The effect of BNT162b2 SARS-CoV-2 mRNA vaccine on menstrual cycle symptoms in healthy women

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Synopsis: Significant rates of menstrual changes including irregular bleeding were found following the BNT162b2 SARS-CoV-2 mRNA vaccination

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Abstract

Objective: To investigate the impact of the SARS-CoV-2 mRNA BNT162b2 vaccine on women's menstural cycle.

Methods: In this questionnaire-based cross-sectional study, we assessed menstrual pattern and changes of women who completed the SARS-CoV-2 mRNA BNT162b2 vaccine three months before and after receiving the vaccine. Included were women aged 18-50 without known gynecological comorbidities who regularly monitor their menstruation through electronic calendars. All participants competed a detailed questionnaire on their menstrual symptoms including information on any irregular bleeding. To minimize bias, each woman served as a self-control before and after vaccination. Primary outcome was rate of irregular bleeding following vaccination and secondary outcome was presence of any menstrual change, including irregular bleeding, mood changes or dysmenorrhea following the vaccine.

Results: A total of 219 women met the inclusion critieria. Of them, 23.3% (n=51) experienced irregular bleeding following the vaccine. Almost 40% (n=83) of study participants reported any menstrual change following vaccination. Parity was positively asssociated with irregular bleeding with 50% (n=26) of those suffering from irregular bleeding being multiparous as compared to only 31.5% (n=53) of women with no irregular bleeding (nulliparous 46% vs 60%, multiparous 50% vs 31%, rest 4% vs 8%, p=0.049). The presence of medical comorbidities was also significantly higher among

patients who experienced irregular bleeding (20.0% vs 6.0%, p=0.003).

Conclusion: Our study shows relatively high rates of irregular bleeding and menstrual changes after receiving the SARS-CoV-2 mRNA BNT162b2 vaccine. Further research is needed to confirm our findings and to better characterize the magnitude of change and any possible long term implications.

Introduction

Coronavirus disease 19 (COVID-19), caused by SARS-CoV-2 infection was decalred by the World Health Organization a pandemic in 2019(1). In an effort to minimize morbidity and mortality, vaccines based on different platforms were rapidly devolped. Among them, included are two novel mRNA-based vaccines: mRNA-1273 of Moderna and BNT162b2 of Pfizer-BioNTech who received Emergency Use Authorization by the Food and Drug Administration (FDA) in December 2020.

Great efforts are currently ongoing to characterize the safety and adverse effect profile of these recently approved COVID-19 vaccines.

Reported side effects of the BNT16b2 mRNA vaccine include fatigue, headache, muscle pain, joint pain, chills, tachycardia, fever, gastointestinal discomfort, vomiting and myocarditis(2-6).

Shortly after mass vaccination began, public concerns have been raised on possible menstrual cycle changes. Reported changes include changes in bleeding pattern, menstrual period length alteration, intermenstrual spotting, and menorrhagia(7,8). In response, health authorities called for more research on the effect of the COVID-19 vaccine on menstrual cycle

changes(9,10).

Israel was amongst the first countries to initiate a mass vaccination campaign using the BNT162b2 mRNA vaccine, with the vast majority of the adult population receiving two doses of the vaccine (11). Shortly after the initiation of the vaccination campaign, claims about possible changes in the menstrual cycle have arisen among Israeli women (12) leading to concerns and anxiety regarding vaccine safety and possible implications on fertility (13). Hence, we aimed to investigate the possible impact of the BNT162b2 mRNA SARS-CoV-2 vaccine on women's menstural cycle.

Methods

We conducted a survey-based cross-sectional study. The study was carried out at a tertiary medical center between July 2021 and October 2021. Inclusion criteria were women aged 18-50 who completed the two-dose series of the SARS-CoV-2 BNT162b2 mRNA vaccine. We excluded women who had previously contracted COVID-19, were pregnant or lactating during the study period, or had background hematologic or gynecologic diseases. Women were asked to retrospectively report their menstrual pattern and symptoms during the three-month period before the first vaccine dose administration and during the three-month period after the second vaccine dose administration. To minimize bias, each woman served as a self-control, and each woman's bleeding pattern and symptoms were compared between the three cycles she reported before being vaccinated and the three cycles reported after being vaccinated.

All women completed a questionnaire including: (1) demographic data; (2) medical and gynecologic background; and (3) menstrual symptoms including:

duration of menses, frequency, regularity and volume, as well as premenstrual symptoms. We included only women who regularly follow their periods with an electronic diary, menstrual cycle tracking Apps or any other written documentation.

