

Evaluation of menstrual symptoms after Coronavirus disease 2019 vaccination in women with endometriosis

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Abstract

Background: Vaccination can have an impact on menstruation, and this impact may be more notable in women with inflammatory gynecological pathologies such as endometriosis.

Objectives: We aimed to investigate the impact of mRNA-based SARS-CoV-2 vaccines on menstrual cycle-related symptoms in women with endometriosis and assess the effect of hormonal therapy on potential SARS-CoV-2 vaccination-induced menstrual changes.

Design: A total of 848 women who received at least two doses of mRNA-based COVID-19 vaccines were prospectively recruited: 407 with endometriosis (endometriosis group) and 441 healthy controls (non-endometriosis group).

Methods: Data regarding demographics, clinical characteristics, hormonal treatment, and menstrual-associated symptoms in the first and second cycle after vaccination were collected through an online survey.

Results: A similar percentage of patients in both the endometriosis and the non-endometriosis group self-reported menstrual-associated changes the first (52.6% versus 48.8%, respectively) and second cycle after vaccination (29.0% versus 28.1%, respectively). Although the total symptoms recorded were not different between the two groups, several specific symptoms were statistically more frequent in the endometriosis group. These were pain disorders and fatigue in the first cycle after vaccination and pain disorders, menstrual headache and fatigue in the second cycle after vaccination. Bleeding frequency/regularity disorders were found to be more frequent in the non-endometriosis group in the first cycle after vaccination. Patients under hormonal treatment reported fewer changes in menstrual symptoms in the first and second cycle after vaccination compared with those not receiving this treatment. Similarly, patients in the endometriosis group receiving hormonal treatment reported fewer changes in menstrual-associated symptoms compared with those not following any hormonal treatment in the first and second menstrual cycle after the last vaccination.

Conclusion: Women with endometriosis immunized with mRNA-based SARS-CoV-2 vaccines did not perceive greater worsening or new menstrual-associated symptoms after complete COVID-19 vaccination compared with healthy controls. Hormonal treatment may have a protective effect against worsened or new menstrual symptoms induced by COVID-19 vaccination.

Keywords

COVID-19 vaccination, endometriosis, hormonal therapy, immunization, menstrual abnormalities, SARS-CoV-2 vaccine

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Introduction

The Coronavirus disease 2019 (COVID-19) pandemic declared by the World Health Organization (WHO) in 2020 involved the rapid development of safe and effective vaccines to cope with the devastating worldwide health consequences induced by this pandemic.¹ Generally, vaccine clinical trials do not adequately monitor and collect menstrual-related issues, and no clinical trial evaluating SARS-CoV-2 vaccines has provided

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information on menstrual outcomes postvaccination.^{2–5} Recently, several studies evaluated menstrual-related issues associated with SARS-CoV-2 vaccination, reporting abnormalities in menstrual patterns (early/late onset, dysmenorrhea, and heavier bleeding, among others).^{6–12} These changes were not described as uncommon or dangerous and were largely temporary. In addition, previous studies have evaluated menstrual-related issues, such as abnormal amount of menstrual bleeding and irregular menstruation after other immune challenges, such as human papillomavirus vaccination, showing there was no association between human papillomavirus vaccination and reported post-vaccination symptoms.¹³

The menstrual cycle is a reflection of the general health status and fertility of women and should not be considered as standard and stationary since inter- and intra-individual differences may occur along life.¹⁴ The International Federation of Gynecology and Obstetrics considers the regularity, frequency, volume, and duration of menses to define normal menstruation and the menstrual cycle. It is well known that environmental stress may induce variability in ovulation leading to menstrual variations including skipped cycles or temporary changes in the frequency, regularity, duration, or volume of periods.¹⁵ Moreover, immune challenges such as vaccination can also have an impact on menstruation, which is not only a hormonal but also an inflammatory process.^{16,17} Therefore, the impact of vaccination on the menstrual cycle could be more notable in women with inflammatory gynecological pathologies, such as endometriosis.^{18,19} Endometriosis is a common condition affecting 10%–15% of women of reproductive age,²⁰ and it usually presents cyclical or perimenstrual symptoms, such as dysmenorrhea, ovulation pain, and abnormal bleeding.²¹ In addition, it has been suggested that endometriosis could affect susceptibility to COVID-19.²² Thus, it would be interesting to gather information on the potential impact of SARS-CoV-2 vaccination to advise and foresee specific care in patients with endometriosis, since the COVID-19 pandemic has already had a significant impact on this population.^{23–25} Moreover, many doubts have arisen in the last years about the use of hormonal treatments during vaccination against COVID-19²⁶ and, to our knowledge, no information about the effect of these treatments on menstrual symptoms among endometriosis patients or healthy women has been reported.

The present study aimed to investigate the impact of mRNA-based SARS-CoV-2 vaccines on the menstrual cycle of women with endometriosis by characterizing worsened or new menstrual-associated symptoms in the first and second menstrual cycle after complete SARS-CoV-2 vaccination, as well as assessing the effect of hormonal therapy on potential SARS-CoV-2 vaccination-induced changes.

Material and methods

Study design and participants

This prospective study aimed to investigate the impact of mRNA-based COVID-19 vaccines on the menstrual cycle of women with endometriosis.

