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Post-COVID-19 Menstrual Symptom Disorders Relating to Anxiety and Long COVID-19 Symptoms

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Abstract

Objectives: Coronavirus disease 2019 (COVID-19) can affect the menstrual cycle and menstrual flow. To examine changes in menstrual symptoms of women recovering from COVID-19 and to identify factors that influence these changes.

Materials and Methods: A questionnaire, prepared using Google Forms, was completed by 180 women (26.08±6.62 years) recovered from COVID-19. The menstrual symptoms, menstrual pain, fatigue severity and anxiety level of the participants were evaluated respectively with the Menstrual Symptom Questionnaire (MSQ), visual analogue scale (VAS), fatigue severity scale (FSS), and coronavirus anxiety scale (CAS).

Results: Post-COVID-19 individuals' MSQ totals, subgroup scores, FSS scores and menstrual pain levels showed significant increase compared to pre-COVID-19. Regression analysis identified that age at menarche, changes in FSS and VAS scores as contributors to 38.4% of the variance explained in the significant regression for change in MSQ score. Individuals with prolonged fatigue, muscle–joint pain and dyspnea symptoms showed increase in MSQ total scores ($P=0.006$, $P=0.009$, $P=0.046$ respectively) and MSQ negative effects/somatic complaints scores ($P=0.004$, $P=0.002$, $P=0.017$ respectively). Individuals with prolonged gastrointestinal symptoms showed increase in MSQ pain symptoms ($P=0.029$) and MSQ coping methods scores ($P=0.002$), while those with prolonged muscle and joint pain showed increase in MSQ coping methods ($P=0.022$) scores.

Conclusions: The results of this study indicated that menstrual symptoms, fatigue, and menstrual pain severity are deteriorated in women recovered from COVID-19. Age at menarche, changes in fatigue and menstrual pain after COVID-19 were determiners of the deteriorated menstrual symptoms. Menstrual symptoms were more severe in those who have prolonged fatigue, dyspnea, muscle–joint pain and gastrointestinal symptoms.

Keywords: Public health, Evaluation, Experience

Introduction

Coronavirus disease 2019 (COVID-19) is a viral infectious disease that affects many organs of the body, most commonly the lungs, and has short- and long-term consequences (1). Regardless of disease severity. the most frequently reported persisting symptoms after COVID-19 are fatigue and dyspnea (2).

The World Health Organization (WHO) has revealed that women's health is more adversely affected by COVID-19 than that of men (3). Angiotensin-converting enzyme 2 (ACE2), which plays a key role in the entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into cells, is expressed to be high in amount in the female genital organs, such as the ovaries, uterus, vagina, and placenta, which may pose a risk for female reproductive functions, leading to infertility, fetal distress, or menstrual cycle disorders. ACE2 is responsible for balancing the level of angiotensin II enzyme, which initiates menstruation (4). ACE2 expression in the uterine tissue varies according to age and menstrual cycle phase (5), and these changes may result in impaired uterine bleeding (4).

Limited number of studies have examined the effects of COVID-19 on the menstrual cycle (6-10). Li et al. examined menstrual cycle in women who had been recuperated from COVID-19 and determined that one-fifth of infected women, more commonly those with severe disease, have decreased menstrual flow or prolonged menstrual cycle (8). SARS-CoV-2 may cause an increase in interleukin (IL)-6, IL-8, tumor necrosis factor-α (TNF-α) and other inflammatory cytokines and changes in the hypothalamic-pituitary-gonadal (HPG) axis by affecting the immune system. Normal functioning of the HPG axis is necessary for a regular menstrual cycle. The HPG axis is susceptible to insufficient sleep, physical and psychological stress, which causes abnormal sex hormone secretion (11). In a study examining sex hormones in COVID-19 patients, it was found that lower Anti-Müllerian hormone and higher follicle-stimulating hormone, prolactin, and testosterone hormone levels. This may cause further menstrual problems (11, 12).

