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COVID-19 (SARS-CoV-2) mRNA vaccination does not affect basal sex hormone levels (follicle-stimulating hormone, luteinizing hormone, estradiol) in reproductive-age women

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Objective: People vaccinated with the coronavirus disease 2019 (COVID-19) (severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2]) mRNA vaccine have reported experiencing various adverse effects. For instance, reproductive-age women have presented with complaints of abnormal uterine bleeding or menstrual cycle changes. We speculated that differences in basal sex hormone levels before and after vaccination may be present in women who experienced irregular bleeding or menstrual cycle changes; thus, this study aimed to investigate the differences in basal sex hormone levels of women before and after two doses of SARS-CoV-2 mRNA vaccination.
Methods: This retrospective study included patients who received SARS-CoV-2 mRNA vaccines between January 2021 and February 2022 at a single center. In an outpatient setting, patients were queried regarding their menstrual cycle, the date of SARS-CoV-2 mRNA vaccination, vaccination type, and vaccination side effects. Differences in basal hormone levels (menstrual cycle days 2–3, follicle-stimulating hormone [FSH], luteinizing hormone [LH], and estradiol) before and after vaccination were compared.
Results: Among the 326 patients, patients with no laboratory records of the hormones were excluded. The median time interval between SARS-CoV-2 mRNA vaccination and the laboratory test day was 79 days (interquartile range, 44 to 127). A comparative analysis of these hormones before and after vaccination revealed no significant differences. Subgroup analyses based on age and reported adverse events also found no statistically significant differences.
Conclusion: This study showed no significant differences in basal hormone levels (FSH, LH, and estradiol) before and after SARS-CoV-2 mRNA vaccination.

Keywords: Menstrual cycle; mRNA vaccine; SARS-CoV-2; Sex hormone

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection was first reported in China in December 2019, and the virus is known to cause severe respiratory symptoms and multisystem complications [1-3]. In January 2020, the World Health Organization declared coronavirus disease 2019 (COVID-19) a pandemic [1]. Since then, numerous pharmaceutical companies and medical professionals have developed various vaccines against the virus. Notably, new types of vaccines utilizing messenger RNA technology, such as the Pfizer-BioNTech mRNA vaccine (BNT162b2) and the Moderna mRNA vaccine (mRNA-1273), have been introduced and approved by the U.S. Food and Drug Administration [4,5]. These vaccines employ nucleoside-modified mRNA that encodes the viral spike glycoprotein of the SARS-CoV-2 virus, facilitating the entry of mRNA into cells. Once inside the host cell, the mRNA prompts the cell to produce the spike

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protein, which in turn triggers an immune response [4,6-9]. A range of adverse reactions has been reported in individuals who have received these vaccines. These events range from mild symptoms, such as headaches, muscle pain, and dizziness, to severe reactions, including anaphylactic shock, myocarditis, and pericarditis [7,10,11]. However, the mechanisms underlying these severe adverse events following SARS-CoV-2 mRNA vaccination remain unclear and are not fully understood. Moreover, some women, particularly those of childbearing age, have reported abnormal uterine bleeding or changes in their menstrual cycles after receiving the SARS-CoV-2 mRNA vaccines [6,10]. Additionally, although the precise mechanism has yet to be fully elucidated, there have been reports that SARS-CoV-2 mRNA vaccination in premenopausal women may be associated with thrombocytopenia syndrome and thrombosis, potentially due to an excessive immune response [12,13].

In Korea, as of May 25, 2023, a total of 44,349,952 individuals have been vaccinated against COVID-19, with more than 100 million doses administered to this population. Additionally, the Korean government has recognized that abnormal uterine bleeding and changes in the menstrual cycle are side effects of COVID-19 vaccination [14,15].

