# The relationship between menstrual cycle characteristics, premenstrual syndrome prevalence and blood phenylalanine level in women with PKU

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## ABSTRACT

Phenylketonuria (PKU) results from a deficiency in phenylalanine hydroxylase, catalyzing the conversion of phenylalanine (Phe) to tyrosine. Premenstrual syndrome (PMS) consists of physical, behavioral, and emotional symptoms occurring during the last week of luteal phase. The aim of the study was to determine the incidence of PMS, and document menstrual cycle characteristics of PKU patients to reveal the relationship with blood Phe levels. The study was conducted on 74 patients with a mean age of $21.7 \pm 5.4$ years. The mean age at menarche was $12.7 \pm 1.3$ years and 82.4 % had regular menstrual cycles. The periods of most patients (47.2 %) lasted 4–5 days. Menstrual cycles of 21–28 days were reported by 73 %, less than 21 days by 8 %, and more than 28 days by 19 % of women. Menorrhagia and dysmenorrhea was observed in 6.7 % and 71.6 % respectively. Adherence to diet was lost in 7 patients during the menstrual period. No significant relationship was found between Phe levels and PMS symptoms ($p > 0.05$). According to PMSS subscales, 52.7 % of patients with PKU had depressive feelings, 16.2 % anxiety, 55.4 % fatigue, 52.7 % irritability, 28.3 % depressive thoughts, 39.1 % pain, 59.4 % changes in appetite, 28.3 % changes in sleeping habits and 43.2 % had swelling. The findings of the study revealed that PMS prevalence was 39.1 % among PKU women. Awareness about this syndrome, will improve the quality of life in women with PKU by evaluating and taking measures for PMS.
*Synopsis:* Evaluating menstrual cycle characteristics and premenstrual syndrome in phenylketonuria patients provides valuable insights for enhancing their overall health profile and personalizing treatment and management plans.

## 1. Introduction

Phenylketonuria (PKU) and premenstrual syndrome (PMS) are two distinct medical conditions that impact the lives of individuals. PKU is an autosomal recessive inborn error of phenylalanine metabolism caused by the deficiency in the enzyme phenylalanine hydroxylase that converts phenylalanine to tyrosine. When left untreated, PKU leads to high phenylalanine (Phe) levels and metabolites in the blood and brain, causing intellectual disability, seizures, and behavioral problems. A lifelong Phe-restricted diet and adjunctive pharmacological treatments such as sapropterin or pegvaliase are administered [1].

Menstruation is a normal physiological process that begins at puberty, occurring approximately every month in women. It can lead to various physical and emotional changes, [2] and approximately 75 % of the population experience problems associated with menstruation. In addition, other health conditions, especially eating disorders, may affect the menstrual cycle [3].

PMS consists of physical, behavioral, and emotional symptoms occurring during the last week of luteal phase. PMS is a common health problem in women in the reproductive age and the global prevalence of PMS has been determined to be 47.8 %, with rates ranging from 12 % to 98 % in different countries [4]. The cause of PMS is not well understood. Some theories propose that menstrual issues may be linked to hormonal fluctuations, genetic predisposition, stress, dietary factors, and lack of physical activity [5]. Excessive carbohydrate intake and reduced protein intake can lead to an increase in serotonin concentration and its subsequent release in the brain, potentially influencing PMS symptoms. In addition, it was reported that a low plant-based and a high animal-based

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protein intake is related to an increased frequency of PMS [6]. In the majority of PKU patients, the ingestion of natural protein and dietary Phe is restricted to 25 % or less of a standard diet to maintain blood Phe concentrations within the target ranges. This typically necessitates the avoidance or limitation of high-protein food sources, encompassing meat, poultry, fish, eggs, as well as plant-based protein-rich foods such as nuts, seeds, quinoa, and various grains including wheat, oats, rye, and barley [1]. Prevalence of PMS syndrome may differ in PKU patients who need to avoid high-protein diets compared to other women. In addition, in some cases, high Phe levels in PKU patients can lead to symptoms that may be mistaken for or overlap with some of the emotional and psychological symptoms of PMS. When adults with PKU have elevated Phe levels due to poor dietary management or non-compliance, they can experience cognitive and psychological issues that may include irritability, mood swings, anxiety, depression, difficulty in concentration and fatigue [7]. These symptoms can sometimes resemble PMS symptoms like mood swings and irritability. PKU already requires strict dietary management to control Phe levels, and the emotional and physical symptoms of PMS can further complicate their well-being.