The study included women referred to the Gynecological Service of the Hospital Clinic (Barcelona, Spain). Individuals were consecutively recruited between September 2021 and March 2022. All patients had previously undergone a transvaginal sonography in our center which diagnosed or discarded endometriosis or other pelvic gynecological pathologies. The study included females >18 years old, who had received at least two doses of mRNA-based COVID-19 vaccines approved by the European Medicines Agency (EMA) (Spikevax [Moderna] or Comirnaty [Pfizer-BioNTech]). The vaccines were administered at least 2 months before the survey. The exclusion criteria were patients <18 years old; menopausal status or receiving GnRH analog treatment; malignancy; gynecological diseases other than endometriosis; patients who did not receive at least two doses of the mRNA COVID-19 vaccines approved by the EMA, and inability to complete the questionnaire or provide informed consent.

Participation was voluntary, and all participants signed an informed consent form prior to study inclusion. This study was approved by the Clinical Research Ethics Committee of the Hospital Clinic (HCB/2021/1093) and was conducted in accordance with the Declaration of Helsinki.²⁷

Endpoints

The primary outcome of the study was to characterize worsened or new menstrual-associated symptoms in the first and second menstrual cycle after complete COVID-19 vaccination in women with endometriosis. The secondary outcome was to assess the effect of hormonal therapy on potential COVID-19 vaccination-induced changes in women with and without endometriosis. Patients were asked to describe the symptoms after the last dose of COVID-19 vaccination received (second or third).

Data collection and analysis

Data were collected prospectively using a pilot-tested online survey (Supplementary file). The questionnaire consisted of 36 items covering three domains: demographics; clinical characteristics and treatment; and questions about menstrual-associated symptoms in the first and second cycle after vaccination. A prototype of the questionnaire was administered to five endometriosis patients and four healthy women (selected with the same criteria as the participants in the final validation), who evaluated all the questions.

The patients included were divided into two groups: women with endometriosis (endometriosis group) and women without endometriosis (non-endometriosis group). The non-endometriosis group included healthy premenopausal women with no benign or malignant gynecological condition.

Demographic, clinical, and menstrual-associated symptoms data after vaccination were also obtained from a self-reported questionnaire.

We followed the STROBE Guidelines when preparing the manuscript.

Statistical analysis

This was a preliminary study to investigate the menstrual symptoms after COVID-19 vaccination in women with endometriosis with an arbitrarily decided sample size based on previous studies analyzing the impact of the COVID-19 pandemic on patients with endometriosis.²³

The results of the descriptive analysis of qualitative variables were expressed as frequencies and percentages, and quantitative variables were expressed as mean and standard deviation (SD).

A Shapiro–Wilk test was used to ascertain whether continuous variables had a normal distribution. Continuous and normally distributed variables were presented as mean $\pm$ standard deviation (SD). Categorical variables were presented as absolute values and percentages. Univariate comparisons were performed using the Student's *t* test, Pearson's chi-square test, or the Fisher's exact test. Results were considered statistically significant with $p < 0.05$ (two-sided). The results obtained with the univariate analysis were further analyzed by multivariate logistic regression analysis. The multivariate model included patients' ages (<36 years, 36–44 years, and >45 years) and all other variables showing statistical significance in the univariate model. The level of significance adopted was 0.05. Statistical analysis was performed with the SPSS software package (version 25.0 SPSS Inc., Chicago, IL, USA).

Results

Patient disposition

A total of 2300 women were invited to participate: 695 (30.2%) were excluded because they did not complete the questionnaire, and 28 were excluded because of incomplete answers. A total of 729 women were excluded for not meeting the inclusion criteria and the final evaluable population consisted of 848 individuals (407 in the endometriosis group and 441 in the non-endometriosis group) (Figure 1).

Baseline characteristics of the patients included

The baseline sociodemographic and clinical characteristics of the study participants are shown in Table 1. In summary, no significant differences in age, menarche age, work situation, or ethnicity were recorded between groups. The endometriosis group included significantly more smokers, non-parous individuals and a higher number of women under hormonal therapy than the non-endometriosis group. Regarding SARS-CoV-2 vaccination, there was a higher percentage of women with only two doses in the group of women with endometriosis and a higher percentage with three doses in the non-endometriosis group (Table 1).

Menstrual cycle abnormalities after COVID-19 vaccination

Menstrual-associated symptoms in the first and second menstrual cycle after the last dose of the COVID-19 vaccine were recorded in both study groups (Table 2). There were no significant differences between groups in the first or the second cycle after vaccination (Table 2). The main menstrual-associated changes reported by women were bleeding and pain disorders. Although the total symptoms recorded were not different between the two groups, several specific symptoms were statistically more frequent in the endometriosis group. These were pain disorders and fatigue in the first cycle after vaccination (Table 2) and pain disorders, menstrual headache, and fatigue after the second cycle after vaccination (Table 2). Bleeding frequency/regularity disorders were found to be more frequent in the Non-endometriosis group in the first cycle after vaccination (Table 2).