However, few studies have reported on the side effects of SARS-CoV-2 mRNA vaccination in women of reproductive age [5,16-22]. Research has indicated that the BNT162b2 mRNA vaccine does not impact follicular function [5]. In one study, researchers compared a vaccinated group (n=9) with a control group (unvaccinated and uninfected, n=14), finding that follicular steroidogenesis was similar between the two groups. Additionally, two studies reported that anti-Müllerian hormone (AMH) levels remained unchanged post-vaccination [20,22]. In the United States, researchers prospectively collected and analyzed menstrual cycle tracking data to investigate the relationship between COVID-19 vaccination and menstrual cycle alterations [18]. They observed that COVID-19 vaccination could influence the menstrual cycles of vaccinated women. Although there were statistically significant differences between the vaccinated and unvaccinated groups, the observed change in the study group was less than 1 day, leading the authors to consider these findings not clinically significant.

Only a few studies have reported on hormonal differences associated with the menstrual cycle in women vaccinated against COVID-19. Moreover, the evidence explaining the cause of these side effects is currently inadequate. Consequently, we hypothesized that if the SARS-CoV-2 mRNA vaccine affects the female endocrine or reproductive systems, there might be noticeable changes in the basal hormone levels (follicle-stimulating hormone [FSH], luteinizing hormone [LH], and estradiol) on the third day of menstruation compared to levels before vaccination.

Methods

This retrospective study evaluated female patients who received their second dose of the SARS-CoV-2 mRNA vaccine at the CHA Fertility Center Gangnam between March 2021 and February 2022. A total of 326 patients were included. The clinicians recorded the date of vaccination, the type of vaccine administered, and any side effects experienced. Additionally, patient data regarding age, body mass index (BMI), parity, medical history, and menstrual cycle were collected retrospectively. The study compared differences in basal hormone levels, including FSH, LH, and estradiol, on days 2 to 3 of the menstrual cycle before and after vaccination. These hormone levels were measured on the second or third day of the menstrual cycle during the patients' first clinic visit following their vaccination. The median time between the SARS-CoV-2 mRNA vaccination and the day of the laboratory test was 79 days (interquartile range [IQR], 44 to 127). The post-vaccination laboratory results were then compared with the patients' basal hormone levels prior to vaccination.

Patients who received only the SARS-CoV-2 mRNA vaccination were included. This study excluded patients who underwent cross-vaccination or received different types of vaccines, those lost to follow-up, and individuals who lacked basal hormone testing on day 3 of their menstrual cycle both before and after vaccination.

1. Statistical analysis

Differences in basal hormone levels (menstrual cycle day 2–3) examined before and after vaccination were calculated. Statistical calculations were performed to determine whether the data were normally distributed. If the data were not normally distributed, the Wilcoxon signed-rank test was used. For comparisons between more than three groups, the chi-square test was used. The Fisher exact test was used for results when more than 20% of the cells of a contingency table had expected frequencies less than 5. All statistical calculations were performed with SPSS Statistics for Windows ver. 23 (IBM Corp.). A $p \leq 0.05$ was considered to indicate statistical significance.

2. Ethical statement

The study was approved by the Ethics Committee of the Institutional Review Board of the CHA Gangnam Medical Center (IRB approval number: 2022-12-010-002). This study is a retrospective study, we collected patients' data from their medical records. Therefore, we did not need to obtain a informed consent from each patient, and our study was approved by the IRB.

Results

In total, 264 patients were included in this retrospective study. The

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mean age of this group was 36.92±4.25 years, and the mean BMI was 21.32±2.80 kg/m^2. The mean AMH level was 2.99±2.40 ng/mL. Furthermore, 205 patients had regular menstrual cycles (77.7 %) and 59 patients had irregular cycles (22.3%). In total, 176 patients (66.7%) had no side effects after vaccination. Twenty-two patients (8.3%) complained of mild symptoms (myalgia, headache, and fever), and 11 patients (4.2%) complained of other symptoms (cardiovascular, pulmonary, allergic reaction, and neurologic symptoms). Seven patients (2.7%) complained of abnormal uterine bleeding and 48 patients (18.2%) reported changes in their menstrual cycle. Approximately 80 patients had no changes in blood test results for their basal hormone levels (FSH, LH, and estradiol) after vaccination. The median time interval between SARS-CoV-2 mRNA vaccination and laboratory test day was 79 days (IQR, 44 to 127).