Menstrual pain is the most common menstrual problem (10). In a study examining the effect of pandemic stress on the menstrual cycle, 36.9% of women had irregular

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Key Messages

- Menstrual symptoms, fatigue and menstrual pain severity are deteriorated in women recovered from COVID-19.
- Fatigue, menstrual pain differences after COVID-19 and age at menarche were determiners of the changes in menstrual symptoms.
- Menstrual symptom changes after COVID-19 are more severe in women who have prolonged fatigue, dyspnea, muscle–joint pain and gastrointestinal symptoms.

menstrual cycles and 38.8% experienced menstrual pain (9). In addition, 52.6% of women have reported a change in their menstrual cycle during the quarantine period. Therefore, stress during the pandemic is significantly associated with changes in sexual behaviors (6) and menstrual cycle (7).

The effects of COVID-19 on body system and function are being investigated from the different perspectives. The studies examining the effects of COVID-19 on the menstrual cycle are limited, to the best of our knowledge, no study evaluated the changes in menstrual symptoms of women who have had COVID-19 (7-9). We hypothesized that menstrual symptoms may be worsened in women who had been recuperated from COVID-19. Therefore, we intended to examine the changes in menstrual symptoms of women who had been recuperated from COVID-19 and to determine the factors affecting these changes.

Materials and Methods

This cross-sectional study was based on retrospective and prospective inquiries. An online questionnaire was prepared using Google Forms application and was sent to 196 women between May 18 and 31, 2021. All volunteers who answered the questionnaire, were aged 18–45 years, diagnosed with COVID-19 based on a reverse real time-positive polymerase chain reaction test (RT-PCR) on nasal swab, that was emailed to us, and they were all fluent in Turkish, and were in the menstrual phase at the time of inclusion. Individuals who were in the premenopausal–postmenopausal period, unable to email their PCR results, or unable to answer the questionnaire adequately were excluded.

Data on sociodemographic characteristics, the history of COVID-19, and prolonged symptoms were recorded. Menstrual symptoms, menstrual pain severity, fatigue severity, and anxiety levels were assessed using the Menstrual Symptom Questionnaire (MSQ), visual analogue scale (VAS), Fatigue Severity Scale (FSS), and coronavirus anxiety scale (CAS), respectively.

Participants were asked to answer all questions included in the MSQ, taking into account their menstrual periods before and after their COVID-19 diagnosis. The MSQ consists of 22 items divided into three subgroups (Factor 1-negative effects/somatic complaints [questions 1 to 13], Factor 2-pain symptoms [questions 14 to 19], and Factor 3-coping methods [questions 20 to 22]), with each item scored from 1 to 5, designed to assess menstrual pain and symptoms. The total MSQ score is calculated by adding the mean scores of the items included in the subgroups and ranges from 22 to 110. Higher scores indicate increased menstrual symptom severity (13,14).

VAS was used to score patients' menstrual pain severity, with scores ranging from 0 (no pain) to 10 (most severe pain) (15).

The FSS questionnaire consists of nine Likert-type questions, with each question scored from 1 to 7, and scores ≥4 indicating severe fatigue. The participants were asked to answer all questions, while considering what they experienced before and after their COVID-19 diagnosis. The total score ranges from 9 to 63, with higher scores indicating greater severity (16,17).

The CAS is used to assess dysfunctional anxiety. Participants were asked to rate their frequency of anxiety episodes when exposed to thoughts or information about COVID-19 on a five-point scale, ranging from 0 (not at all) to 4 (almost every day). A total score of ≥9 indicated coronavirus-related anxiety (18,19).

The Statistical Package for Social Science program (v23; SPSS, Chicago, IL) was used in statistical analysis. Data were expressed as mean ± standard deviation or percentages. The Kolmogorov–Smirnov test was used to analyze the normality of the variables, all parameters were non-normally distributed. The Wilcoxon signed-rank test was used for the comparison of menstrual symptoms, menstrual pain severity, and fatigue severity of individuals before and after COVID-19. Inter correlations between the changes ((post COVID-19) - (pre-COVID)) in MSQ, MSQ subgroup scores, fatigue and menstrual pain and coronavirus anxiety were computed using Spearman correlation. Independent variables based on univariate analysis were analyzed by multiple linear regression analysis to determine the multivariate influence of the predictors of the Δ MSQ scores. The adjusted R^2 was used to explain the total variance. Subjects' the Δ MSQ scores and subgroup scores was being compared based on demographic features and prolonged COVID-19 symptoms using Mann-Whitney U test or Kruskal-Wallis test. Statistical significance was set at $P < 0.05$ for all analysis.

