

Original Article

Analysis of the effects of hypothalamic-pituitary-adrenal axis activity in menstrual cycle on ankle proprioception, dynamic balance scores and visual-auditory reaction times in healthy young women

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Abstract

Objectives: Menstrual cycle (MC) can affect not only the female reproductive system, but also functions such as neuromuscular performance. For this reason, the aim of this study is to investigate the effect of hypothalamic-pituitary-adrenal axis (HPA) activity in MC on proprioception, balance and reaction times. **Methods:** For cortisol analysis, saliva samples were taken from the same women (n=43) in the four phases of MC. While State Trait Anxiety Inventory-I (STAI-I) was applied in each phase to support cortisol analysis, pain was measured with visual analogue scale (VAS). Proprioception, dynamic balance, visual and auditory reaction times (VRT-ART) measurements were made in the four phases of MC. **Results:** Cortisol, STAI-I and VAS scores, angular deviations in proprioception measurements, dynamic balance scores, VRT and ART measurements were found to show statistically significant difference between MC phases ($p<0.05$). As a result of the post hoc test conducted to find out which MC phase the statistical difference resulted from, it was found that statistically significant difference was caused by the menstruation (M) phase ($p<0.05$). **Conclusions:** It was found that neuromuscular performance and postural control was negatively affected by HPA axis activity in M phase of MC and by pain, which is a significant menstrual symptom.

Keywords: Dynamic Balance, Hypothalamic-Pituitary-Adrenal Axis, Menstrual Cycle, Proprioception, Reaction Time

Introduction

Proprioception, balance, visual and auditory reaction time (VRT, ART) are important components of neuromuscular performance and postural control¹. These parameters which can be affected by hypothalamic pituitary adrenal (HPA) axis

activity in menstrual cycle (MC) are the basic requirements to be able to move independently in life². Considering that women experience an average of 480 MC (2500-3500 days) in their lives, analysis of physiological changes that occur in MC becomes important³. Proprioception occurs with the integration of sensory signals coming from various mechanoreceptors and it is accepted as one of the parameters that ensure the protection of postural control⁴⁻⁶. In most of the ankle proprioception activities, the ankle-foot complex, becomes an important component of the postural control since it is the only part of the body that touches the ground⁷. For the continuity of postural control and balance, the central nervous system integrates visual, vestibular and proprioceptive information to generate motor commands

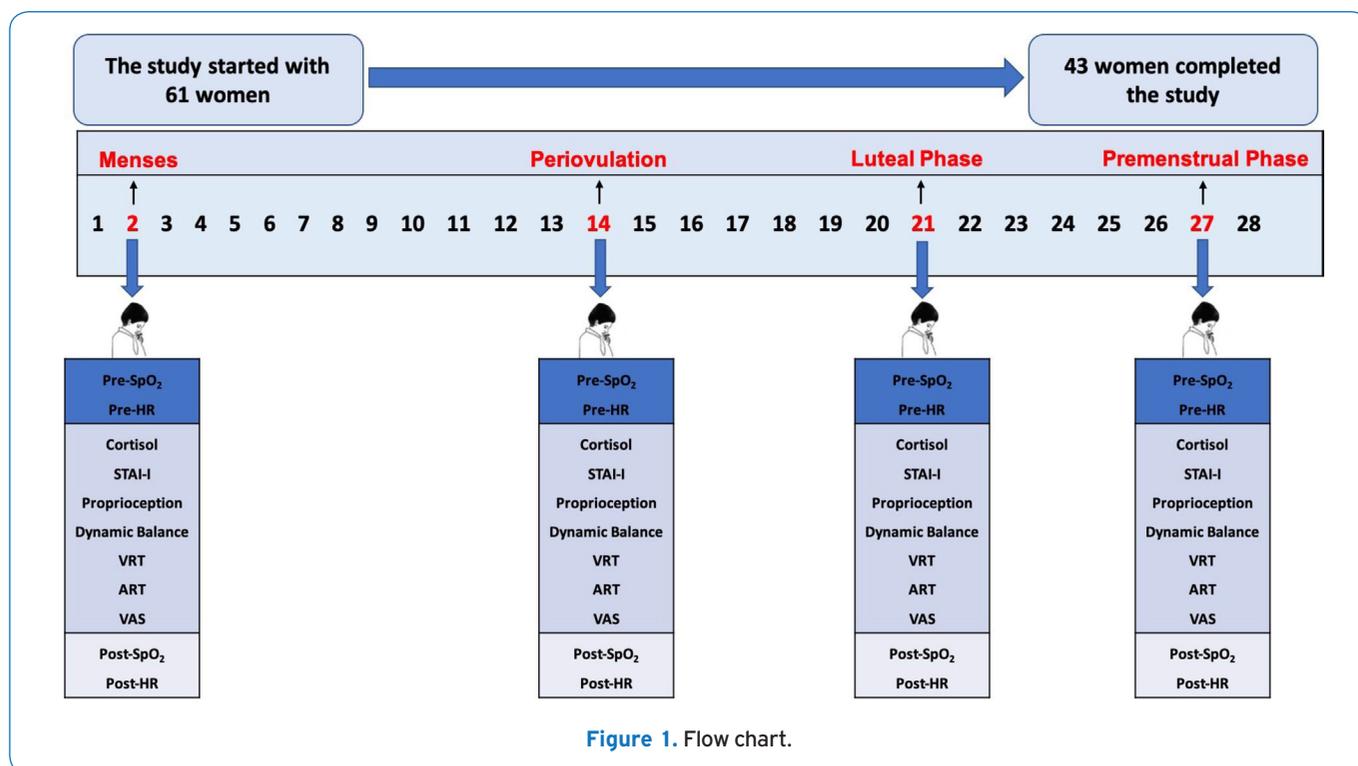
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that coordinate the activation patterns of muscles^{5,8}. The studies examined show that ankle proprioception is affected by HPA axis activation of static and dynamic balance and thus by cortisol level^{9,10}.