Until now, the menstrual characteristics among female PKU patients has not been addressed in any previous study. The aim of the study was to determine the incidence of PMS and document menstrual cycle characteristics of PKU patients to reveal its relationship with blood Phe levels. Therefore, in order to improve the reproductive health of PKU women in puberty and early adulthood, it is necessary to collect and evaluate basic data about their menstrual cycle patterns, the status of clinically significant PMS and their related factors in association to metabolic control of Phe levels.

## 2. Materials and methods

### 2.1. Participants

The study was conducted in a single-center at the Division of Pediatric Nutrition and Metabolism in Istanbul University Children's Hospital, Turkey. The study group consisted of female PKU patients diagnosed biochemically and genetically. Inclusion criteria included female PKU patients on dietary treatment experiencing menstruation for more than two years. The exclusion criteria encompassed the absence of concurrent conditions that may exhibit symptoms analogous to those of PMS, including but not limited to depression, dysthymia, generalized anxiety disorder, personality disorders, and mental disorders. Those who were pregnant, or taking hormonal medicines such as oral contraceptives, or disagreed to participate where excluded from the study. Participants who signed the informed consent were included in this study.

### 2.2. Data collection

The study was designed to evaluate the relationship between Phe levels, and PMS and menstrual cycle characteristics. Female patients with PKU filled a self-administered structured questionnaire that included personal information, dietary and daily habits, and Premenstrual Syndrome Scale (PMSS) [8]. The Personal Information Form included characteristics of participants age, height, weight, marital status, physical activity, sleeping problems, smoking, daily caffeine intake, and family history of PMS. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. The BMI cut-offs proposed by the WHO for underweight, overweight and obesity categories were used (1,2and BMI for underweight<18.5; normal weight18.5–24.9; overweight 25.0–29.9; obesity was 30.0–40 [9]. Patients who were sedentary or did not exercise at all were accepted as no physical activity, and patients who performed some degree of physical exercise were accepted being physically active. Menstrual history included age at menarche, menstrual pattern, duration of menstrual bleeding (in days), amount of bleeding, menstrual period (days), menstrual regularity

(regular/irregular), menorrhagia and dysmenorrhea. PMSS adapted by Gençdogan [8] in alignment with DSM III and DSM IV criteria, designed for the assessment of the intensity of premenstrual symptoms was used. This scale was employed to scrutinize the physical, psychological, behavioral, and social aspects of PMS symptoms and their influence on the daily lives of women afflicted by this condition. The scale utilized a 5-point Likert-type format encompassing nine subdimensions and a total of 44 items. These items are evaluated by the respondents considering their experiences one week prior to menstruation. The scale yields a minimum score of 44 and a maximum of 220, and scores exceeding 110 are indicative of having PMS. A high PMSS score indicates more severe premenstrual symptoms [8]. The plasma Phe and tyrosine levels, measured using a high-performance liquid chromatography (HPLC) device closest to the time the patients completed the PMS scale, were documented. The time interval between the plasma Phe level measurements and the completion of the PMS scale was a maximum of three months. Good metabolic control was defined as Phe levels below <600 μmol/L according to the criteria of the European Society for Phenylketonuria. Participants were categorized into two groups with low Phe (<600 μmol/L) and high Phe (>600 μmol/L), defined as having good or poor metabolic control, respectively [10].

### 2.3. Statistical analysis

The data were imported into an Excel spreadsheet of the Microsoft Office package and were subsequently analyzed using SPSS (Statistical Package for Social Sciences) programme Version 22. Data were examined via the mean, standard deviation for quantitative variables and the frequency and percentage for qualitative variables. Continuous variables were assessed for normality using the Kolmogorov-Smirnov test. Following the classification of participants into PMS and non-PMS or control groups, differences between these groups in terms of parametric data were analyzed using the independent sample $t$-test. Nonparametric data were evaluated with the Mann-Whitney $U$ test. The significance level was set at $p < 0.05$.

The study was approved by the Research Ethical Committee of Istanbul University, Istanbul Medical Faculty (IRB study protocol: 28.04.2023–1,736,005). An informed consent form was obtained from each participant.

## 3. Results

### 3.1. General characteristics of the participants

The study was conducted on 74 female PKU patients with a mean age of 21.7 ± 5.4 (range: 15.1 to 44.3) years. All participants self-identified as women. The demographic characteristics of the participants are presented in Table 1. In the study group 88 % were single. In terms of BMI, 60 % ($n = 45$) were normal; 10 % ($n = 7$) were underweight; 20 % ($n = 15$) were overweight; 10 % ($n = 7$) were obese. With respect to physical activity, 51.4 % described a sedentary lifestyle with little or no physical exercise and 48.6 % performed some degree of physical exercise. Seven of the patients (9 %) reported experiencing sleep disturbance symptoms. The occurrence of PMS in first-degree relatives of the patients was 17.5 %, 60.8 % of the patients were consuming coffee regularly, and 84 % of the patients were non-smokers.