There were no statistically significant differences in the mean number of menstrual cycles with menstrual changes (mean $\pm$ SD: endometriosis group: 3.98 ± 2.3 versus non-endometriosis group: 4.7 ± 3.1 ; $p = 0.320$). The comparison between patients who received two or three vaccine doses showed no differences in the reported worsened or new menstrual-associated symptoms after the first (two doses: 247 (29.12%) versus three doses: 182 (21.46%); $p = 0.834$) or second menstrual cycle (two doses: 145 (17.09%) versus three doses: 182 (11.43%); $p = 0.539$).

Up to 65.8% of endometriosis patients were receiving hormonal treatment, and this could have had an impact on study results. Thus, we explored the potential role of hormonal treatment on the worsening or induction of menstrual-associated symptoms after COVID-19 vaccination. Among the women under hormonal treatment, 64.3% received estroprogestins and 35.7% progestins. Analysis of the whole population showed that patients receiving hormonal treatment reported fewer changes of

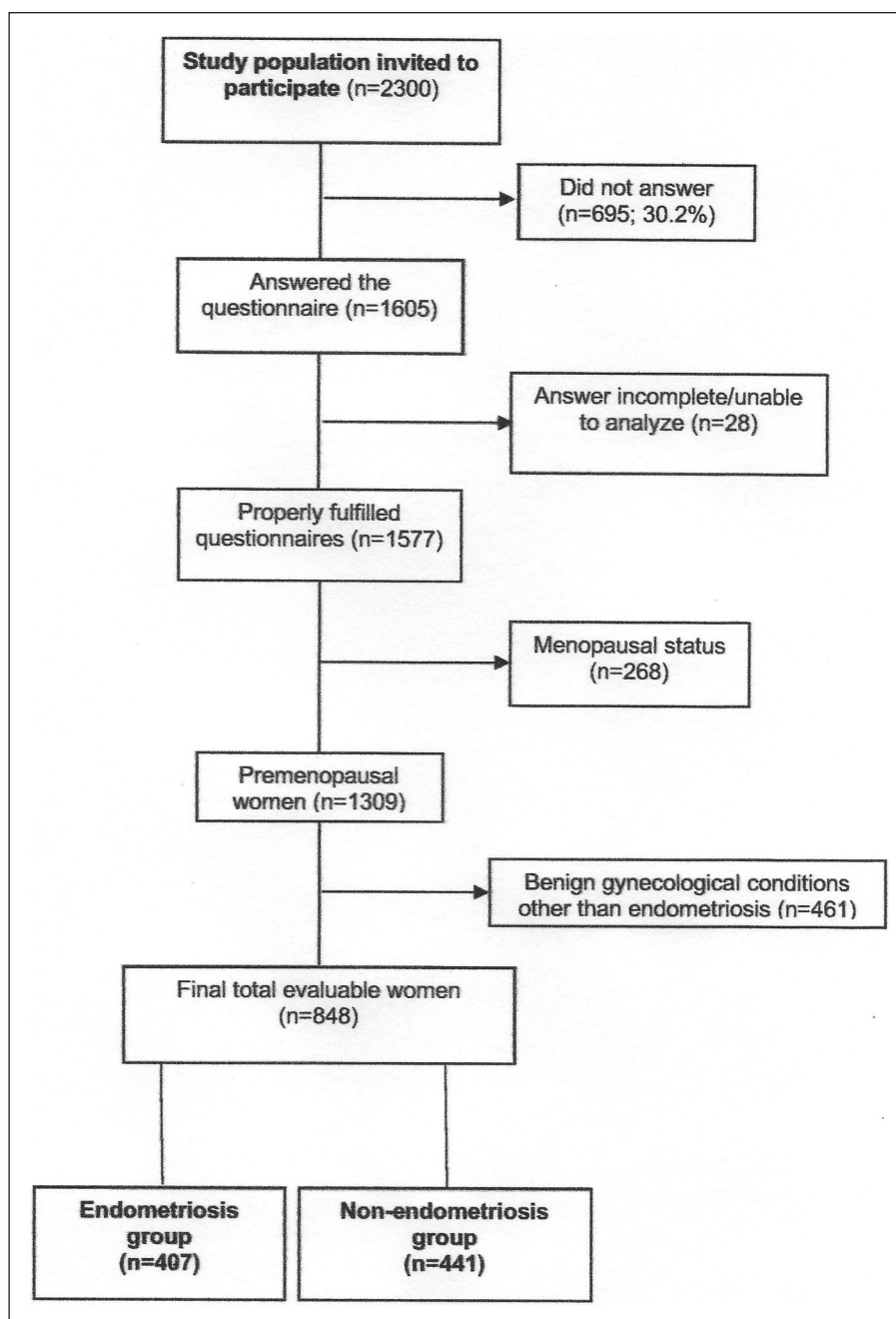


Figure 1. Flow chart of patient inclusion and dropouts.

menstrual symptoms compared with those not receiving this treatment in the first (46.7% versus 53.3%, respectively; $p=0.02$) and second cycle after vaccination (24.5 versus 31.3, respectively; $p=0.03$). Specifically, hormonal treatment showed a protective effect on menstrual-associated symptoms in women with endometriosis (Table 3). A significantly higher number of endometriosis patients not taking hormonal treatment reported worsened or new menstrual-associated symptoms during both

the first and second cycle after vaccination (Table 3). Only 18% (80/441) of patients in the non-endometriosis group were on hormonal treatment. The subanalysis of this group showed no significant differences in relation to perceived symptoms after vaccination between patients receiving or not hormonal treatment (data not shown). The type of treatment received (estroprogestins or progestins or the route) did not influence the results (data not shown).