Reaction time (RT) is the time between the presentation of a sensory stimulus and the following behavioural reaction¹¹. For a move fit for the purpose, sensory and motor systems should be working in coordination. In humans, reaction speed is a direct indicator of nerve transmission speed¹². In addition to studies which show that RT is affected by stress and anxiety, there are also studies which show that RT's are longer in menstrual period^{13,14}.

MC grouped into menstruation (M), periovulation (PO), luteal phase (LP) and premenstrual (PM) phase physiologically¹⁵. MC is under the control of HPA axis activity and changes are seen in hormonal levels in different phases of the cycle because of oestrogen (E) and progesterone (P) fluctuations released from the ovaries. High P level in MC can cause higher free cortisol level as a response to stress¹⁶. High level of cortisol inhibits HPA axis activation and thus sympathetic nerve system activity increases. All these interactions may be due to the effects of gonadal hormones on neural functions, as well as the changes in cortisol level.

Considering the effects of hormonal fluctuations in MC on cardiac autonomic functions, their possible effects on heart rate (HR) and saturation (SpO₂) are frequently seen in studies reviewed¹⁷. However, while evaluating the study parameters, no studies were found which examined their effects on HR and SpO₂.

Although studies which examine in detail the physiological states caused by gonadal hormones during MC are frequently seen in literature, there are few studies on the effects of HPA axis activity in MC phases on proprioception, dynamic balance and reaction times. Since fluctuations which occur in HPA axis activity and hormones in MC affect the central nervous system in addition to regulating the reproductive function, they can cause deterioration of integration and thus an imbalance between systems¹⁸. Based on this hypothesis, the aim of this study is to analyse the effects of HPA axis activity in MC and pain on ankle proprioception, dynamic balance, VRT and ART scores and to analyse their effects on HR and SpO₂ during assessments.

Materials and methods

Research group

Malatya Clinical Research Ethics Committee approved the study protocol (2019/209). 61 healthy females who volunteered to participate in the study were interviewed face-to-face. The volunteers were informed about the study and they signed consent forms. Since the cycles of 17 of the 61 participants were longer than 35 days (between 42 and 45 days) were excluded from the study. Analyses and test protocols were performed on the remaining 43 participants who completed the study protocol.

In the face-to-face interview, information about the length of participants' MC was noted. Based on the length of cycles during the last three months, a calendar was created for each

of the participants. Expected timing of M, PO, LP and PM was calculated accordingly. MC day-count, starting with day 1 as the first day of the last menstruation: Phase I; 1 day from the 2nd or 3rd day (1-3 days) is M, phase II; 1 day from the 12th to 17th day (especially 14-17 days) is PO, phase III; 1 day from the 18th to the 23rd day (especially 20-21 days) is LP and phase IV; 1 day from the 24th to the 28th day (especially 24-27 days) is PM¹⁹.