Results

A total of 196 individuals initially met the inclusion criteria; however, 16 individuals were excluded from the study because they did not complete the survey. Finally, 180 participants were included in the study. The mean age was 26.08 ± 6.62 years, while the mean age at menarche was 13.28 ± 1.35 years.

The patients' sociodemographic and COVID-19 disease related data are shown in Table 1. None of the participants were diagnosed with female reproductive diseases. Three (1.7%) participants had been admitted due to pneumonia

Table 1. Sociodemographic and Clinical Characteristics of the COVID-19 Women

	N (%) or Mean ±SD
Age (years)	26.08±6.62
BMI (kg/m²)	23.05±4.24
Menarche age (years)	13.28±1.35
Marital status	
Single	129 (71.7 %)
Married	51 (28.3 %)
Education	
Secondary school	9 (5 %)
Higher school	33 (18.3 %)
Bachelor	125 (69.4 %)
Master/Doctoral	13 (7.2 %)
Smoking history	
Smoking	36 (20 %)
Never smoked	124 (68.9 %)
Ex-smoker	20 (11.1 %)
Comorbidities	
None	154 (85 %)
Asthma	10 (5.6 %)
Vascular pathologies	5 (2.8 %)
Thyroid gland pathologies	3 (1.7 %)
Type 2 diabetes	4 (2.2 %)
Dyslipidemia	5 (2.8 %)
Time after reverse RT-PCR test (days)	104.66±60.22
4-12 weeks	85 (47.2 %)
12 weeks-6 months	80 (44.4 %)
> 6 months	15 (8.3 %)
Prolonged COVID-19 symptoms	
Fatigue	95 (52.8 %)
Headache	58 (32.2 %)
Cough	33 (18.3 %)
Dyspnea	39 (21.7 %)
Muscle and joint pain	69 (38.3 %)
Secretion	28 (15.6 %)
Loss of smell and taste	45 (25 %)
Gastrointestinal problems	21 (11.7 %)
CAS (0-20)	3.22±3.99

SD: standard deviation, BMI: body mass index, kg: kilogram, RT-PCR: real time polymerase chain reaction; CAS, Coronavirus Anxiety Scale.

and hypoxemia, 17 (9.4%) participants had COVID-19-related pulmonary radiological findings, and 95 (52.8%) participants had been treated with favipiravir. The most common prolonged COVID-19 symptoms were fatigue (52.8%), muscle–joint pain (38.3%), and headache (32.2%).

Pre- and post-COVID-19 MSQ scores, FSS scores, and VAS scores are shown in Table 2. After the diagnosis of COVID-19, the individuals had significant higher MSQ total scores (Z = -4.196), negative effects/somatic complaints (Z = -3.970), pain symptoms (Z = -3.342), coping methods subgroup scores of MSQ (Z = -2.469), FSS scores (Z = -8.929), and menstrual pain scores (Z = -5.265) than those before the diagnosis of COVID-19.

The correlation between Δ MSQ scores and age, body mass index, age at menarche, Δ FSS scores, Δ menstrual pain, and CAS scores was examined. Δ MSQ scores had a significant negative mild-to-moderate correlation with the age at menarche (r = −0.158) and a significant positive mild-to-moderate correlation with the Δ FSS score (r = 0.516) and the Δ menstrual pain score (r = 0.334). A negative significant correlation was found between age at menarche and Δ MSQ-negative effects/somatic complaints subgroup scores (r = -0.160) and Δ MSQ-coping methods subgroup scores (r = -0.185). Δ FSS and Δ menstrual pain scores were positively correlated with negative effects/somatic complaints subgroup scores (r = 0.528 and r = 0.299, respectively), pain symptoms subgroup scores (r = 0.45 and r = 0.337, respectively) and coping methods subgroup scores (r = 0.368 and r = 371, respectively) (Table 3).

Multiple linear regression analysis identified age at menarche and FSS and VAS scores as significant contributors to 38.4% of the variance explained in the significant regression for MSQ scores (F (3.176) = 38.23, $P < 0.001$; Table 4).

