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The Evaluation of Autonomic Dysfunction in Adolescent Patients with Premenstrual Syndrome

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Abstract

Introduction: The relationship between premenstrual syndrome (PMS) and autonomic nervous system (ANS) is complex, with limited data on PMS-related stress further inducing disturbances in the ANS balance. We aimed to investigate the ANS functions through heart rate changes in adolescents with and without PMS.

Method: Participants aged 12-18 years were evaluated for the presence of PMS with the premenstrual syndrome scale and seperated into PMS and control groups. All participants were evaluated by 12-lead surface electrocardiography (ECG) and 24-hour rhythm Holter recordings during the follicular and luteal phases of the menstrual cycle.

Results: A total of 48 participants (29 PMS, 19 control) were included in our study. The mean age was 15.37 ± 1.42 years in the PMS group and 14.66 ± 1.36 years in the control group. ECG (ventricular rate, PR interval, QRS duration, QT and QTc) and holter (SDNN-ms, SDNNi, RMS_SD, Triangular index) data did not differ in both groups and between phases.

Conclusions: Our results showed that autonomic activity in adolescents with PMS does not vary from that of the control group or according to menstrual cycle phases. This might be attributed to the potential correlation between the augmentation of autonomic activity response and both age and the severity of the illness.

Keywords: Premenstrual syndrome, Adolescent, Autonomic nervous system, Heartrate variability, Autonomic dysfunction, Sympathetic activity

Introduction

Premenstrual symptoms are physical, emotional, and behavioral symptoms that occur between ovulation and the beginning of menstruation. Premenstrual syndrome (PMS) is defined as a condition in which these symptoms lead to impairment in academic, social, or individual functioning [1,2]. Common symptoms include abdominal bloating, weight gain, edema, swelling of the breasts, headaches, fatigue, irritability, mood swings, depression, tension, and overeating [1]. The rate of adolescents who fulfill the diagnostic criteria for PMS is between 42-78%, the rate varies due to the difference in diagnostic criteria used [3].

The etiology of PMS has not been fully clarified. Current symptoms are thought to be related to increased sensitivity to changes in estrogen and progesterone hormone levels during the menstrual cycle [4,5]. Increased sensitivity to estrogen

and progesterone fluctuations have been shown to cause emotional symptoms via serotonin, dopamine, γ-aminobutyric acid (GABA) pathways in PMS [6,7]. Additioanlly, symptoms experienced in PMS can also create significant stress for individuals. Based on these pathophysiologic reasons, PMS is considered a disorder both caused by and causing psychophysiologic stress.

The autonomic nervous system (ANS) consists of the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). These two systems balance each other's activities to maintain almost all important homeostatic processes in the body such as regulating blood pressure, heart rate, respiration, digestion, and sexual arousal [8]. Various methods are used to diagnose autonomic dysfunction. Heart rate variability (HRV) is one of them which allows us to obtain information about the autonomic functions of the heart [8]. The predominance of the sympathetic system in the face of stress leads to increased heart rate and decreased HRV, whereas the predominance of the parasympathetic system in the resting phase leads to slowing heart rate and increased HRV [9,10]. Although many methods have been used in the evaluation of cardiac autonomic functions, the 24-hour rhythm Holter is frequently used in clinical practice because it provides more reliable information [11].

Hormonal fluctuations during PMS can potentially lead to an imbalance between sympathetic and parasympathetic functions [12]. Endocrinologic and other physiologic effects of the menstrual cycle on autonomic function have been investigated previously but no clear results have been obtained [1]. In individuals with PMS psychophysiologic stress might further induce disturbances in the ANS balance [12]. There is a limited amount of research on the assocation between alterations in the ANS and PMS. Given these theories, we aimed to investigate HR changes on ECG and holter measurements during the follicular and lutheal phases of the menstrual cycle in adolescents with and without PMS.