The inclusion criteria were being physically healthy, not having a medical disability such as vision or hearing, not having received a surgical intervention of the eye and ear. The exclusion criteria were determined as using sedative, contraceptive and pain killer drugs, using herbal products such as drugs to decrease pain during the MC, quitting the use of cigarette and tobacco products at least three hours before saliva samples were taken, having orthopaedic problems of the upper and lower extremity.

In order to minimize the effects of extra test factors on cortisol levels, the participants were instructed in the preliminary information given that all samples had to be given at 10.00 a.m. and that they had to avoid cigarette, caffeine and physical effort for three hours before their appointment. They were asked to have a course with low fat and protein and avoid all foods and drinks 1 hour before their appointment²⁰. Figure 1 summarizes the flow chart of the study.

Data collection process

Analysis of cortisol in saliva

Saliva samples were collected with passive drool method as indicated by Granger et al²¹. Saliva samples taken were kept at -20°C in a laboratory freezer. After thawing, the samples were centrifuged for 10 min at 4000 g and the supernatant was used for enzyme linked immune sorbent assay (ELISA) analyses. All samples were diluted at 1:5 and assayed in triplicate with assay buffer. Cortisol-bovine serum albumin (BSA) stock solution (1 mg/mL) was diluted with carbonate buffer, pH 9.6, and added to a 96-well microtiter plate at 200 µL/well with ELISA procedure. The microtiter plate was incubated at +4°C for one night and washed for five times with washing buffer by using eight-channel pipette. Using the blocking buffer (200 µL/well), some of the binding places without coating antigen were blocked at 37°C for two hours. Following washing, a duplicate including standard solutions or samples (40 µL/well) and diluted first Ab (antiserum) (40 µL/well) was incubated for 45 min at 37°C. After the washing process, biotinylated anti-rabbit antibody was included (100 µL/well) and the plate was incubated for 30 min at 37°C. Next, following a process of washing for five times, streptavidin peroxidase solution (100 µL/well) was added and the plate was incubated at +4°C for 15 min. Following another washing process of the plate for five times, substrate solution (150 µL/well) was added and the plate was incubated for 10 min in dark. Following incubation, stop solution (50 µL/well) was also included and the absorbance was measured at 450 nm with microplate reader. While the rate of inter-assay coefficients of variation (CV) was 5.6%, the rate of inter-assay variation was 7.8%.

A single laboratory and a single expert performed the ELISA test²².

State Trait Anxiety Inventory-I (STAI-I)

STAI-I scale was used to support the cortisol analyses. The validity and reliability studies of the Turkish version of the STAI-I were performed by Öner and Le Compte²³.

Pain analysis

On a 10 cm scale with 0 = no pain, 10 = unimaginable pain, respectively, the patient was asked to mark the pain level. Marked distance measured from left end with ruler²⁴.

Ankle proprioception measurements

The proprioception accuracy of ankle joints was measured with a Biodex System 3 promulti-joint system isokinetic dynamometer (Biodex Medical Inc., Shirley, New York, USA).

Each participant to be measured for proprioception was made to sit comfortably on dynamometer seat and positioned as the hip joint flexed and the knee joint was at 45° flexion. Ankle joint was brought to neutral position. 10° dorsiflexion (DF), 11° plantar flexion (PF) and 25° PF angles were taught as eyes open (EO) and eyes closed (EC). The participants were given 10 seconds to remember the positions and three trials were made. Following this, the ankle was taken to start position and the participant was asked to press the warning button when she thought the predetermined angles were caught with eyes closed. Deviation from the target angle (angular error) was recorded^{9,25}. While passive positioning mainly measures the ability of capsular receptors, active positioning, which is the ability to actively bring the extremity back to target position, measures the ability of muscle and capsular receptors²⁶.

Dynamic balance measurements

Biodex Balance System (Biodex, Inc, Shirley, New York) was used in the study for balance measurement. Antero-posterior (AP), mediolateral (ML) and general (OA) balance indices of the women who were measured were tested dynamically with eyes open. The participants were asked to stand on the platform with eyes open, bare feet, feet as wide as the shoulder, knees bent 15°, arms crossed over the chest and looking opposite. According to the standard software configuration, three trials of 20 seconds each at a stability level of 8 are calculate with 10 second rest between trials. For the trial to be complete, balance needed to be maintained for 20 seconds. Level 8 is the easiest, level 1 is the hardest level. The test can be repeated for eight levels or until the individual reports that he/she tired and do not want to continue. In our study, there was no participant who could complete level 1 and 2. The test started at level 8 for 60 seconds and ended at level 3 for each participant. OA index is accepted as the best indicator for balance skill among the balance indices taken. A high OA index indicates that the loss of balance is high²⁷.