The primary outcome was the rate of irregular bleeding following vaccination, defined as early or delayed menstruation of 7 days or more than the expected time of menstruation. Secondary outcome was the presence of any menstrual change, defined as one of the following: irregular bleeding (as aforementioned defined in the primary outcome), mood change during the bleeding following vaccination, or dysmenorrhea after vaccination.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (version 25, IBM Corporation, NY, USA). Patient demographics and characteristics, as well as menstrual characteristics were reported by means ± standard deviation or percent, as appropriate. We further compared rates of irregular bleeding and any menstrual change according to baseline charactaristics, using unpaired t-test and chi-square test, as appropriate. A P-value of less than 0.05 was considered statistically significant for all analyses.

Ethical approval

Approval was obtained from the institutional review board (IRB) of our medical center before recruitment (0490-21-HMO 7 JULY 2021). Informed consent was given by all participants.

Results

We recruited 241 women to this study. Of them, 2.2% (n=5) were excluded due to incomplete response and 7.7% (n=17) were excluded due to background disease (polycystic ovarian syndrome, n=11; uterine fibroids, n=4; endometriosis, n=1 and hematologic disease, n=1). Two hundred and nineteen women met the inclusion criteria. Baseline characteristics of women are showed in Table 1. Mean age was 29.6±8.6 years and mean parity was 1.1±1.5. All participants completed the two-dose series of the BNT161b2 mRNA vaccine with a mean interval of 22.1±5.1 days between doses.

Distribution of baseline menstrual characteristics is shown in Table 2. The average menstrual cycle length before the vaccine was 29.4±7.6 days with duration of menses of 5.0±1.3 days.

Of the 219 women who participated in the study, 23.3 % (n=51) experienced irregular bleeding following the vaccine. Of them, 39.2% (n=20) and 60.8% (n=31) reported irregular bleeding after the first and second dose of the SARS-CoV-2 BNT162b2 mRNA vaccine, respectively. Of the 51 women who experienced irregular bleeding, 66.7% (n=34) reported irregular bleeding that preceded their estimated menstrual date (mean 9.9 ± 3.0 days) and 33.3% (n=17) reported a delay in their expected menstrual date (mean 12.3±6.3 days). Irregular bleeding was reported as light in its severity in 47% (n=24), moderate in 21.6% (n=11) and heavy in 31.4% (n=16). Among those who reported irregular bleeding, 31.4 % (n=16) reported persisted irregular bleeding during the three-month period following vaccination, whereas 68.6% (n=35) reported a transient change which did not continue throughout the study period.

Thirty-seven percent (n=83) of study participants reported any menstrual change (including irregular bleeding, mood changes or dysmenorrhea) following vaccination.

Nearly 68% (n=55) of study participants reported dysmenorrhea following vaccination. Amongst them, 47.3% (n=26) reported new-onset dysmenorrhea or increase in the severity of pre-existing dysmenorrhea. Other menstrual symptoms were reported by 55.5% (n=45) of study participants after receiving the vaccine, including: abdominal pain (n=24); pelvic pain (n=11); appearance of new acne (n=11); breast tenderness (n=4); hot flushes (n=1).

Mood changes associated with menstruation after the vaccine (that were not reported before the vaccine) were reported by 9.6% (n=21) of women.

There was no significant association between use of oral contraceptive pills and irregular bleeding or any menstrual change following the vaccine: 18% (n=11) of women who used oral contraceptive pills reported irregular bleeding following the vaccine, as compared to 25.5% (n=40) of women which did not use oral contraceptives (P=0.28). Twenty-nine percent of the women (n=18) which used oral contraceptives pills reported Any menstrual change, as compared to 41.4% (n=65) of women who did not use oral contraceptives pills (P=0.12).

A comparison of rates of irregular bleeding and any menstrual change according to baseline characteristics of women is presented in Table 3.

The rate of parous women reporting irregular bleeding was significantly higher, as compared to nulliparous women with 50% (n=26) of those suffering from irregular bleeding being multiparous as compared to only 31.5% (n=53) of

women with no irregular bleeding (nulliparous 46% vs 60%, multiparous 50% vs 31%, rest 4% vs 8%, p=0.049). The presence of comorbidities was also significantly higher (20.0% vs 6.0%, p=0.003) among patients who experienced irregular bleeding. The only variable that was found to be significantly associated with the composite outcome of any menstrual change was use of regular medications (p<0.001). Among the participants who reported any menstrual change, women using medications regularly were less likely to report any menstrual change. Any menstrual change was reported in 13.3% (n=11) of women using regular medications, as compared to 53% (n=72) of women not using medication (P<0.001).