Methods

Study design and participants

This study was conducted at XXXX University XXXX Children's Hospital, clinics of Adolescent Medicine and Pediatric Cardiology. Between January 2022 and June 2023, female adolescents between the ages of 12 and 18, were included in the study. Study approval (GO 20/838) was obtained from the XXXX University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee for this study. The inclusion criteria was that the participants had been menstruating regularly for at least 3 months and had normal vital signs of resting heart rate, blood pressure, and body temperature. Exclusion criteria were if the participant was taking any medication that affects blood pressure and sympathetic activity (oral contraceptives, beta-blockers, ACE and calcium channel blockers, diuretics, steroids, etc.), had a chronic disease, and had been smoking, using alcohol and/or other substances.

The body weight and height of each participant were measured. Body weight was measured in kilograms using an electronic scale (Scale-Seca 220) and height was measured in centimeters using a Harpenden stadiometer. Body mass index (BMI) was calculated as body weight divided by the square of height (kg/m^2). Pubertal staging was determined according to the Tanner-Marshall method.

Demographic information such as age, height, body weight, BMI, pubertal stage, pathologic physical examination findings and menstrual cycle characteristics (age at menarche, menstrual duration, and menstrual cycle length) were questioned.

After the participant gave assent and their family gave written consent for the study, the premenstrual syndrome scale (PMSS) was completed by the participants and cardiological assesments were done at the folicular and lutheal phases of the menstrual cycle.

To coincide with the follicular period all appointments were scheduled for the 7th day of each participant's next menstrual cycle and to coincide with the luteal phase appointments were scheduled for 7-10 days before the onset of the next estimated menstruation. During this second evaluation during the lutheal phase progesterone leves were also measured.

Premenstrual syndrome scale

Each participant completed the PMSS, which is a diagnostic scale used in adolescents as a diagnostic scale for PMS in Turkey. It was developed by Gençdoğan in 2006 according to DSM III and DSM IV-R and aims to measure the severity of premenstrual symptoms. In this scale, there are 44 items that the individual marks by thinking about the occurance of criteria " one week before menstruation". The five-point Likert-type PMSS consists of 9 subscales (depressive affect, anxiety, fatigue, irritability, depressive thoughts, pain, appetite changes, sleep changes, bloating). The lowest score that can be obtained from the scale is 44 and the highest score is 220. Those with a PMSS total score of more than 50% are classified as PMD-positive [13]. According to the scale score, scores of 110 and above were included in the PMS group and scores below 110 were included in the control group.

Cardiologic assessments

During both the follicular and luteal phase, a 12-lead surface electrocardiography (ECG) was recorded in the supine position at 25 mm/ms and 10 mV/sec. A 24-hour rhythm Holter recorder

was applied on the same day. Holter recordings were analyzed with Cardioscan 12.0 software. All recordings were performed according to the European Society of Cardiology guidelines [14,15]. The next day, the device was removed by the physician and the data were transferred to the computer and recorded. All measurements were performed and interpreted by the same pediatric cardiologist at the follicular and luteal visits.

In ECG measurements, ventricular rate, PR interval, QRS duration and QT were evaluated. Ventricular rate is calculated by measuring the distance between two consecutive R-R waves. PR interval is the time between the onset of the P wave and the onset of the QRS complex. It indicates the total time required for depolarisation of the atria and passage of the stimulus to the atrioventricular (AV) node, His bundle and Purkinje fibres. The normal value for the PR interval is 0.12-0.20 seconds (3-5 small squares). The QRS complex indicates ventricular depolarisation. The normal QRS duration is 0.04 - 0.12 seconds (1 - 3 small boxes). The QT interval is the total time taken for depolarization and repolarization of the ventricles. It is from the beginning of the QRS complex to the end of the T wave. QTc refers to the corrected QT. The upper limit of QTc is 0.44 [16].

SDNN, SDNN-ms, RMS-SD, Triangular index were evaluated in Holter recordings. NN is the interval between two neighbouring R waves along the holter recording in time-based measurements. SDNN is the most commonly used time-based measure and is referred to as the standard deviation of all RR (NN) intervals over a 24-hour recording. SDNN-ms is the standard deviation of NN (R-R) in ms. RMS-SD is associated with short-term, rapid changes in heart rate. It is the standard deviation of the root mean square of the NN (R-R) intervals. The triangular index is the total number of NN intervals divided by the NN histogram height [15].