The Δ MSQ scores of the individuals did not differ according to education level, smoking status or time passed after the diagnosis of COVID-19. The Δ MSQ scores of the individuals were compared according to the prolonged COVID-19 symptoms. Individuals with prolonged fatigue, muscle–joint pain, and dyspnea symptoms showed increased Δ MSQ total scores (Z = -2.775, Z = -2.594, Z = -1.994, respectively) and Δ negative effects/somatic complaints subgroup scores (Z = -2.907, Z = -3.052, Z = -2.393, respectively). Individuals with prolonged gastrointestinal symptoms showed increased Δ pain symptoms subgroup scores (Z = −2.182) and coping methods subgroup scores (Z = −3.082), while those with prolonged muscle and joint pain symptoms showed increased Δ coping methods subgroup scores (Z = -2.288) (Table 5).

A post-hoc power analysis calculated using the G*Power 3.1.9.4 Sample Size Calculator program (Universitat Düsseldorf), considering our sample (180 women) and the Δ MSQ total score after COVID-19 diagnosis (2.29 ± 8.16). Accordingly, the power of the study was calculated to be 96.2% (α = 0.05).

Discussion

Our cross-sectional study aimed to examine the changes in menstrual symptoms of women who had been recuperated from COVID-19 and determine the factors associated with these changes. Our results showed that

Table 2. Menstrual Symptom Questionnaire, Fatigue Severity Scale and Menstrual Pain Scores Before and After COVID-19

	Pre-COVID-19 Mean±SD	Post-COVID-19 Mean±SD	Δ Mean±SD	*P*
MSQ (22-110)	64.96±16.61	67.26±17.37	2.29±8.16	<0.001*
Factor 1: Negative effects/somatic complaints	36.14±9.72	37.46±10.11	1.32±4.70	<0.001*
Factor 2: Pain symptoms	18.04±5.24	18.76±5.44	0.72±2.96	0.001*
Factor 3: Coping methods	7.39±3.56	7.57±3.61	0.17±0.89	0.009*
FSS (9-63)	38.17±12.66	44.51±13.29	6.33±9.25	<0.001*
Menstrual pain (0-10)	3.47±2.79	4.19 ±2.99	0.72±1.97	<0.001*

SD: standard deviation, Δ: (post COVID-19) - (pre-COVID), MSQ: menstrual symptom questionnaire, FSS: fatigue severity scale, *P<0.05.

Table 3. The Correlations Between Δ MSQ and Age, BMI, Menarche Age, CAS, Δ FSS, and Δ menstrual pain

	Δ MSQ	Δ Factor 1- Negative Effects/ Somatic Complaints	Δ Factor 2- Pain Symptoms	Δ Factor 3- Coping Methods
Age	P=0.334	P=0.282	P=0.658	P=0.672
BMI	P=0.796	P=0.613	P=0.870	P=0.728
Menarche age	P=0.035*	P=0.032*	P=0.051	P=0.013*
CAS	P=0.320	P=0.347	P=0.469	P=0.124
Δ FSS	P<0.001	P<0.001	P<0.001	P<0.001
Δ Menstrual pain	P<0.001*	P<0.001*	P<0.001*	P<0.001*

Δ: (post COVID-19) - (pre-COVID), BMI: body mass index, FSS: fatigue severity scale, MSQ: Menstrual Symptom Questionnaire, CAS: coronavirus anxiety scale. *P<0.05.

Table 4. Multiple Regression Analysis for Δ MSQ

Dependent Variables	Independent Variables	B	Standard Error $_B$	β	T	*P*	95% CI	Adjusted R^2	*P*
Δ MSQ	Δ FSS	0.447	0.052	0.507	8.626	<0.001*	0.34/0.54	0.384	<0.001
	Menarche age	-0.822	0.355	-0.136	-2.315	0.022*	-1.52/-0.12		
	Δ Menstrual pain	1.379	0.242	0.334	5.697	<0.001*	0.90/1.85		

Δ: (post COVID-19) - (pre-COVID), MSQ: Menstrual Symptom Questionnaire, FSS: fatigue severity scale, CI: confidence interval. *P<0.05.

menstrual symptoms, fatigue, and menstrual pain severity was deteriorated in women after being diagnosed with COVID-19. In addition, age at menarche and fatigue and menstrual pain scores differences after COVID-19 were determiners of the changes in menstrual symptoms. Menstrual symptoms were more severe in women with prolonged fatigue, dyspnea, muscle–joint pain, and gastrointestinal symptoms.