Table 1. Baseline clinical and demographic characteristics of the patients included in the study.

	Endometriosis group (n = 407)	Non-endometriosis group (n = 441)	p value
Age (years)	38.9 ± 6.3	38.6 ± 8.9	0.148
Menarche (years)	12.5 ± 1.7	12.4 ± 1.5	0.230
Work situation			
Working	285 (70.0)	321 (72.8)	0.075
Studying	8 (2.0)	19 (4.3)	
Working and studying	37 (9.1)	43 (9.8)	
Unemployed	26 (6.4)	18 (4.1)	
Not working for health reasons	27 (6.6)	16 (3.6)	
Not working neither studying	24 (5.9)	24 (5.4)	
Ethnicity			
White or Caucasian	369 (90.7)	384 (87.1)	0.383
African	3 (0.7)	6 (1.4)	
Asian	2 (0.5)	4 (0.9)	
Latin-American	33 (8.1)	47 (10.6)	
Smoking habit	66 (16.2)	43 (9.7)	0.005
Alcohol habit	11 (2.7)	13 (2.9)	0.498
Non-parous	241 (59.2)	224 (50.8)	0.016
Receiving hormonal therapy	273 (65.8)	80 (18.1)	<0.0001
Number of COVID-19 doses			<0.0001
2 Doses	268 (65.8)	216 (49)	
3 Doses	139 (34.2)	225 (51)	

Results are expressed as mean ± SD or n (%). Bold-faced values show p < 0.05.

Table 2. Worsened or new menstrual-associated symptoms in the first and second menstrual cycle after the last dose of the COVID-19 vaccine in both study groups.

	Endometriosis group (n = 407)	Non-endometriosis group (n = 441)	p value
First cycle after vaccination			
Worsened or new menstrual-associated symptoms	214 (52.6)	215 (48.8)	0.405
Pain disorders	118 (29.0)	94 (21.3)	0.021
Disturbances of flow heaviness/duration	159 (39.1)	153 (34.7)	0.516
Bleeding frequency/regularity disorders	130 (31.9)	152 (34.5)	0.033
Menstrual headache	111 (27.3)	93 (21.1)	0.082
Breast tenderness	53 (13.0)	46 (10.4)	0.424
Fatigue	106 (26.4)	74 (16.8)	0.002
Second cycle after vaccination			
Worsened or new menstrual-associated symptoms	118 (29.0)	124 (28.1)	0.129
Pain disorders	75 (18.4)	57 (12.9)	0.007
Disturbances of flow heaviness/duration	80 (19.7)	90 (20.4)	0.487
Bleeding frequency/regularity disorders	80 (19.7)	86 (19.5)	0.890
Menstrual headache	56 (13.8)	42 (9.5)	0.036
Breast tenderness	32 (7.9)	33 (7.5)	0.900
Fatigue	56 (13.6)	38 (8.6)	0.008

Results are expressed as n (%). Bold-faced values show p < 0.05.

Table 4 shows the results of the adjusted multivariate ORs for selected variables of worsened or new menstrual-associated symptoms in the first and second menstrual cycle after the last dose of the COVID-19 vaccine in all patients. Endometriosis patients showed an increased risk

of pain disorders and fatigue in the first and second menstrual cycle after the last dose of the COVID-19 vaccine. Patients receiving hormonal treatment had a lower risk of total worsened or new menstrual-associated symptoms and less bleeding frequency/regularity disorders compared

Table 3. Worsened or new menstrual-associated symptoms in the first and second menstrual cycle after the last dose of the COVID-19 vaccine in endometriosis patients according to whether there were receiving or not hormonal treatment (n=407).

	On hormonal treatment (N=273)	No hormonal treatment (N=134)	p value
First cycle after vaccination (women with endometriosis, n=407)			
Worsened or new menstrual-associated symptoms	132 (48.4)	82 (61.2)	0.014
Pain disorders	77 (28.2)	41 (30.6)	0.260
Disturbances of flow heaviness/duration	107 (39.2)	52 (38.8)	0.610
Bleeding frequency/regularity disorders	67 (24.5)	63 (47.1)	<0.0001
Menstrual headache	68 (24.9)	43 (32.1)	0.504
Breast tenderness	29 (10.6)	24 (17.9)	0.256
Fatigue	62 (22.7)	44 (32.8)	0.399
Second cycle after vaccination (women with endometriosis, n=407)			
Worsened or new menstrual-associated symptoms	67 (24.5)	51 (38.1)	0.005
Pain disorders	48 (17.6)	27 (20.1)	0.063
Disturbances of flow heaviness/duration	67 (24.5)	43 (32.1)	0.135
Bleeding frequency/regularity disorders	39 (14.3)	41 (30.6)	0.016
Menstrual headache	32 (11.7)	22 (16.4)	0.940
Breast tenderness	15 (5.5)	11 (8.2)	0.213
Fatigue	29 (10.6)	23 (17.2)	0.354

Results are expressed as n (%). Bold-faced values show $p < 0.05$.

with those without hormonal treatment in the first and second menstrual cycle after the last dose of the COVID-19 vaccine.

