106	81	
		56.7%	43.3%	
	Moderna	32	29	
		52.5%	47.5%	
	I don't know	23	8	
74.2%		25.8%		

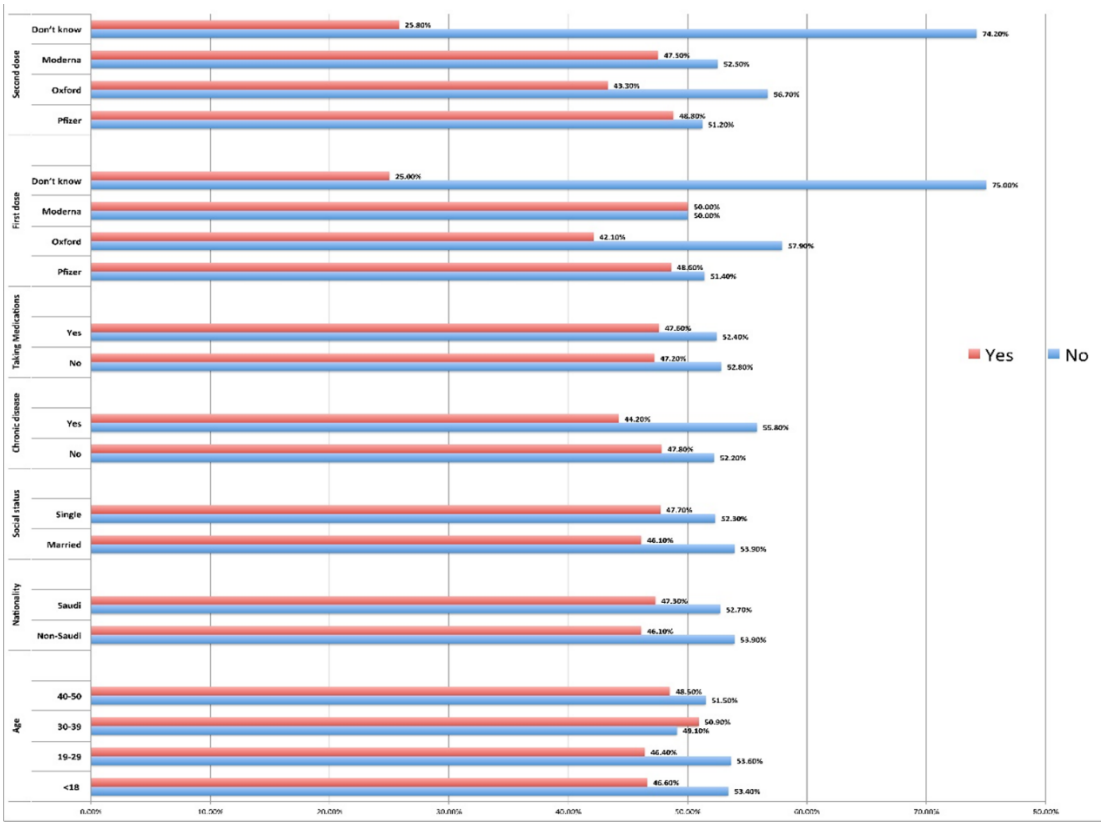


Figure 3. Relationships between menstrual problems after taking the vaccine and baseline characteristics.

A multivariate logistic regression analysis was carried out to identify the risk factors associated with menorrhagia disturbances in females (Table). The study included various independent variables such as age, nationality, region, education level, employment status, social status, presence of chronic diseases, medication history, vaccination status (type and doses), pre-existing menstrual problems, and emotional factors related to the COVID-19 pandemic. Among these variables, education level and employment status emerged as statistically significant predictors, with postgraduate education [OR=2.11 (0.98-4.72), P = 0.015] and employment [OR=2.18 (0.95-4.86), P = 0.049] being associated with increased odds of menorrhagia disturbances. Additionally, Pfizer vaccine [OR = 2.09 (0.96-4.10), P= 0.029] and experiencing menstrual problems after the second vaccine dose [OR=3.21(1.23-5.21), P = 0.030] were also significant predictors. Mental health and emotional factors such as periods affected by fear, worries, and emotional problems other similar issues that triggered stress, were or also associated with increased odds of menorrhagia disturbances [OR=1.78 (0.76-3.21), P=0.033]. However, variables such as nationality, region, chronic diseases, medication history, vaccine status, pre-existing menstrual problems, did not show significant associations with menorrhagia disturbances.

Table 5. Logistic regression to predict the risk factors of menorrhagia disturbances in female .

Dependent variable = menorrhagia disturbances	Odd's Ratio	95% confidence interval		p value
Age(=19-29years)	2.07	0.66	6.50	0.209
Nationality	0.57	0.25	1.29	0.181
Region	1.17	0.62	2.19	0.624
Education=Postgraduate	2.11	0.98	4.72	0.015
Employment	2.18	0.95	4.86	0.049
Social status	1.76	0.94	3.31	0.076
Chronic diseases	0.91	0.47	1.74	0.781

Medications	0.95	0.65	1.39	0.775
Type of vaccine taken= Pfizer	2.09	0.96	4.10	0.029
Doses taken= 2 doses	1.59	0.74	3.29	0.014
Suffered from any menstrual problems before taking vaccine	0.91	0.45	2.21	0.412
Menstrual problems occurred after the second dose	3.21	1.23	5.21	0.030
Period is affected by fear, worries, stress, or any emotional problems	1.78	0.76	3.21	0.033