Discussion

In the current study assessing the effect of the SARS-CoV-2 mRNA BNT162b2 vaccine on menstrual changes, almost 40% (n=83) of women experienced menstrual changes and almost one fifth reported irregular bleeding following the vaccination. Higher parity and the presence of medical comorbidities were associated with the occurrence of irregular bleeding following vaccination.

Few recent studies examined the influence of COVID-19 vaccines on the menstrual cycle. In a large survey web-based software platform designed study of women without known gynecological disorders Lee et al reported high rates of heavier and longer menstrual bleeding after vaccination (14). Changes in the timing and amount of menses after receiving the SARS-CoV-2 mRNA BNT162b2 vaccine was reported also in another retrospective study (15). A study from the UK, specifically assessing women with regular periods prior to the vaccine, has reported a 20% rate of menstrual changes, up to 4 months

after receiving the first dose of the vaccine (16). Of note, these studies suggest that menstrual changes are not specific to a particular COVID-19 vaccine.

The effect of the vaccine on the menstrual cycle may be explained by several mechanism. Inflammatory and immunologic mediators, secreted by endometrial cells, play key roles in endometrial breakdown, regeneration and repair (17). The vaccine's mechanism of action involoves modulation of the immunologic milieu (18) and this may provide a possible explanation for the association between vaccination and menstrual changes. Previous studies showing the effect of certain vaccines on the immunogical and hormonal environment, may lend support to this hypothesis (19,20,21,22). The effect of stress on menses is well established (23) with some studies showing that stress and/or emotional instability may have an effect on the estrogen-progesterone balance, thus leading to irregular bleeding and other menstrual symptoms (24). Recent studies have described vaccine-associated stress (25), which may also partially account for the association between vaccination and menstrual changes. In addition, a possible association between the SARS-CoV-2 mRNA BNT161b2 vaccine and menstrual cycle changes may be also explained by changes in sex hormones regulation. Ovulation is regularly controlled by Follicle Stimulating Hormone and Luteinizing Hormone levels. Under severe illness, the levels of these hormones are altered, as described by Li et al (26) in a study assessing 91 women who had been affected by SARS-CoV-2, suggesting their possible role in this regard.

Accordingly, we estimated that women who use hormonal therapy will be less affected by the vaccine due to suppression of the normal hormonal axis. However, in our study 22% of women who used hormonal therapy reported

irregular bleeding or any menstrual change, though no significant correlation was found. Similarly, Male et al (17) reported no association between hormonal therapy and timing of the next period, but described that the period following vaccination was different from usual-mostly heavier in 42% of women participated. Albeit Li et al described longer and heavier menstrual bleeding for hormonal therapy users during the period following vaccination (26).

Our finding of higher rates of irregular bleeding in parous women warrants further confirmation and research. The association found between irregular bleeding following vaccination and the presence of comorbid conditions is not surprising, given the large body of literature reporting menstrual changes in those with non-gynecologic comorbidities (27).

Concerns were raised about the possible influence of the SARS-CoV-2 mRNA BNT162b2 vaccine on women's fertility. These concerns were refuted with the publication of a number of articles as well as an official statement from The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal Fetal Medicine (SMFM) stating clearly that the vaccine has no negative effect on female fertility (28,29). Therefore, even if the vaccine is associated with temporary menstrual changes, it is extremely unlikely that this has any effect on current or future fertility. This is further supported by the current study finding that among those who experienced irregular bleeding following vaccination, the occurrence of any abnormal symptom was mostly transient and resolved during the study period.

Importantly, significant menstural changes are reported also after SARS-CoV-2 infection (26,30). In a prospective study of 127 women, Khan et al (30) reported irregular menstruation, increase of premenstrual symptoms and

infrequent menstruation after severe illness with SARS-CoV-2. Among 177 women who recorded their menstural pattern Li et al (26) described that nearly 20% of patients exhibited menstrual volume decrease or cycle length alterations.