The baseline hormonal characteristics on days 2–3 of the patients' menstrual cycles are presented in Table 1; no significant differences were observed between the two groups. To more accurately assess the impact of vaccination on the female reproductive system, a subgroup analysis was conducted on patients who had their basal hormone levels tested within a 3-month period post-vaccination. This analysis also showed no significant differences (Table 2). Additionally, we compared hormonal levels between patients who experienced side effects and those who did not (Supplementary Table 1), finding no statistically significant differences between these groups. Among the patients who reported side effects, 13 experienced changes in their menstrual periods, and five reported abnormal uterine bleeding (Table 3). Further analysis of those with menstrual period changes or abnormal uterine bleeding showed no significant differences in basal hormone levels in blood tests conducted before and after vaccination.

The patients with blood test results for basal hormone levels (FSH, LH, and estradiol) before and after vaccination were divided into age groups (30–34, 35–39, and >40 years) for a subgroup analysis. During this analysis, we noted that the number of patients in their 20s was limited, totaling only five. Given the need for an equitable distribution when forming groups, it was deemed impractical to include patients in their 20s due to the broad age range this category represents. Consequently, the subgroup analysis included a total of

Table 1. Baseline hormonal characteristics

Characteristic	Mean ± SD	Median (Q1–Q3)	*p*-value
FSH (mIU/mL) (n = 81)			0.307
Before vaccination	7.78 ± 2.76	7.35 (6.14–8.82)	
After vaccination	8.01 ± 3.44	7.36 (6.50–8.90)	
LH (mIU/mL) (n = 72)			0.126
Before vaccination	5.85 ± 2.41	5.98 (4.61–7.55)	
After vaccination	5.71 ± 2.82	5.64 (3.96–7.35)	
Estradiol (pg/mL) (n = 76)			0.702
Before vaccination	45.36 ± 28.36	38.78 (29.36–54.16)	
After vaccination	40.87 ± 24.58	35.05 (26.08–51.89)	

Wilcoxon signed-rank test. A $p<0.05$ indicates a significant difference.
SD, standard deviation; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Table 2. Basal hormone levels of patients who had blood test results within 3 months

Characteristic	Mean ± SD	Median (IQR)	*p*-value
FSH (mIU/mL) (n = 62)			0.451
Before vaccination	8.81 ± 3.93	7.72 (6.32–10.06)	
After vaccination	9.15 ± 5.13	7.38 (6.54–10.69)	
LH (mIU/mL) (n = 60)			0.054
Before vaccination	5.90 ± 2.43	5.78 (4.78–6.89)	
After vaccination	5.64 ± 3.07	5.26 (3.69–7.31)	
Estradiol (pg/mL) (n = 59)			0.456
Before vaccination	44.02 ± 29.22	36.90 (26.64–52.04)	
After vaccination	40.41 ± 22.43	34.94 (23.22–57.15)	

Wilcoxon signed-rank test. A $p<0.05$ indicates a significant difference.
SD, standard deviation; IQR, interquartile range; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Table 3. Basal hormone levels in patients who had side effects of menstruation changes or abnormal uterine bleeding

Variable	Before vaccination	After vaccination	*p*-value
Menstruation period change (n = 13)			
FSH (mIU/mL) (n = 13)	7.74 (5.48–10.94)	7.41 (3.52–9.15)	0.81
LH (mIU/mL) (n = 13)	4.90 (1.81–7.42)	4.45 (1.54–7.09)	0.33
Estradiol (pg/mL) (n = 13)	32.54 (20.86–51.12)	28.48 (15.39–34.31)	0.25
Abnormal uterine bleeding (n = 5)			
FSH (mIU/mL) (n = 5)	8.61 (4.96–11.66)	7.73 (5.64–15.21)	0.69
LH (mIU/mL) (n = 5)	6.64 (6.15–8.46)	6.37 (3.16–14.93)	0.69
Estradiol (pg/mL) (n = 5)	51.03 (29.00–65.34)	44.78 (27.12–56.54)	0.69

Values are presented as median (interquartile range). Wilcoxon signed-rank test. A $p<0.05$ indicates a significant difference.
FSH, follicle-stimulating hormone; LH, luteinizing hormone.