Progesterone measurement

Progestreone levels were measured during the second appointment coinciding with the lutheal phase to ensure the data was obtained during the luteal phase. Data were excluded if the progesterone value was below 3.5 ng/ml [17]. For this evaluation, serum progesterone level was measured on the day the serum sample was collected by chemiluminescence microparticle immunoassay (Chemilumines-cent microparticle immunoassay [CMIA]; Abbott Diagnos- tics, USA) using a monoclonal anti-progesterone acridinium-labelled conjugate. The analytical range was 0-40 ng/mL and the analytical sensitivity was <0.01 ng/mL.

Statistical analyses

Statistical analyses were conducted using IBM SPSS Version 25.0. For numerical variables, descriptive statistics were presented as mean ± standard deviation, while categorical variables were summarized as frequencies and percentages. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Differences between two independent groups for continuous variables were analyzed using either Student's t-test or Mann-Whitney U test, depending on the distribution of the data. Paired sample t-test or Wilcoxon test were used for comparing the folicular and lutheal phase findings of the participants, accordingly. Categorical variables were evaluated using the chi-square test. Statistical significance was defined as a p-value less than 0.05.

Results

We included a total of 48 participants in our study. According to the PMSS score, 29 were included in the PMS group and 19 in the control group. Some participants did not attend the control in the luteal phase despite attending in the follicular phase, resulting in fewer luteal phase participants. Additionally, several Holter recordings were canceled due to insufficient recording time, artefacts, or last-minute cancellations. Consequently, we obtained varying numbers of ECG and Holter measurements at each stage. The flow chart demonstrating the final number of participants in the PMS and control groups at follicular and luteal stages according to the conducted measurements has been presented in **Figure 1**.

The mean age was 15.37 ± 1.42 years in the PMS group and 14.66 ± 1.36 years in the control group. Height, body weight, and BMI values were similar in both groups. Age at menarche and duration of menstrual cycles were also similar. There was no statistically significant difference between the pubic stage and breast stage distribution of the participants (p=0,242, p=0,194). PMSS values were significantly different as expected (p<0.001). The comparsion of antropometric, pubertal, and menstrual data of adolescents with and without PMS is presented in **Table 1**.

Ventricular rate, PR interval, QRS duration, QT, and QTc values on ECG and SDNN-ms, SDNNi, RMS_SD, Triangular index, Percent Analyzed values on Holter were analyzed during follicular or luteal phase between both groups. These data were similar between both groups (**Tables 2** and **3**).

Follicular and luteal ECG and Holter data of the PMS group were compared. ECG data were not statistically different between both phases. In Holter data, SDNN-ms was lower in the luteal phase compared to the follicular phase (p=0.043).

Follicular and luteal ECG and Holter data were compared in the control group. ECG data were not statistically different between both phases. In the Holter data of the control group, the values between phases were similar. Interphase ECG values of PMS and control groups are presented in **Table 4** and interphase Holter data comparison is presented in **Table 5**.