Discussion

We evaluated the impact of the mRNA-based COVID-19 vaccination approved by the European Medicines Agency (Spikevax [Moderna] or Comirnaty [Pfizer-BioNTech]) on menstrual-associated symptoms in women with endometriosis. The main result arising from this study was that there were no differences in menstrual-associated symptoms between women with endometriosis compared with controls, although some specific symptoms such as pain or fatigue were more frequently reported by endometriosis patients.

A recently published study evaluated the effect of the SARS-Cov-2 BNT162b2 vaccine (Pfizer-BioNTech) on the symptoms of 86 women with endometriosis compared with 88 women with no diagnosis or suspected diagnosis of endometriosis. In this study, endometriosis was shown to be a significant risk factor for worsening of menstrual symptoms compared with the control group.²⁸ In the present study, up to 50% of the individuals included reported worsened or new menstrual-associated symptoms in the first cycle after vaccination, regardless of the presence of endometriosis. These alterations were reported to be transitory, because after the second cycle the rate decreased to ~30% in both groups. Along this line, recent studies including healthy individuals reported an association between having received the COVID-19 vaccine and changes in menstrual bleeding.⁷⁻⁹ In addition, Lee et al.⁷ reported that

women with conditions often associated with altered menstrual bleeding, such as endometriosis, reported experiencing a heavier menstrual flow after receiving the vaccine than the respondents without diagnosed reproductive conditions.

In the present study, women with endometriosis self-reported more pain disorders after both cycles than controls. This finding is not unexpected, since menstrual pain is a common disease feature in women with endometriosis.²⁹ After the first cycle, women with endometriosis reported less bleeding frequency disorders than the non-endometriosis group. An explanation for this is that although the presence of endometriosis itself is commonly accompanied by bleeding during ovulation, a shorter cycle length, and longer bleeding,^{30,31} a high percentage of endometriosis patients were receiving hormonal treatment that may reduce bleeding frequency/regularity disorders. However, the multivariate analysis confirmed that endometriosis patients showed an increased risk of pain disorders and fatigue but not a decreased risk of bleeding/regularity disorders in the first and second menstrual cycle after the last dose of the COVID-19 vaccine.

Similarly to vaccinated women, COVID-19-infected women of child-bearing age have reported transient menstrual changes, mainly prolonged cycles and decreased volume, as well as shortened or disordered menstrual cycles and increased volume.³² On the other hand, increases in interleukin-15 and interferon gamma, interleukin-6, and IP-10/CXCL10 levels have been observed in both previously COVID-19-infected individuals and after vaccination with BNT162b2 mRNA (Pfizer/BioNTech).³³ Furthermore, COVID-19 is frequently complicated by

Table 4. Adjusted multivariate odds ratios for selected variables of worsened or new menstrual-associated symptoms in the first and second menstrual cycle after the last dose of the COVID-19 vaccine.

	Worsened or new menstrual-associated symptoms	Pain disorders	Disturbances of flow heaviness/duration	Bleeding frequency/regularity disorders	Menstrual headache	Breast tenderness	Fatigue
First menstrual cycle							
Endometriosis							
No	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	1.17 (0.76–1.79)	2.45 (1.37–3.56)	1.03 (0.87–1.32)	0.97 (0.77–1.49)	1.65 (0.47–1.82)	1.37 (0.87–1.96)	1.98 (1.27–2.98)
Receiving hormonal treatment							
No	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	0.84 (0.59–0.92)	0.92 (0.67–1.35)	1.25 (0.81–1.54)	0.64 (0.42–0.95)	0.97 (0.77–1.90)	1.42 (0.87–2.18)	0.95 (0.67–1.90)
Age							
<36 years	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
36–44 years	1.27 (0.97–1.79)	1.37 (0.67–2.01)	1.42 (0.97–2.08)	1.37 (0.88–2.61)	1.23 (0.81–1.81)	1.72 (0.90–2.08)	1.42 (0.97–2.08)
>45 years	1.12 (0.77–1.54)	0.88 (0.58–1.76)	0.99 (0.51–1.58)	0.90 (0.46–1.33)	0.97 (0.45–1.51)	0.97 (0.77–1.54)	1.02 (0.31–1.44)
Smoking habit							
No	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	1.16 (0.65–1.68)	1.42 (0.77–2.10)	1.50 (0.76–1.91)	1.49 (0.51–2.11)	1.30 (0.81–2.01)	1.01 (0.82–1.75)	1.53 (0.77–2.57)
Non-parous							
No	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	1.17 (0.67–1.99)	0.84 (0.62–1.25)	1.23 (0.85–1.67)	1.66 (0.77–1.91)	1.17 (0.76–1.79)	1.33 (0.88–1.78)	1.47 (0.82–2.48)
Number of COVID-19 doses							
Two doses	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Three doses	1.21 (0.80–1.98)	1.30 (0.64–1.78)	1.18 (0.88–2.01)	1.65 (0.67–1.75)	0.87 (0.36–1.56)	0.98 (0.56–1.78)	1.12 (0.78–1.59)