4. Discussion

The findings of this study provided valuable insights into the impact of vaccination on menstrual health and highlighted the need for further research. We have shown that the major menstrual cycle problems were significantly associated with COVID-19 vaccination ($P=0.049$) either in those who had (43%) or had no issues prior to vaccination. The evidence became stronger with increasing complaints after the second dose, consistent with other studies[3]. Examination of menstrual disruptions in the context of diverse factors, including patients’ demographic characteristics, revealed significant findings. For instance, menstrual issues, with emphasis on cycle timing disturbances, were also associated to young women in reproductive age ($P=0.0575$) who were otherwise healthy. Although SARS-CoV-2 does not adversely affect issues such as ovarian reserve[27], vigilance has become imperative regarding how the virus disrupts menstrual cycles in young healthy women, in contrast to reported issues in older ages [28]. These findings are also interesting in the context of the previously reported youth and female resistance to SARS-CoV-2 infections[29]. However, the notion on women’s resistance to infections is partly due to estrogen, which curtails pro-inflammatory cytokines[30], albeit distinct evidence exists on immune modulation by uterine microbiome [14,31] with further proof of concept from those undergoing hysterectomy[15].

In the current study, stress was also a major factor implying potential concerted actions through dysbiosis. Majority of the patients reported fear, stress, mental health, worries about the pandemic, and/or emotional problems were the major reasons for their menstrual issues. This is in agreement with the growing evidence on stress- microbiome induced immune-modulations. We and others have previously reported on stress, mental health, and/or anxiety as leading factors in the cycle and immune reaction issues in this and different regions[32,335]. Thus, while the immune response to infections is often envisioned as similar in both sexes, the FRT imparts sex bias differences with increased autoimmune reactions in women[30]. Thus, there is an association between increased menstrual disturbances, vaccines, and mental health issues. However, the exact mechanism(s) on a potential concerted action is not yet clear.

In this study, the majority of participants had no menstrual problems before vaccination, and in those who had worsened their menstrual problems worsened after vaccination. However, the issues were predominantly multiple transient nonspecific problems that specifically simultaneously occurred, except for the cycle irregularity in the timing, which was the highest common issue. The minor issues ranged from 2 to 4%, either in decreased days or amount of blood, missed periods, increased blood volume, or increased bleeding days. A systematic review represented the most contemporary and largest evidence on the predictors and rates of menstrual problems after COVID-19 vaccination in 78 138 patients. In the aforementioned study, although 52.05% revealed menstrual problems post-COVID-19 vaccination, there were significant heterogeneities, and most studies were unable to report on distinct profiles of menorrhagia (heavy bleeding), oligomenorrhea (irregularities), and dysmenorrhea (pain during period). Furthermore, in three studies, advanced age predicted menstrual problems after the COVID-19 vaccination. Other predictors included smoking, drinking, addiction, history of an unstable family, and pregnancy [34]. Given that these latter issues are largely irrelevant in women of this region, it is plausible that stress and dysbiosis in the female reproductive tract were inducers. However, despite the similar complexity and structure of neurophysiology and neurochemicals in the reproductive tract and gut-brain axis dysbiosis, the involvement of the former has been overlooked. More importantly, recent studies employing pyrosequencing concluded that

the upper FRT is not sterile. Significant differences were found in microbial communities in the endocervix and endometrium; these signatures' compositions were out of balance in women with menorrhagia versus dysmenorrhea ($p = 0.024$) [16]. Thus, "post-acute COVID-19 syndrome", as dubbed by Meringer and Mehendru (2022) [35] as well as the post-COVID-19 vaccination syndrome have created important areas for research in the aftermath of SARS-CoV-2 pandemic. The post vaccination menorrhagia syndrome in this study is potentially induced by vaccination and the concerted actions of stress and FRT dysbiosis in the absence of major predictors such as smoking, drinking, addiction, history of unstable family, and pregnancy issues in this region. These findings have similar mechanisms of stress induced gut microbiome dysbiosis and the consequences of gastroesophageal and inflammatory bowel syndromes post-COVID-19 (IBS)[1528–323334].

5. Conclusions

The devastating COVID-19 pandemic has created several gaps in host-pathogen interactions during acute as well as long-COVID phases including post-vaccination syndromes. While many syndromes were directly associated to host-viral interaction, the gender-specific mechanism(s) such as to that of menstrual-disturbance post-COVID-19 vaccination has been quite subtle. In this study, we have surveyed and identified major factors and patterns of disruptive menorrhagia post-COVID-19. We present statistically significant evidence that menstrual disturbances were associated to COVID-19 vaccinations in healthy, mostly young women of reproductive age. In addition to vaccine, fear, stress, mental health, worries about the pandemic, and emotional problems were the major factors reported. These are consistent with the emerging evidence on the concerted actions of cortisol and dysbiosis on cycle mis-signaling. This is plausible in the absence of significant factors related to old-age, chronic diseases, and lifestyle-behaviors. The findings have significant clinical and public health implications and vaccine improvement strategies. Future vertical studies on cortisol response and uterine-dysbiosis in mis-signaling is warranted.

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Funding: This research received no external funding.

Institutional Review Board Statement: The standard guidelines were followed during this research according to the IRB protocols. The ethical application for this study was reviewed and approved by the Research Ethics Committee (REC at the University of Ha'il (KSA)), dated 22/10/2020 and endorsed by University President letter number Nr. 13675/5/42 dated 08/03/1441 H; for Deanship Project RG20064, REC# H-2022/21-187. The KACST Institutional Review Board (IRB) registration numbers are H-8-L-074 IRB log 2021-11, which also approved the study.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: no additional data is available elsewhere other than this manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

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