Menstruation, which is controlled by the uterus, ovary, and brain, can be affected by various infections, medications, or other organ dysfunctions (20). The detrimental effects of COVID-19 include hyper inflammatory processes, damage to ovarian follicles, abnormal sex hormone secretion, and HPG axis dysfunction (21). Therefore, it has been reported that SARS-CoV-2 may cause menstrual cycle disorders by affecting female reproductive functions (4). Among the women who had been diagnosed with COVID-19, 20% and 19% reported a reduced menstrual flow and prolonged menstrual cycle, respectively. The changes in sex hormones as a result of ovarian suppression have been observed as a possible cause (8). In a study, 38.8%, 37%, and 29.8% young adolescents reported menstrual pain, menstrual flow changes, and menstrual cycle duration changes, respectively (9). Previous studies have primarily focused on the effects of COVID-19 on menstrual flow and menstrual cycle duration. According to our knowledge, our study is the first to identify increased menstrual symptoms and related factors in women who had been recuperated from COVID-19. Considering the previous findings, it is conceivable that the worsening menstrual symptoms in this study may be due to the negative effects of COVID-19 on the female genital organs, sex hormone secretion and HPA axis, or the persistence of symptoms after COVID-19.

The rapid decrease in estrogen levels during menstruation causes menstrual pain, muscle–joint pain, and gastrointestinal symptoms (21). During menstruation, as the basal contraction level of the uterus rises from 10 mmHg to 150–180 mm Hg, uterine

Table 5. The Comparison of ΔMSQ in Terms of Sociodemographic Features, Time After PCR Test, Prolonged COVID Symptoms and Medical Treatment During COVID-19

	ΔMSQ Mean±SD	*P*	Δ Factor 1 Mean±SD	*P*	Δ Factor 2 Mean±SD	*P*	Δ Factor 3 Mean±SD	*P*
Education Level								
Secondary school (n=9)	-0.66±3.77	0.507	-0.22±2.10	0.434	-0.33±1.11	0.315	-0.11±0.78	0.601
High school (n=33)	1.09±9.44		0.60±4.68		0.18±3.84		0±0.79	
Bachelor (125)	2.64±7.93		1.52±4.85		0.88±2.71		0.22±0.90	
Master/Doctoral (n=13)	4.00±8.97		2.23±4.43		1.30±3.49		0.38±1.12	
Prolonged COVID-19 Symptoms								
Headache Yes=58 No= 122	3.01±8.53 1.95±7.99	0.264	1.50±5.0 1.23±4.56	0.290	1.01±2.99 0.58±2.95	0.454	0.27±0.89 0.13±0.89	0.234
Fatigue Yes=95 No=85	3.62±9.09 0.81±6.72	0.006*	2.12±4.94 0.42±4.26	0.004*	1.03±3.43 0.37±2.29	0.340	0.27±1.01 0.07±0.73	0.076
Cough Yes=33 No=147	4.24±12.15 1.85±6.94	0.800	2.03±6.80 1.16±2.03	0.956	1.54±4.19 0.53±2.59	0.163	0.48±1.41 0.10±0.72	0.114
Dyspnea Yes=39 No= 141	4.61±9.14 1.65±7.78	0.046*	2.89±5.58 0.88±4.34	0.017*	1.23±3.03 0.58±2.94	0.148	0.33±0.95 0.13±0.88	0.063
Muscle and joint pain Yes=69 No=111	4.23±10.89 1.09±5.58	0.009*	2.33±6.05 0.69±3.50	0.002*	1.31±4.01 0.35±1.99	0.271	0.37±1.16 0.05±0.65	0.022*
Secretion Yes=28 No=152	3.67±11.98 2.03±7.27	0.285	1.96±6.17 1.20±4.39	0.544	1.25±4.72 0.62±2.52	0.287	0.28±1.21 0.15±0.83	0.114
Loss of smell and taste Yes=45 No=135	2.62±10.49 2.18±7.26	0.519	1.42±6.06 1.28±4.17	0.390	0.91±3.83 0.65±2.62	0.718	1.14±0.17 0.80±0.06	0.509
Gastrointestinal problems Yes=21 No=159	5.04±9.76 1.93±7.89	0.183	2.71±6.82 1.13±4.34	0.196	0.61±2.870 0.60±2.96	0.029*	0.57±0.87 0.12±0.89	0.002*
Smoking History								
Never smoked (n=124)	2.03±7.90	0.634	1.14±4.41	0.292	0.69±2.98	0.999	0.14±0.82	0.678
Smoking (n=36)	2.41±7.72		1.33±4.86		0.83±2.64		0.13±0.68	
Ex-smoker (20)	3.7±10.53		2.4±6.05		0.70±3.46		0.45±1.50	
Time After Positive PCR Test								
4-12 weeks (n=85)	2.61±8.15	0.891	1.36±4.46	0.876	0.85±3.06	0.570	0.27±1.06	0.490
12 weeks-6 months (n=80)	1.80±6.64		1.21±4.24		0.47±2.21		0.08±0.65	
> 6 months (n=15)	3.13±14.18		1.66±7.80		1.26±5.24		0.13±0.99	