(Continued)

Table 4. (Continued)

	Worsened or new menstrual- associate symptoms	Pain disorders	Disturbances of flow heaviness/duration	Bleeding frequency/ regularity disorders	Menstrual headache	Breast tenderness	Fatigue
Second menstrual cycle							
Endometriosis							
No	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	1.22 (0.67–2.78)	1.73 (1.13–2.76)	1.03 (0.87–1.32)	0.58 (0.579–2.15)	1.42 (0.37–1.94)	1.68 (0.93–2.53)	1.67 (1.17–2.54)
Receiving hormonal treatment							
No	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	0.71 (0.41–0.82)	0.86 (0.54–1.90)	1.15 (0.17–1.87)	0.58 (0.21–0.73)	0.75 (0.63–1.89)	1.35 (0.37–2.14)	0.90 (0.19–1.76)
Age							
<36 years	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
36–44 years	1.07 (0.43–2.63)	1.90 (0.89–2.77)	1.42 (0.61–1.85)	1.37 (0.88–2.61)	1.12 (0.64–1.94)	1.19 (0.56–2.27)	1.29 (0.77–2.78)
>45 years	1.72 (0.83–2.61)	1.34 (0.33–2.23)	0.84 (0.42–1.77)	0.91 (0.37–1.82)	0.89 (0.67–1.19)	0.77 (0.42–2.15)	1.31 (0.21–1.14)
Smoking habit							
No	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	1.12 (0.44–1.63)	1.19 (0.64–2.23)	1.47 (0.26–2.12)	1.81 (0.96–2.42)	1.03 (0.73–2.40)	1.72 (0.95–2.17)	1.64 (0.90–2.34)
Non-parous							
No	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	1.47 (0.77–1.98)	0.87 (0.21–2.57)	1.20 (0.72–1.85)	1.57 (0.84–1.98)	1.15 (0.87–1.27)	1.10 (0.77–1.90)	1.63 (0.38–2.15)
Number of COVID-19 doses							
Two doses	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Three doses	1.79 (0.83–2.17)	1.36 (0.37–1.13)	1.07 (0.58–2.24)	1.43 (0.51–1.90)	0.97 (0.79–1.16)	0.63 (0.49–1.21)	1.35 (0.59–1.72)

Results are expressed as OR (95% CI).

OR: odds ratio; CI: confidence interval. Bold faced values show statistically significant results.

thrombosis, and in some cases of severe COVID-19, fibrinolysis may be markedly enhanced within a few days, resulting in fatal bleeding.^{26,34} Thus, it could be reasonable to hypothesize that menstrual changes are caused by a proinflammatory and procoagulative state induced by immune challenges. Indeed, crosstalk between inflammatory homeostasis and menstrual cycle regulation has previously been described.³² However, further studies evaluating whether these menstrual changes are due to changes in hemostatic, inflammatory, and/or immune pathways should be carried out.

Hormonal therapy (oral contraceptives, gonadotropin-releasing hormone, and hormonal intrauterine devices, among others) is the first-line treatment for women with endometriosis.²¹ In the present study, up to 65.8% of endometriosis patients were on hormonal treatment, and these individuals showed less postvaccine menstrual-related issues than those not taking hormonal treatment after the first (on hormonal treatment: 132 (48.4%) versus no hormonal treatment: 82 (61.2%); $p=0.014$) or second menstrual cycle (on hormonal treatment: 67 (24.5%) versus no hormonal treatment: 51 (38.1%); $p=0.005$). The multivariate analysis showed that patients receiving hormonal treatment had a lower risk of total worsened or new menstrual-associated symptoms and less bleeding frequency/regularity disorders compared with those without hormonal treatment in the first and second menstrual cycle after the last dose of the COVID-19 vaccine. This suggests a protective effect of treatment and reduces the potential bias factor of psychological stress reported during the COVID-19 pandemic.³⁵ Nevertheless, hormone use is dependent on health and personal individual situations, such as the severity of disease, reproductive conditions, personal choices, or effectiveness of treatment approaches for managing symptoms, among others. Moreover, a range of hormonal treatments are available and here they were considered as a whole, thereby making it difficult to draw firm conclusions regarding their protective effect. Nonetheless, the protective effect of estrogen exposure on COVID-19 has previously been demonstrated, with an association being observed between estrogen exposure and mitigation of severity of COVID-19-related clinical outcomes.³⁶

The main strength of our study is that it includes more than 800 individuals, thus providing a large sample with reliable results.