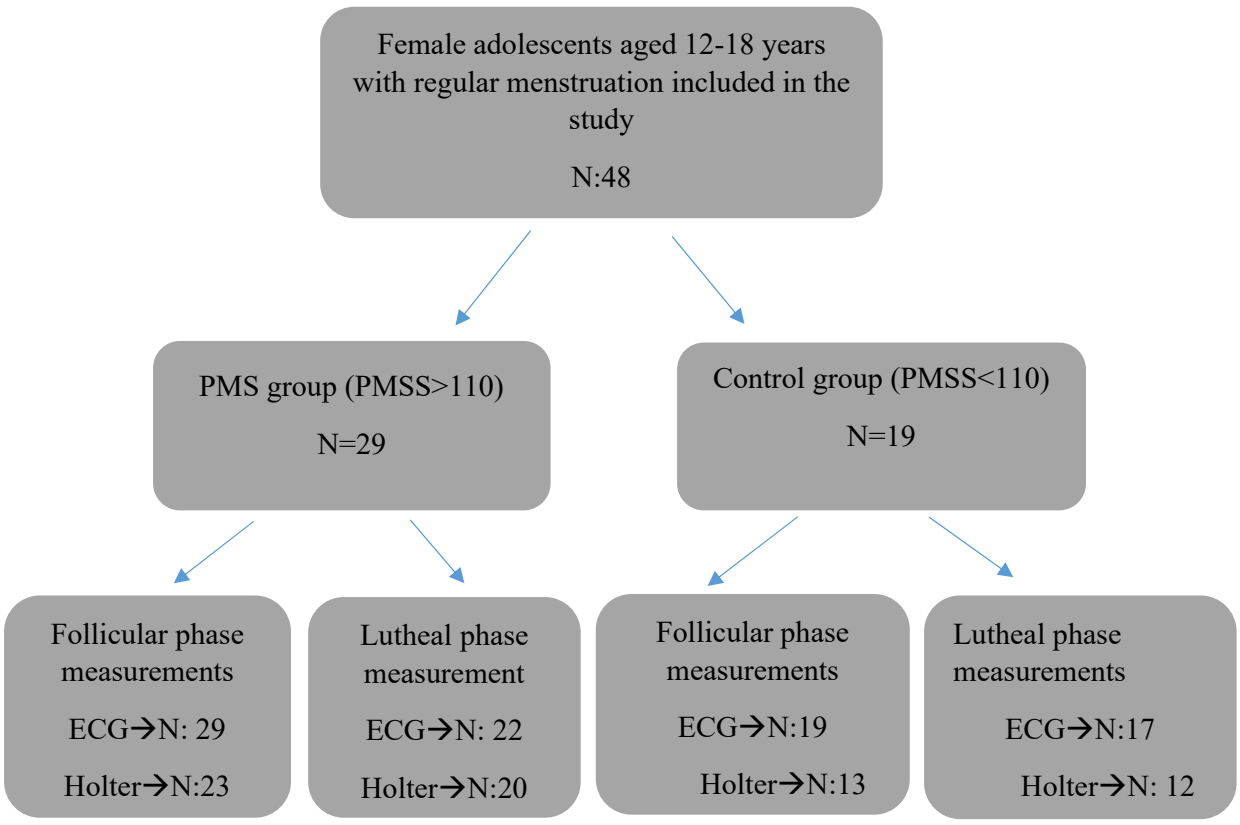

Figure 1. Flowchart of participants in follicular and luteal phases.

Table 1. Anthropometric, pubertal and menstruation data of the participants.

PMSS score, anthropometric measurements and menstrual characteristics	**PMS n: 29**	**Control n: 19**	**p-value**
PMSS scores	146.63 ± 23.53	87.64 ± 17.76	**<0.001**
Age (year)	15.37 ± 1.42	14.66 ± 1.36	0.093
Height (cm)	159.1 ± 6.36	158.55 ± 6.75	0.778
Body weight (kg)	56.50 ± 9.8	53.60 ± 12.7	0.258
BMI (kg/m^2)	22.06 ± 3.66	20.67 ± 3.28	0.186
Age at menarche (year)	11.75 ± 1.09	11.68 ± 1.19	0.982
Menstrual duration (day)	5.72 ± 1.06	6.05 ± 1.22	0.484
Menstrual cycle length (day) 21-25 days 26-30 days 31-45 days	 3 (10.34) 24 (82.75) 2 (6.89)	 0 (0) 18 (94.73) 1(5.26)	 0.407
Time after menarche (year)	3.78 ± 1.70	3.25 ± 1.66	0.374

Results are presented as mean ± standard deviation or n (%).
BMI: Body Mass İndex

Table 2. Comparison of the ECG data between adolescents with and without PMS during the follicular and luteal phases.

	PMS	Control	p-value
Follicular	**n: 29**	**n: 19**	
Ventricular rate (seconds)	78.13 ± 10.73	78.36 ± 10.13	0.620
PR interval (seconds)	125.10 ± 18.31	157.15 ± 142.63	0.841
QRS duration (seconds)	77.58 ± 8.09	78.00 ± 11.92	0.428
QT (seconds)	364.22 ± 16.26	353.29 ± 22.64	0.096
QTc (seconds)	414.19 ± 24.81	403.88 ± 16.85	0.109
Luteal	**n: 22**	**n: 17**	
Ventricular rate (seconds)	78.31 ± 12.34	80.11 ± 10.65	0.635
PR interval (seconds)	123.72 ± 19.29	129.70 ± 19.50	0.346
QRS duration (seconds)	78.22 ± 11.82	80.41 ± 7.04	0.221
QT (seconds)	364.78 ± 31.14	360.88 ± 23.00	0.637
QTc (seconds)	411.67 ± 20.98	409.47 ± 19.02	0.722
Results are presented as mean ± standard deviation			

Table 3. Comparison of the holter data between adolescents with and without PMD in follicular and luteal phases.