### 3.2. Menarche age and menstrual cycle patterns and, association with Phe levels

The mean age at menarche was 12.7 ± 1.3 (range: 9–16) years. Regular and irregular menstruation was reported in 82.4 % and 17.6 % of the participants respectively. The menstrual characteristics of the study group is given in Table 2. The periods of most patients ($n = 35$, 47.2 %) lasted 4–5 days. In menstrual periods, 59 patients (80 %) used 2–4 pads per day, 9 patients (12 %) used fewer than 2 pads per day, and

**Table 1**
Demographic characteristics of the study group consisting of female phenylketonuria patients.

| Variable | PMS group | Non-PMS group | *P* value |
|---|---|---|---|
| Study group (n) | 29 | 45 | |
| Age (year) | 21.4 ± 5.8 | 22.6 ± 5.2 | 0.855 |
| BMI (kg/m$^2$) | 24.4 ± 6.6 | 23.3 ± 4.1 | 0.934 |
| Mariatal status | | | |
| Single | 25 | 40 | 0.730 |
| Married | 4 | 5 | |
| Smoking | | | |
| Yes | 6 | 6 | 0.523 |
| No | 23 | 39 | |
| Caffeine intake | | | |
| Yes | 17 | 28 | 0.754 |
| No | 12 | 17 | |
| Physical activity | | | |
| Yes | 17 | 20 | 0.234 |
| No | 12 | 25 | |
| PMS in the family | | | |
| Yes | 7 | 6 | 0.233 |
| No | 22 | 39 | |

6 patients (8 %) used more than 4 pads per day. Menstrual cycles of 21–28 days which is considered normal for women was reported in 73 % of the study group. Menstrual cycles with intervals less than 21 days, and menstrual cycles exceeding 28 days were experienced in 8 % and 19 % respectively. Menorrhagia and dysmenorrhea were reported in 5 (6.7 %) and 71.6 % respectively. Sixty-eight percent of the patients had fully adhered to their diet during the menstrual periods. Adherence to diet was lost in 7 patients (9.4 %) during the menstrual periods. 21.7 % of the patients were able to consume the entire amount of the Phe-free protein substitute. There was no difference in intake of Phe-free protein substitute during the menstrual period compared to non-menstrual periods. Patients reporting consumption of forbidden food during their menstrual periods was 48.6 %, while 51.4 % had not. The median Phe level of 68 patients during the three months preceding the questionnaire completion was determined. Regarding the degree of Phe levels in the study group, 47 % of the patients were evaluated as having good metabolic control, while 53 % were assessed to have poor metabolic control, with Phe levels >600 μmol/L. When analyzing the PMS scores and comparing this among women with irregular and regular cycles, no differences were found ($p > 0.05$). Furthermore, there was no correlation between the PMS score and duration of menstrual bleeding, cycle duration, amount of bleeding, nor with the duration of menses ($p > 0.05$). The incidence of PMS was found to be higher in patients with dysmenorrhea compared to those without dysmenorrhea ($p < 0.05$). The relationship between phenylalanine levels and premenstrual syndrome in female phenylketonuria patients is illustrated in Fig. 1. There was no correlation between the Phe levels and menstrual cycle pattern, duration of menstrual bleeding, duration of the menstruation cycle, amount of bleeding, dysmenorrhea, and menorrhagia ($p > 0.05$).

Menstrual characteristics of the participants are presented in Table 2.

### 3.3. PMSS prevalence and symptoms in association with Phe levels

The median Phe level of 68 patients during the three months preceding the questionnaire completion was determined, and the analysis of PMSS prevalence and symptoms was conducted based on this subset. The mean PMSS score of the participants was 103.4 ± 38.3 (median = 98.5, min = 44, max = 212). PMS prevalence was 39.1 %. All participants 74 (100 %) suffered from some type of PMS symptoms. The most frequent PMS symptoms were changes in appetite and fatigue.