RT measurements

Hubbard Scientific Reaction Timer (Model: 6027, USA) device was used in the study to measure participants' VRT and ART. 2 different warnings can be taken from Reaction Timer device: visual (light) and auditory (sound). Reaction Timer button was put 10 cm away from the table in front of the participant and the participant was told to place her dominant hand on the table. Then the participant was told to press the buttons in shortest time possible after the "ready" command when a light or sound stimulant was given. Each participant performed 10 trials for sound and light stimuli, the first five of which were considered as exercise. RT was determined as the average of the last five trials²⁸. Measurements were recorded in milliseconds (ms).

Heart rate (HR) and oxygen saturation (SpO₂)

Jumper Pulse Oxymeter (Model: JPD-500E, Shenzhen Jumper Medical Equipment Co. Ltd. China) was used in the study for HR and SpO₂ assessments. This disposable device measures HR and SpO₂ with the help of light attached to the fingertip of the patient that passes tissue²⁹. Measurements were recorded before and after the tests in each phase.

Statistical analysis

Normality distribution of the data was tested with Kolmogorov Smirnov test. Median, minimum (min) and maximum (max) values were given for the data which were not normally distributed. Kruskal Wallis H test was used to compare cortisol, STAI-I, VAS, proprioception, dynamic balance and RT scores in MC phases. According to the results of Kruskal Wallis H test, in order to find out which phase of MC the difference resulted from among the parameters with statistically significant difference, Mann Whitney U test was applied on the data, post hoc test was conducted and adjusted significant values were given. The changes in SpO₂ and HR before and after tests were analysed with Wilcoxon test. $p < 0.05$ value was considered as statistically significant. IBM SPSS Statistics 22.0 program was used in analyses.

Results

43 participants who completed the measurements in all phases were included in the study. Median age (min-max) of the participants was 20 (19-23) years. median height (min-max) of the participants was 166.5 (150-176) cm, median weight (min-max) of the participants was 59 (42-75) kg and median BMI (min-max) of the participants was 20.8 (15.2-28.5) kg/m².

Table 1 shows that descriptive values of the women who participated in the study.

Table 2 shows median (min-max) values of cortisol (Ng/ml), STAI-I (score) and VAS (score) measurements in four phases of MC. According to the Kruskal Wallis H test analysis results, statistically significant difference was found between cortisol, STAI-I and VAS and four phases of MC ($p < 0.05$).

Table 3 shows median (min-max) values of proprioception

Table 1. Demographic features of the women in the study.

Variable	Median (min-max)
Age (year)	20 (19-23)
Height (cm)	166.5 (150-176)
Weight (kg)	59 (42-75)
BMI* (kg/m ²)	20.8 (15.2-28.5)

(*BMI: Body mass index).

Table 2. Median (min-max) values of Cortisol, STAI-I and VAS in MC and Kruskal Wallis H test analysis results.

Period	Cortisol	STAI-I	VAS
M	28.6 (0.77-330.7)	45 (28-58)	4 (0-10)
PO	23.5 (3-217.7)	40 (30-50)	1 (0-8)
LP	23 (0.85-307.5)	38 (28-50)	1 (0-4)
PM	25.3 (0.1-292)	38.5 (30-51)	1 (0-6)
<i>p</i> value	.025	.038	.000

(LP: Luteal phase, M: Menses, PO: Periovalution, PM: Premenstruation, STAI-I: State Trait Anxiety Inventory-I, VAS: Visual Analog Scale).

measurements in four phases of MC. According to the Kruskal Wallis H test analysis results, statistically significant difference was found between four phases of MC and EC 10°DF and EC 11°PF proprioception scores ($p < 0.05$).

Table 4 shows median (min-max) values of VRT and ART scores (ms) and OA, AP and ML dynamic balance scores in four phases of MC. According to the Kruskal Wallis H test analysis results, statistically significant difference was found between four phases of MC and OA, AP and ML dynamic balance scores and VRT and ART scores ($p < 0.05$), (Table 4).

Table 5 shows median (min-max) values of pre-test and post-test SpO₂ and HR values of the women who participated in the study. According to Wilcoxon test analysis results, no statistically significant difference was found between pre-test and post-test SpO₂ measurements ($p > 0.05$), while statistically significant difference was found between pre-test and post-test HR results ($p < 0.05$).