259 patients aged over 30 years. The incidence of side effects, such as changes in menstrual cycle or abnormal uterine bleeding, appeared to increase with patient age (Table 4); however, no statistically significant relationship was found. To further explore the relationship and distribution between age and side effects, we presented the test results in a scatter plot. No significant differences were observed before and after vaccination (Supplementary Figure 1).

Discussion

The primary aim of our study was to examine the differences in basal hormone levels—specifically FSH, LH, and estradiol— measured on the third day of menstruation, before and after SARS-CoV-2 mRNA vaccination in a cohort of vaccinated individuals. Our findings indicated that there were no significant changes in the basal hormone levels among the women who received the vaccine. This lack of variation persisted even when focusing on the subgroup of participants who had their blood tested within 3 months post-vaccination. Following the COVID-19 pandemic, the administration of the SARS-CoV-2 mRNA vaccine has become mandatory or recommended in most countries to curb the spread of the virus [1]. Given that this is the first vaccine to utilize the mRNA of the virus in humans, there have been concerns about its safety. Among the known adverse events, women of reproductive-age have expressed particular concern regarding the potential impact on their reproductive health after receiving the SARS-CoV-2 mRNA vaccine or following infection [23].

In our study, we compared basal sex hormone levels in women before and after SARS-CoV-2 mRNA vaccination. The results indicated no significant differences in hormone levels post-vaccination. These findings are consistent with previous reports on the impact of SARS-CoV-2 mRNA vaccination on women's sex hormones [2,14,16,17,24].

Women who received the COVID-19 vaccination have reported experiencing abnormal uterine bleeding and changes in their menstrual cycles [16,24]. In the United States, a study was conducted to assess the impact of SARS-CoV-2 mRNA vaccination on menstrual cycles. This study analyzed the menstrual cycles of 23,754 female patients and concluded that there is an association between SARS-CoV-2 mRNA vaccination and alterations in menstrual cycles. The authors noted that similar observations have been made in other countries [10,21].

The hypothalamic-pituitary-ovarian (H-P-O) axis in females responds to both the negative and positive feedback of estradiol, which is secreted by the developing follicle [25-28]. Consequently, the female reproductive system requires a highly adaptable H-P-O axis to maintain optimal functionality, and it is vulnerable to a variety of factors, including nutrition, endocrine disorders, and psychological and physiological stress. Disruption of this axis can lead to abnormal uterine bleeding. Ovulatory disorders, encompassing both ovulatory and anovulatory dysfunctions, are associated with abnormal uterine bleeding [29-32]. This form of abnormal uterine bleeding is characterized by its irregular and unpredictable nature. Moreover, hormonal disturbances are the most common cause of irregular bleeding among women of reproductive age. We hypothesized that if there are differences in basal sex hormone levels before and after COVID-19 vaccination, then the SARS-CoV-2 mRNA vaccine may influence the H-P-O axis [18,19,21,24].

However, this retrospective study found no statistically significant differences in hormonal levels in women before and after vaccination. However, our analysis was limited to only three sex hormones measured on menstrual cycle days 2–3, and we did not assess every hormone involved in the menstrual cycle. Given that a range of factors can influence menstrual cycles, our study had a limited ability to clarify the relationship between SARS-CoV-2 mRNA vaccination and menstrual cycle changes. Furthermore, while the H-P-O axis is essential, the regulation of hemostasis also plays a crucial role in the normal menstrual cycle. An imbalance in these physiological processes can lead to abnormal uterine bleeding, which may stem from issues with hemostasis, abnormal blood vessels, or the dysregulation of immune cells and cytokines [33,34]. These factors can cause abnormal uterine bleeding even when the H-P-O axis functions properly. The purpose of this study was to investigate whether changes in menstruation or abnormal uterine bleeding following SARS-CoV-2 mRNA vaccination are due to alterations in key hormones regulated by the