SD: standard deviation, Δ: (post COVID-19) - (pre-COVID), Factor 1: negative effects/somatic complaints, Factor 2: pain symptoms, Factor 3: coping methods, RT-PCR: real time polymerase chain reaction. *P<0.05.

ischemia develops and the released anaerobic metabolites stimulate type-C pain fibers, causing menstrual pain. In addition, the incidence of symptoms, such as nausea, vomiting, and diarrhea, increases with the stimulation of the gastrointestinal system by prostaglandins (22). In our study, individuals with prolonged gastrointestinal symptoms after COVID-19 had higher pain symptoms and coping methods subgroup scores. In addition subjects with prolonged muscle–joint pain had higher changes in MSQ total score, negative/somatic effects and coping methods subgroup scores. Similarities between persistent post-infection symptoms and the physiological symptoms that occur during the menstrual period may lead to the disturbed menstrual symptoms.

Regardless of disease severity, the most frequently reported persist symptoms were fatigue and dyspnea (2). In our study, 21.7% individuals had prolonged dyspnea and had increased negative effects/somatic complaints subgroup scores. In studies investigating airway sensitivity during menstrual periods, a significant increase in bronchial hyperactivity was found during the luteal phase (23, 24). In a study by Gibbs et al (25), 40% patients with asthma experienced deteriorating symptoms and reduced peak expiratory flow during the premenstrual period. In

our study, individuals with prolonged dyspnea symptoms after COVID-19 had higher difference in MSQ total score and negative/somatic effects subgroup scores. This result shows that there is a link between the subjective respiratory symptoms and menstrual symptom disorders especially associated with somatic complaints after recovery from COVID-19.

Fatigue is a premenstrual symptom and has been associated with excessive bleeding during menstruation (26, 27). Juhi et al (28) reported that muscle fatigue occurs with decreased estrogen levels in the early follicular and luteal phases. Among women who were evaluated 60 days after being diagnosed with COVID-19, 53.1% reported persistent fatigue (2). El Sayed et al (29) emphasized that the symptoms of fatigue and anhedonia persist in individuals who had been recuperated from COVID-19. Therefore we specifically focused on fatigue as a frequent ongoing symptom in those subjects. Consistent with this outcome, fatigue was the most common persistent COVID-19 symptom in our study, and individuals with prolonged fatigue had higher changes in MSQ total score and negative/somatic effects subgroup scores.

Individuals with increased menstrual pain severity presented higher anxiety levels (10). The risk of developing depression, anxiety, and post-traumatic stress disorder is high in people who had been recovered from COVID-19, and this tendency is more common in women (30). In our study, although the negative effects/somatic complaints subgroup scores are increased in women after COVID-19, no correlation was identified between the coronavirus anxiety and changes in menstrual symptom scores. A possible reason is that the CAS is not a sensitive scale for evaluating anxiety disorders caused by post-traumatic stress or other reasons. In future studies, using a more comprehensive measurement tool to evaluate the relationship between menstrual symptoms and anxiety is recommended.