According to Kruskal Wallis H test analysis results, in order to find out which phase of MC the difference resulted from among the parameters with statistically significant difference, Mann Whitney U test was applied on the data and post hoc test was conducted. Table 6 shows the image of Model Viewer showing adjusted significant values as a result of the analysis results. According to post hoc analysis results, it was found that M phase which created the statistically significant difference in Cortisol, STAI-I, VAS scores, EC 10°DF and EC 11°PF proprioception measurements, OA, AP, ML dynamic balance scores and VRT and ART scores (Table 6).

Table 3. Median (min-max) values of ankle proprioception scores in MC and Kruskal Wallis H test analysis results.

Period	EO 10°DF	EO 11°PF	EO 25°PF	EC 10°DF	EC 11°PF	EC 25°PF
M	2° (0-9)	2° (0-6)	3° (0-11)	5° (0-12)	5° (0-13)	4° (0-12)
PO	1° (0-6)	2° (0-6)	3° (0-10)	2° (0-7)	3° (0-7)	2° (0-10)
LP	1° (0-4)	2° (0-6)	2° (0-7)	3° (0-6)	3° (0-7)	3° (0-8)
PM	1° (0-5)	1.5° (0-7)	2° (0-6)	2.5° (0-7)	2° (0-8)	2° (0-7)
<i>p value</i>	.749	.872	.086	.039	.032	.055

(DF: Dorsiflexion, , EO: Eyes Open, EC: Eyes Close, LP:Luteal phase, M:Menses, PO:Periovalution, PM: Premensturation, PF: Plantar flexion).

Table 4. Dynamic balance scores in MC, median (min-max) values of VRT and ART and Kruskal Wallis H test analysis results.

Period	OA	AP	ML	VRT	VRT
M	4.6 (2.2-10.6)	3.8 (1.3-8.7)	3.3 (1.7-8.3)	46.2 (30.6-52.6)	43.9 (28.4-56.4)
PO	3.8 (2.6-8.9)	2.5 (1.2-7.3)	2.8 (2.1-8.2)	43.4 (32.2-61.2)	41.9 (25-50.8)
LP	3.7 (1.7-9.8)	2.5 (0.9-7.2)	2.7 (0.9-7.1)	44.2 (30.2-57.2)	43 (25.4-53)
PM	3.4 (2.1-6.3)	2.4 (0.8-4.7)	2.6 (1.6-5.9)	42.2 (31.6-54.8)	41.2 (28.2-56.6)
<i>p value</i>	.009	.011	.007	.035	.041

(AP: Antero-posterior, ART: Auditory reaction time, LP: Luteal phase, M: Menses, ML: Mediolateral, PO: Periovalution, PM: Premensturation, OA: Overall, VRT: Visual reaction time).

Table 5. Median (min-max) values of pre-test and post-test SpO₂ and HR values and Wilcoxon test analysis results.

Period	Pre-SpO ₂	Post-SpO ₂	<i>p value</i>	Pre-HR	Post-HR	<i>p value</i>
M	98 (82-99)	98 (94-100)	.060	95.5 (57-141)	98 (42-146)	.036
PO	98 (92-104)	98 (95-100)	.423	95 (51-122)	98 (66-144)	.039
LP	98 (92-103)	98 (93-100)	.429	97 (63-132)	101 (62-126)	.042
PM	98 (95-100)	97 (91-100)	.058	89 (61-118)	96 (67-131)	.012

(HR: Heart rate, LP: Luteal phase, M: Menses, PO: Periovalution, PM: Premensturation, SpO₂: Oxygen saturation).

Table 6. Model Viewer image showing the adjusted significant values of the parameters on which post hoc test was conducted by applying Mann Whitney U test.

Period	Cortisol	STAI-I	VAS	EC 10°DF	EC 11°PF	OA	AP	ML	VRT	ART
M-PO	.015	.021	<0.001	.023	.045	.002	.245	.005	.011	.055
M-LP	.028	.047	<0.001	.027	.011	.044	.022	.018	.007	.017
M-PM	.023	<0.001	<0.001	.018	.010	.001	.005	.010	<0.001	.001
PO-LP	.347	.123	.790	.215	.534	.435	.112	.778	.123	.116
PO-PM	.183	.214	.528	.333	.099	.232	.078	.081	.214	.410
LP-PM	.215	.471	.380	.245	.712	.208	.095	.351	.471	.362

(AP: Antero-posterior, ART: Auditory reaction time, LP: Luteal phase, M: Menses, ML: Mediolateral, OA: Overall, PO: Periovalution, PM: Premensturation, VRT: Visual reaction time).