	PMS	Control	p-value
Follicular	**n:23**	**n:13**	
SDNN-ms (ms)	144.69 ± 34.30	133.30 ± 26.65	0.277
SDNNi (ms)	66.08 ± 14.16	64.46 ± 16.65	0.770
RMS_SD (ms)	41.56 ± 12.09	40.53 ± 13.75	0.824
Triangular index (ms)	40.86 ± 10.26	37.92 ± 11.49	0.451
Luteal	**n: 20**	**n: 12**	
SDNN-ms (ms)	133.70 ± 36.75	138.75 ± 31.91	0.931
SDNNi (ms)	62.28 ± 19.34	62.21 ± 17.52	0.686
RMS_SD (ms)	41.05 ± 14.37	41.25 ± 11.78	0.966
Triangular index (ms)	38.40 ± 10.50	42.75 ± 15.91	0.411
Results are presented as mean ± standard deviation			

Table 4. Comparison of follicular and luteal phase ECG data in the PMS and control groups.

PMS ECG data	Follicular phase n: 22	Luteal phase n: 22	p-value
Ventricular rate (seconds)	78.36 ± 11.48	78.31 ± 12.34	0.984
PR interval (seconds)	123.90 ± 18.59	123.72 ± 19.29	0.943
QRS duration (seconds)	78.00 ± 8.32	78.22 ± 11.82	0.917
QT (seconds)	364.22 ± 16.26	364.78 ± 31.14	0.913
QTc (seconds)	414.19 ± 24.81	411.67 ± 20.98	0.389

Control ECG data	**Follicular phase n: 17**	**Luteal phase n: 17**	
Ventricular rate (seconds)	77.23 ± 10.10	82.46 ± 10.30	0.153
PR interval (seconds)	169.53 ± 172.72	127.61 ± 19.65	0.723
QRS duration (seconds)	80.61 ± 9.02	80.23 ± 7.72	1.000
QT (seconds)	353.29 ± 22.64	360.88 ± 23.00	0.325
QTc (seconds)	403.88 ± 16.85	409.47 ± 19.02	0.211
Results are presented as mean ± standard deviation			

Table 5. Comparison of follicular and luteal phase holter data in PMS and control groups.

PMS Holter data	**Follicular phase n: 20**	**Luteal phase n: 20**	**p-value**
SDNN-ms (ms)	143.55 ± 34.96	133.70 ± 36.75	**0.043**
SDNNi (ms)	65.20 ± 14.70	64.10 ± 17.03	0.641
RMS_SD (ms)	40.50 ± 12.61	41.05 ± 14.37	0.811
Triangular index (ms)	40.00 ± 9.75	38.40 ± 10.50	0.480
Control Holter data	**Follicular phase n: 12**	**Luteal phase n: 12**	
SDNN-ms (ms)	132.20 ± 30.35	139.80 ± 33.05	0.368
SDNNi (ms)	62.60 ± 18.73	63.80 ± 13.53	0.651
RMS_SD (ms)	38.90 ± 15.26	40.20 ± 11.93	0.481
Triangular index (ms)	38.00 ± 13.06	43.60 ± 16.87	0.334
Results are presented as mean ± standard deviation			