We are aware of some research limitations, and we assume that our results must be interpreted with caution. First, the outcomes were based on subjective opinion and personal experience that might be subjected to bias. The qualitative clinical perception reported by the patients was not medical/objectively confirmed by gynecologists. However, data on objective values is not presented, and the individuals included considered the outcomes according to what they considered normal in their prior daily lives. Second, the design of the survey did not include questions regarding symptomatology prior to COVID-19

vaccination, or whether the patient had COVID-19 disease and its severity, but again, the individuals compared the outcomes according to their prior cycles. Third, as expected, cases and controls showed significant differences in terms of smoking, parity, use of hormonal therapy, and the number of vaccine doses received (two or three), and this may contribute to a selection bias. Nevertheless, these issues have been clarified with a multivariate subanalysis integrating all these variables. A possible explanation for this may be the increased anxiety and stress reported by endometriosis patients during the COVID-19 pandemic.³⁵ Furthermore, smoking has been suggested as a contributor to the severity of chronic pelvic pain in patients with endometriosis.^{37,38} Fourth, some clinical information or detailed symptoms were not included in the questionnaire to avoid lengthening the time to fill it out and lead to improper completion which may bias the results. Fifth, more than 30% of patients invited to participate in the study did not fulfill the questionnaire and, thus, we did not have basic data on these women to be included in the analysis. Finally, although the results showed a trend toward a decrease in menstrual-related symptomatology, our data did not include enough subsequent cycles to investigate this issue, and this should be considered in further research.

Although COVID-19 vaccination-related menstrual changes are reported as being temporary, it is important to gain knowledge about vaccines and further irregular menstrual cycles. Having clear and reliable information on irregular menstrual cycles is very important to plan in advance for potential risks, discomfort, and particularly for women trying to achieve or avoid pregnancy. Furthermore, this is especially important in women with underlying pathologies such as endometriosis, given that patients with symptomatic endometriosis have higher levels of stress, somatization, and fatigue in daily life, and more commonly suffer from depressive and anxiety disorders.³⁹

Conclusions

Women with endometriosis immunized with mRNA-based SARS-CoV-2 vaccines do not present worsened or new menstrual-associated symptoms in the first and second menstrual cycle after complete vaccination compared with women without endometriosis.

Hormonal therapy shows a protective effect against vaccination-induced menstrual abnormalities in women with endometriosis.

Declarations

Ethics approval and consent to participate

Participation was voluntary, and all participants signed an informed consent form prior to study inclusion. This study was approved by the Clinical Research Ethics Committee of the Hospital Clinic (HCB/2021/1093) and was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Author contribution(s)

María Ángeles Martínez-Zamora: Conceptualization; Formal analysis; Investigation; Methodology; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Georgina Feixas: Conceptualization; Formal analysis; Investigation; Methodology; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Meritxell Gracia: Investigation; Methodology; Writing – review & editing.

Mariona Rius: Conceptualization; Formal analysis; Validation; Writing – review & editing.

Lara Quintas: Methodology; Visualization; Writing – review & editing.

Cristian De Guirior: Conceptualization; Investigation; Supervision; Writing – review & editing.

Francisco Carmona: Conceptualization; Data curation; Formal analysis; Methodology; Supervision; Writing – original draft; Writing – review & editing.

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Availability of data and materials

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

References

- World Health Organization (WHO). WHO Director-General's opening remarks at the media briefing on COVID-19—11 March 2020, 2021, <https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020>
- Wallace M, Moulia D, Blain AE, et al. The advisory committee on immunization practices' recommendation for use of Moderna COVID-19 vaccine in adults aged ≥ 18 years and considerations for extended intervals for administration of primary series doses of mRNA COVID-19 vaccines—United States, February 2022. *MMWR Morb Mortal Wkly Rep* 2022; 71: 416–421.
- Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *N Engl J Med* 2020; 383: 2603–2615.
- Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2020; 384: 403–416.
- Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against covid-19. *N Engl J Med* 2021; 384: 2187–2201.
- Alghamdi AN, Alotaibi MI, Alqahtani AS, et al. BNT162b2 and ChAdOx1 SARS-CoV-2 post-vaccination side-effects among Saudi vaccinees. *Front Med (Lausanne)* 2021; 8: 760047.
- Lee KMN, Junkins EJ, Luo C, et al. Investigating trends in those who experience menstrual bleeding changes after SARS-CoV-2 vaccination. *Sci Adv* 2022; 8: eabm7201.
- Edelman A, Boniface ER, Benhar E, et al. Association between menstrual cycle length and coronavirus disease 2019 (COVID-19) vaccination: a U.S. cohort. *Obstet Gynecol* 2022; 139: 481–489.
- Baena-García L, Aparicio VA, Molina-López A, et al. Premenstrual and menstrual changes reported after COVID-19 vaccination: the EVA project. *Womens Health* 2022; 18: 17455057221112236.
- Laganà AS, Veronesi G, Ghezzi F, et al. Evaluation of menstrual irregularities after COVID-19 vaccination: results of the MECOVAC survey. *Open Med (Wars)* 2022; 17(1): 475–484.
- Muhaidat N, Alshrouf MA, Azzam MI, et al. Menstrual symptoms after COVID-19 vaccine: a cross-sectional investigation in the MENA region. *Int J Womens Health* 2022; 14: 395–404.
- Dar-Odeh N, Abu-Hammad O, Qasem F, et al. Long-term adverse events of three COVID-19 vaccines as reported by vaccinated physicians and dentists, a study from Jordan and Saudi Arabia. *Hum Vaccin Immunother* 2022; 18: 2039017.
- Suzuki S and Hosono A. No association between HPV vaccine and reported post-vaccination symptoms in Japanese young women: results of the Nagoya study. *Papillomavirus Res* 2018; 5: 96–103.
- Munro MG, Critchley HOD and Fraser IS. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. *Int J Gynaecol Obstet* 2018; 143: 393–408.
- Kalantaridou SN, Makrigiannakis A, Zoumakis E, et al. Stress and the female reproductive system. *J Reprod Immunol* 2004; 62: 61–68.
- Evans J and Salamonsen LA. Inflammation, leukocytes and menstruation. *Rev Endocr Metab Disord* 2012; 13(4): 277–288.
- Berbic M and Fraser IS. Immunology of normal and abnormal menstruation. *Womens Health (Lond)* 2013; 9(4): 387–395.
- Azlan A, Salamonsen LA, Hutchison J, et al. Endometrial inflammasome activation accompanies menstruation and may have implications for systemic inflammatory events of the menstrual cycle. *Hum Reprod* 2020; 35: 1363–1376.
- Porpora MG, Scaramuzzino S, Sangiuliano C, et al. High prevalence of autoimmune diseases in women with