Discussion

As a result of the study, statistically significant difference was found in M phase in terms of cortisol level, STAI-I, VAS, EC 10°DF, EC 11°PF ankle proprioception, dynamic balance, VRT and ART scores. While no statistically significant difference was found in pre-test and post-test SpO₂ results in four phases of MC, statistically significant difference was found in HR measurements.

Neurochemical changes in MC disrupt neurotransmission during periods of stress and can endanger the prefrontal cortex functions³⁰. There are a large number of studies in literature examining cortisol levels in MC. While there are studies reporting that salivary cortisol level does not change during menstrual cycle in LP and PO phases there are also studies which report that cortisol level changes in MC phases^{20,31,32}. The reason why there is no consensus in literature about cortisol level analysed in MC phases can be the fact that the studies were conducted in different age groups, hours in which samples were taken or sociodemographic differences. As a result of this study, it was concluded that cortisol level was statistically significantly higher in M phase when compared with other MC phases.

It can be seen that there are a large number of studies in literature about proprioception since it is one of the important criteria of neuromuscular performance. However, no studies have been found which associated ankle proprioception in MC phases with HPA axis activity. In studies conducted on ankle proprioception in MC phases, while there are studies reporting statistically significant decrease in proprioception in PO and LP phases, there are also studies which have found that the angular difference in ankle joint is the highest in M phase^{33,34}.

As a result of ankle proprioception measurements conducted in this study, it was concluded that there were statistically significant differences in EC 10°DF and EC 11°PF ankle proprioception assessments in M phase. Since protecting the functional joint stability of the ankle is more important than ankle proprioception in terms of neuromuscular control of the movement, it was included in this study assessments³⁵. Different methods and wide age range used in measuring proprioception may have affected the results.

Although a large number of studies were found in literature on the assessment of balance in MC phases, it is quite difficult to find studies examining the effects of stress factor on balance. There are studies reporting that hormonal fluctuations in MC negatively influence postural balance³⁶. There are also studies which have associated the change in postural balance with pain³⁷. While more detailed studies have reported that balance and physical performance is negatively influenced in M phase, there are also studies which have reported that M and PM phases have statistically significant difference when compared with other phases^{18,38}.

In the dynamic balance assessment in this study, statistically significant difference was found in MC phase in

terms of OA, AP and ML scores. When balance parameters analysed with post hoc test by applying Mann Whitney U test were examined, the change in dynamic balance in M phase was statistically significant when compared with other MC phases. This situation was because of the negative effects of both pain, which we found to increase significantly in M phase, and increased cortisol level in M phase.

There are studies about RT advocating that salt and water retention, which affect the process of axonal conduction and availability of neurotransmitters at the synapse, is the cause of delay in reaction responses in M phase^{3,39}.

Although studies conducted have shown different results and different causes for increased reaction responses in VRT-ART, general view is that hormonal fluctuations in MC affect VRT and ART^{39,40}. The increased reaction response in VRT and ART that occurred in M phase of our study both supports the literature and reveals a new idea that the increase in cortisol level may cause this increase.

In pre-test and post-test HR and SpO₂ assessments during the measurement of parameters evaluated in all phases of MC, while statistically significant difference was found in HR, no change was found in SpO₂. The fact that tests conducted increase stress factors and that they were difficult and tiring may have caused HR to increase.

In this study, it was concluded that EC 10°DF, EC 11°PF ankle proprioception, dynamic balance and VRT-ART scores were statistically significantly different in M phase when compared with the other phases of MC. When compared with other phases, it was found that cortisol level and STAI-I test were statistically significantly higher in M phase. It was concluded that higher stress and pain in M phase when compared with the other phases had a negative effect on dynamic balance, VRT-ART and ankle proprioception scores. Since present study is the first study which analyses HPA axis activity and pain as significant indicators of neuromuscular performance in four phases of MC, it will both contribute to literature as a new idea and be a guide in fields such as physical medicine, physiology and sport sciences.

Authors' contribution

DŞ, ŞT, YE and SY were responsible for the design of the study, and DŞ and AK were responsible for the statistical analysis. ŞT, CU and DÖ aided with data collection, and all authors were responsible for the interpretation of the data and drafting of the manuscript.

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