Discussion

Experimental studies have shown that estrogens modulate the ANS, increasing vagal activity and decreasing sympathetic activity, thus providing a cardiovascular protective function. Progesterone, on the other hand, appears to have the opposite effect by increasing noradrenaline release. Considering these effects, changes in progesterone and estradiol during the premenstrual phase may lead into changes in ANS function [18]. In individuals with PMS psychophysiologic stress may further increase the sympathetic tonus leading to more evident HR changes. Therefore, we hypothesized that HRV would increase paralel to the increased sympathetic activity in adolescents with PMS compared to the control group. Additionally, we hypothesised HRV would be higher in the luteal phase compared to the follicular phase in both groups. However, our findings of 12-lead ECG recordings and 24-hour holter data did not support this hypothesis. In contrast to our results according to a study by Tamaki et al., women with more premenstrual symptoms were shown to have higher sympathetic activity in the late luteal phase than women with fewer symptoms [1]. It has been reported that women experiencing premenstrual symptoms exhibit higher levels of peripheral resistance and norepinephrine response compared to women who do not experience such symptoms when exposed to mental stress tests [19] and that there are some irregularities in the ANS [20]. According to these studies, PMS symptoms are thought to be caused by increased sympathetic activity due to the modulation of neurotransmitters as a result of hormonal fluctuation. In other words, the altered functioning of the ANS in the late luteal phase is associated with various psychosomatic or behavioral symptoms that occur before menstruation [12]. But these studies were conducted in adult women and to the best of our knowleadge this is the first study analysing autonomic function changes in adolescents with PMS. Studies have shown that HRV decreases with age and parasympathetic function decreases faster than sympathetic function. It has been reported that this may be related to cardiovascular physiology that changes with age [21]. In other words, HRV changes observed in the adult age group may not be observed in the adolescent age group.

Autonomic dysfunction has been shown to be more prominent in severe PMS. In a study of thirty healthy young

women, autonomic nervous system activity was assessed during the follicular and late luteal phases. No differences were detected between the follicular and luteal phases in women with mild and moderate PMS. In contrast, sympathetic nervous system activity was significantly increased in the late luteal phase in women with severe PMS [1]. In our study, we did not include patients with premenstrual dysphoric disorder. The reason we did not observe a difference may have been due to the severity of the disorder. In another study, HRV was evaluated in 28 women with premenstrual dysphoric disorder (PMDD) and 11 asymptomatic women without symptoms. Time- and frequency-based HRV was assessed during both the symptomatic luteal phase and the non-symptomatic follicular phase of the menstrual cycle. In PMDD patients, only RMSSD and SDNN values and high frequency values reflecting parasympathetic activity were lower in the follicular phase. This may be related to the reduced vagal tone in PMDD compared to controls, and this difference was most pronounced in the non-symptomatic follicular phase of the menstrual cycle, but not in the late luteal phase. Furthermore, no difference was found between menstrual phases in high-frequency power in both groups [22].

Although this was the first study to evaluate autonomic dysfunction in adolescents, it has some limitations. The small number of participants and limited number of adolescents with severe PMS symptoms were the main limitations of this study. Future studies with larger sample sizes, particularly those incorporating adolescents with severe PMS, would be beneficial in further elucidating PMS-related ANS changes. Conducting a multicenter study would enhance the generalizability of findings by incorporating diverse populations from different geographical regions, thereby increasing the robustness of the data. Such a study design would also allow for more comprehensive data collection, potentially uncovering subtle ANS variations linked to PMS across different cohorts. Additionally, aerobic training intensity was not questioned in order to evaluate the activity levels of our patients that affect HRV. On the other hand, HRV was performed in the patient's natural environment with a 24-hour Holter recording. Another limitation is diagnosis of PMS based on the adolescent's self-report which might have created a potantial recall bias or might have resulted in under or overreporting of PMS symptoms. The results of our study may also be due to the luteal timing of Holter measurements, during early luteal phase- 7 days before the expected menstrual bleeding, as PMS symptoms are most intense in the late luteal phase [2]. Finally, our study did not evaluate potential cofounders such as diet, sleep and stress levels which can impact ANS function and symptoms.

In conclusion our results showed that authonomic activity in adolescents with PMS did not vary according to menstrual cycle phases. Autonomic dysfunction cannot be directly responsible for the psycho-physiological changes seen in the adolescent age group of PMS, the etiology of which is still unclear. However, the exact mechanism is still unknown. Further studies involving a larger number of participants are needed in this area.

Conflicts of Interest/Competing Interests

All the authors declare that they do not have any conflict of interest.

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