Zurawiecka and Wronka (31) have reported that an early age at menarche is associated with menstrual pain, and Anikwe et al (32) have reported that the mean age at menarche is 13 ± 1.0 years and that menstrual pain is more common in this age group. However, Çakir et al. (33) did not identify ant relationship between menstrual pain and age at menarche. We found no relationship between age at menarche and the pain symptoms but observed a negative relationship with the coping methods subgroup scores. Moreover, the regression analysis showed that, each 1-year decrease in the age at menarche increased the change in MSQ by 0.82. This finding may indicate an increased incidence of menstrual symptoms in women recovering from COVID-19 who were younger at menarche, and that women's ability to cope with menstrual symptoms may not have developed at an early age.

The effects of COVID-19 on changes in sex hormone levels are controversial (8, 34, 35). Li et al (8) reported no difference in menstrual volume, sex hormones (estrogen, progesterone, testosterone, luteinizing hormone, follicle-stimulating hormone), and anti-Müllerian hormone between women who had been recuperated from mild and severe COVID-19. Furthermore, the menstrual cycle duration was longer in women who had severe COVID-19 than in those who had recovered from mild COVID-19. On the other hand, Ding et al found significantly lower serum anti-Müllerian hormone levels, higher serum testosterone and prolactin levels in the COVID-19 group compared to the healthy control (35). In addition, they found a negative correlation between the anti-Müllerian and estradiol hormone levels as a high ovarian marker and the severity of COVID-19. This result showed that pre-menopausal women may be protected against severe COVID-19 (36). In our study, only three participants had moderate COVID-19, while the others were asymptomatic or had mild disease. Therefore, menstrual symptoms were not compared according to the disease severity in our study. In our study, we focused on the time after COVID-19 and observed that the changes in the MSQ total scores and subgroup scores were not affected by the time after COVID-19. This result may be related to the presence of ongoing COVID-19 symptoms. Furthermore, it may reflect that menstrual symptom may also be considered as an ongoing symptom of COVID-19.

Our study has some limitations. The menstrual cycle duration, menstrual flows and sexual activity of the individuals were not evaluated. Since our participants were aged 18–45 years, our results may not be applicable to women beyond that age range who had been diagnosed with COVID-19 and are actively menstruating. The retrospective assessment of pre-COVID-19 menstrual symptoms is another limitation of our study. Lastly, considering that COVID-19 may cause abnormal sex hormone secretion, the fact that the hormone levels of the participants were not evaluated and individuals with menstrual disorders were not included in the exclusion criteria are other limitations of our study.

In conclusion, we observed deteriorated menstrual symptoms, fatigue, and menstrual pain severity in women after diagnosis of COVID-19. In addition, we found that age at menarche, fatigue, and menstrual pain severity changes determined the changes in menstrual symptoms after COVID-19 diagnosis. Menstrual symptoms were more severe in women with prolonged fatigue, dyspnea, muscle–joint pain, and gastrointestinal symptoms. We examined the effects of COVID-19 on menstrual symptoms and determined the factors associated with menstrual symptom changes. The relationship between menstrual symptoms and menstrual cycle characteristics and long COVID-19 symptoms should be examined in future studies with long-term follow-up periods.

Authors' Contribution

BA, DKD, EG and KP planned and design the experiments. BA, DKS, EG, NC, HYÖ, RK, İK, KP, EK, SA and SB performed the

experiments. BA analyzed the data. BA, DKS, EG, NC, HYÖ, RK, İK, KP, EK, SA and SB wrote the manuscript. BA and DKD reviewed and edited the data.

Conflict of Interests
Authors declare that they have no conflict of interests.

Ethical Issues
The study protocol was approved by the Non-Interventional Ethics Committee of Biruni University (No: 2021/47-45) and was registered at the ClinicalTrials.gov (NCT04806815). The study was conducted according to the principles of the Declaration of Helsinki, and all participants provided informed consent at the beginning of the study.

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