The main limitation of our study is its retrospective nature. This carries an inherent selection bias due to voluntary recruitment of participants. To address this limitation, we mostly recruited patients who attended our clinic. Another limitation is a possible recall bias. In an attempt to minimize this possibility, when menstrual changes were reported, we asked the study participant to attach documentation via menstrual cycle tracking apps so we could validate the report. Another limitation is the possibility of personal interpretation of some of the questions which could not be validated by a physician. To address this, the questionnaire was validated on a group of women as well as on a group of gynecologists before recruiting commenced. Finally, the lack of a control group of women is an additional potential caveat. Our study was conducted on women who received two doses of the SARS-CoV-2 mRNA BNT162b2 vaccine. As such, our findings may not be applicable for other COVID-19 vaccines. However, similar findings were reported in two recently published studies (16,26) examining the SARS-CoV-2 mRNA BNT162b2 vaccine, which further reinforce our finding of a possible effect of the vaccine on women's menses.

Conclusion:

The effectiveness and importance of the vaccine against SARS-CoV-2 to prevent severe morbidity and mortality is now unquestionable (31). In this study,

assessing the association between the SARS-CoV-2 mRNA BNT162b2 vaccine and menstural changes, we found significant rates of menstrual changes following the vaccine. Further research is needed to confirm our findings and to better characterize the magnitude of change, its underlying mechanisms, possible long term implications and ways to attenuate any possible negative effect of the most important tool we have to fight the ongoing pandemic- the vaccine.

Conflict of interests: There is no conflict of interest to declare.

Authorship contributions:

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Table 1. Baseline Characteristics of Study Participants (n=219)

Age (years) Mean [SD]		29.62[8.6]
Parity N (%)	0	130 (59.4)
	1	15(6.8)
	≥2	74(33.8)
Marital status N (%)	Single	142 (64.8)
	Married/permanent relationship	77(35.2)
Background diseases N (%)		22(10.1)
	Endocrine Disorders	7(3.2)
	GI Diseases	3(1.4)
	Pulmonary Diseases	2(0.9)
	Neurological Disorders	1(0.4)
	Cardio-metabolic Diseases	4(1.8)
Regular medications N (%)	SNRI\SSRI	17(7.8)
	Levothyroxine Sodium	4(1.8)
	Ventolin	3(1.4)
	Other	8(3.6)
Hormonal treatment N (%)	OCP	45 (20.5)
	Levonorgestrel IUD	12(5.5)
	Non-hormonal IUD	11(5.0)
	Other	4(1.4)

OCP - Oral contraceptive pill, GI - Gastrointestinal Disease, SNRI- Serotonin-Norepinephrine Reuptake Inhibitors, SSRI- Selective Serotonin Reuptake Inhibitor, IUD - Intrauterine Device.

Table 2. Baseline menstrual characteristics

Age at menarche Mean [SD]		12.8 [1.4]
Cycle length, days Mean [SD]		29.4 [7.6]
Days of bleeding Mean [SD]		5.1 [1.3]
Usual menstrual flow N (%)	Light Moderate Heavy	62 (28.3) 129 (58.9) 38 (17.3)
Dysmenorrhea N (%)	None Mild Moderate Severe	30 (13.7) 55 (25.1) 101 (46.1) 33 (15.1)
Limitation in daily activities N (%)		41 (18.7)

Table 3. Comparison of baseline characteristics between women with or without irregular bleeding and any menstrual change following the vaccine.

		Irregular bleeding			**Any menstrual change***		
		Yes (N=51)	No (N=168)	P-value	Yes (N=83)	No (N=136)	P-value
Age Mean [SD]		31.1 [8.1]	30.2 [7.2]	0.44	31.1 [8.3]	30.0 [6.7]	0.29
Parity N (%)	0	46.0%	60.1%	0.0497	53.7%	58.8%	0.28
	1	4.0%	8.3%		4.9%	8.8%	
	≥2	50.0%	31.5%		41.5%	32.4%	
Presence of background disease N (%)		20.0%	6.0%	0.003	13.6%	6.6%	0.09
Regular medications N (%)		34.3%	32.3%	0.82	22.9%	59.0%	p<0.001
Hormonal treatment N (%)		22.0%	29.8%	0.28	22.0%	31.6%	0.12
Menstrual cycle length Mean [SD]		28.8 [5.8]	29.5 [8.1]	0.59	29.2 [4.9]	29.4 [8.8]	0.85
Days of bleeding Mean [SD]		5.0 [1.3]	5.1 [1.3]	0.74	4.9 [1.3]	5.1 [1.25]	0.59
Presence of dysmenorrhea N (%)		75.5%	83.3%	0.21	83.1%	79.0%	0.45

* Irregular bleeding, mood disturbance or menstrual pain