- endometriosis: a case-control study. *Gynecol Endocrinol* 2020; 36(4): 356–359.
20. Zondervan KT, Becker CM and Missmer SA. Endometriosis. *N Engl J Med* 2020; 382: 1244–1256.
 21. Becker CM, Bokor A, Heikinheimo O, et al. ESHRE guideline: endometriosis. *Hum Reprod Open* 2022; 2022: hoac009.
 22. Barretta M, Savasta F, Pietropaolo G, et al. COVID-19 susceptibility in endometriosis patients: a case control study. *Am J Reprod Immunol* 2022; 88(4): e13602.
 23. Nicolás I, Martínez-Zamora MÁ, Gracia M, et al. Impact of SARS-CoV2 pandemic on patients with endometriosis and their health care. *J Womens Health (Larchmt)* 2022; 31(4): 480–486.
 24. Demetriou L, Cox E, Lunde CE, et al. The global impact of COVID-19 on the care of people with endometriosis. *Front Glob Womens Health* 2021; 2: 662732.
 25. Chudasama YV, Gillies CL, Zaccardi F, et al. Impact of COVID-19 on routine care for chronic diseases: a global survey of views from healthcare professionals. *Diabetes Metab Syndr* 2020; 14(5): 965–967.
 26. Fidicicchi T, Fruzzetti F, Lete Lasa LI, et al. COVID-19, gender and estroprogestins, what do we know. *Eur J Contracept Reprod Health Care* 2022; 27(1): 67–74.
 27. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; 310: 2191–2194.
 28. Gilan A, Laster-Haim S, Rottenstreich A, et al. The effect of SARS-CoV-2 BNT162b2 vaccine on the symptoms of women with endometriosis. *Arch Gynecol Obstet* 2023; 307(1): 121–127.
 29. Vercellini P, Viganò P, Somigliana E, et al. Endometriosis: pathogenesis and treatment. *Nat Rev Endocrinol* 2014; 10: 261–275.
 30. Wei M, Cheng Y, Bu H, et al. Length of menstrual cycle and risk of endometriosis: a meta-analysis of 11 case-control studies. *Medicine (Baltimore)* 2016; 95(9): e2922.
 31. Matalliotakis IM, Cakmak H, Fragouli YG, et al. Epidemiological characteristics in women with and without endometriosis in the Yale series. *Arch Gynecol Obstet* 2008; 277(5): 389–393.
 32. Li K, Chen G, Hou H, et al. Analysis of sex hormones and menstruation in COVID-19 women of child-bearing age. *Reprod Biomed Online* 2021; 42(1): 260–267.
 33. Bergamaschi C, Terpos E, Rosati M, et al. Systemic IL-15, IFN- γ , and IP-10/CXCL10 signature associated with effective immune response to SARS-CoV-2 in BNT162b2 mRNA vaccine recipients. *Cell Rep* 2021; 36(6): 109504.
 34. Yamada S and Asakura H. Coagulopathy and fibrinolytic pathophysiology in COVID-19 and SARS-CoV-2 vaccination. *Int J Mol Sci* 2022; 23: 3338.
 35. Kabani Z, Ramos-Nino ME and Ramdass PVA. Endometriosis and COVID-19: a systematic review and meta-analysis. *Int J Mol Sci* 2022; 23: 12951.
 36. Costeira R, Lee KA, Murray B, et al. Estrogen and COVID-19 symptoms: associations in women from the COVID symptom study. *PLoS ONE* 2021; 16(9): e0257051.
 37. Yosef A, Allaire C, Williams C, et al. Multifactorial contributors to the severity of chronic pelvic pain in women. *Am J Obstet Gynecol* 2016; 215(6): 760.e1–760.e14.
 38. Laganà AS, Condemi I, Retto G, et al. Analysis of psychopathological comorbidity behind the common symptoms and signs of endometriosis. *Eur J Obstet Gynecol Reprod Biol* 2015; 194: 30–33.
 39. Chen LC, Hsu JW, Huang KL, et al. Risk of developing major depression and anxiety disorders among women with endometriosis: a longitudinal follow-up study. *J Affect Disord* 2016; 190: 282–285.