Table 4. Side effects in different age groups

Variable	30–34 yr (n = 87)	35–39 yr (n = 91)	≥ 40 yr (n = 81)	*p*-value	Fisher's exact test
Any side effects	24 (27.6)	32 (35.2)	32 (39.5)	0.253	0.822
Mild symptoms (myalgia, headache, fever)	6 (6.9)	10 (11.0)	6 (7.4)	0.566	
Abnormal uterine bleeding	1 (1.1)	2 (2.2)	3 (4.9)	0.297	
Menstrual cycle changes	13 (14.9)	16 (17.6)	19 (23.5)	0.35	
Other (arrhythmia, dermatitis, chest discomfort, diarrhea, dyspepsia)	4 (4.5)	4 (4.4)	3 (3.7)	0.956	
None	63 (72.4)	59 (64.8)	49 (60.5)	0.253	

Values are presented as number (%). Six cells (50%) had expected frequencies less than 5. The lowest expected frequency was 1.91.

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H-P-O axis. However, considering the various potential side effects of SARS-CoV-2 mRNA vaccination, it is plausible that a cytokine imbalance induced by the vaccine may also be responsible for menstrual changes and abnormal uterine bleeding [6-8,10-12]. Therefore, further research on this topic is necessary.

Moreover, we were unable to confirm endometrial histology in patients reporting these adverse events, representing a limitation of our study. Given our small sample size, it is imperative to conduct further research with a larger cohort.

Our study found that SARS-CoV-2 mRNA vaccination did not impact basal hormone levels during menstrual cycle days 2–3 in a cohort of 81 patients. However, when we stratified the patients by age, we observed an increase in the incidence of abnormal uterine bleeding or menstrual changes with advancing age, although this trend did not reach statistical significance. We hypothesize that the menstrual cycle and endocrine system of older patients may be more susceptible to the effects of SARS-CoV-2 mRNA vaccination than younger patients. Additionally, it is widely recognized that ovarian reserve diminishes with age, which could contribute to the observed irregular menstrual cycles post-vaccination [25,27,35].

Several studies have examined the impact of the SARS-CoV-2 mRNA vaccine on women's fertility and ovarian function [5,20,22]. A prospective study that collected blood samples from patients before and 3 months post-vaccination found no effect of the SARS-CoV-2 mRNA vaccine on AMH levels [20]. Additionally, another study reported that neither SARS-CoV-2 mRNA infection nor vaccination compromised ovarian follicular growth in women [5].

There are a few limitations to this study. First, this was a retrospective cohort study conducted without randomization. Second, a significant number of patients were excluded from the initial group (324 patients), leaving us with a smaller cohort of 81 patients. We were unable to examine basal sex hormone levels on the same day for all participants. Additionally, the time interval between the SARS-CoV-2 mRNA vaccination and the day of the laboratory test varied widely, ranging from 0.2 to 8 months, which could have influenced our findings. We also performed subgroup analyses for patients reporting abnormal uterine bleeding or changes in their menstrual cycle. However, the small number of patients in these subgroups may not be sufficient to represent the broader population, and therefore, caution should be exercised when interpreting these results. Third, this study was subject to selection bias. The majority of patients who visit our institution are women with fertility issues. Consequently, our findings may not accurately reflect the general population of women of childbearing age. Moreover, it is crucial to consider that the presence of structural or functional abnormalities in the reproductive system, which are associated with infertility, may exacerbate this limitation.

Regardless of these limitations, to the best of our knowledge, our study has a larger sample size than previous studies on this issue [5,20,22]. We conducted a subgroup analysis by patient age. Although this analysis did not reveal any statistically significant differences, we observed an increase in the number of patients reporting abnormal uterine bleeding or menstrual cycle changes post-vaccination with advancing age. Consequently, further research with larger sample sizes is warranted.

In conclusion, no hormonal differences were observed on days 2–3 of the menstrual cycle in patients who received the COVID-19 vaccination. We compared basal sex hormones (FSH, LH, and estradiol) before and after vaccination and found no significant differences. Additionally, while changes in the menstrual cycle and abnormal uterine bleeding tended to increase with age, these variations were not statistically significant.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Conceptualization: WSL, JWK. Data curation: HJJ, JEP, JYH. Formal analysis: HJJ. Writing-original draft: HJJ, JWK. Writing-review & editing: HJJ, JWK.

Supplementary material

Supplementary material can be found via https://doi.org/10.5653/cerm.2023.06107.

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