**Table 2**
Menstrual parameters, in patients with good and poor metabolic control (according to phenylalanine levels) and premenstrual syndrome.

| Variable | Phe < 600 μmol/L (n = 32) | Phe > 600 μmol/L (n = 36) | P value | PMS group (n = 29) | Non-PMS group (n = 45) | P value2 |
|---|---|---|---|---|---|---|
| Age at menarche (year) | 12.9 ± 1.2 | 12.4 ± 1.4 | 0.165 | 12.3 ± 1.1 | 13.0 ± 1.4 | 0.180 |
| Menstrual cycle pattern | | | | | | |
| Regular | 27 | 29 | 0.465 | 24 | 37 | 0.605 |
| Irregular | 5 | 7 | | 5 | 8 | |
| Duration of menstrual bleeding (day) | | | | | | |
| 1–3 | 5 | 3 | 0.435 | 4 | 4 | 0.825 |
| 4–5 | 14 | 17 | | 12 | 23 | |
| 5–7 | 12 | 15 | | 12 | 17 | |
| More than 7 | 1 | 1 | | 1 | 1 | |
| Duration of the menstruation cycle (day) | | | | | | |
| < 21 | 4 | 4 | 0.827 | 4 | 2 | 0.354 |
| 21–28 | 24 | 30 | | 20 | 34 | |
| > 28 | 4 | 2 | | 5 | 9 | |
| Amount of bleeding (per day) | | | | | | |
| < 2 pads | 4 | 4 | 0.576 | 4 | 5 | 0.783 |
| 2–4 pads | 24 | 30 | | 22 | 37 | |
| > 4 pads | 4 | 2 | | 3 | 3 | |
| Dysmenorrhea | | | | | | |
| Yes | 23 | 26 | 0.593 | 25 | 28 | **0.022** |
| No | 9 | 10 | | 4 | 17 | |
| Menorrhagia | | | | | | |
| Yes | 2 | 3 | 0.557 | 3 | 2 | 0.324 |
| No | 30 | 33 | | 26 | 43 | |

Phe: phenylalanine; PMS: Premenstrual syndrome.
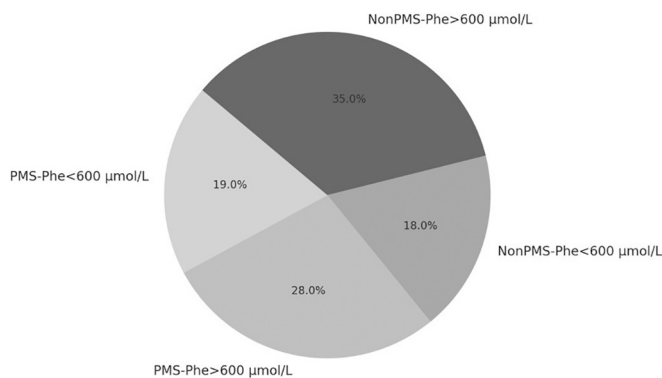


**Fig. 1.** The relationship between phenylalanine levels and premenstrual syndrome in female phenylketonuria patients.
PMS: Premenstrual syndrome; Phe: Phenylalanine.

According to PMSS subscales, 52.7 % of patients with PKU had depressive feelings, 16.2 % anxiety, 55.4 % fatigue, 52.7 % irritability, 28.3 % depressive thoughts, 39.1 % pain, 59.4 % changes in appetite, 28.3 % changes in sleeping habits and 43.2 % had swelling. The total and subscale scores of the Premenstrual Syndrome Scale are presented in

**Table 3**
Total and subscale scores of Premenstrual Syndrome Scale.

| PMS subscale score | PMS group (n = 29) | Non-PMS group (n = 45) |
|---|---|---|
| Depressive feelings | 25.2 ± 5.2 | 14.2 ± 4.4 |
| Anxiety | 18.4 ± 6.4 | 10.0 ± 3.1 |
| Fatigue | 22.4 ± 5.2 | 11.8 ± 4.5 |
| Irritability | 18.3 ± 4.1 | 9.8 ± 3.5 |
| Changes in sleeping habit | 9.0 ± 3.3 | 4.5 ± 1.8 |
| Swelling | 9.1 ± 3.4 | 5.8 ± 3.3 |
| Changes in appetite | 10.4 ± 3.1 | 6.7 ± 3.1 |
| Pain | 8.9 ± 2.3 | 4.8 ± 1.9 |
| Depressive thoughts | 20.9 ± 5.2 | 10.0 ± 3.0 |
| Total score ($X^- \pm SD$) | 142.8 ± 25.3 | 78.0 ± 18.3 |

PMS: Premenstrual syndrome.
*Scores exceeding 110 are indicative of having PMS.

Table 3. Among patients with well-controlled PKU, 13 had PMS while 12 did not and among patients with poorly controlled PKU, 19 had PMS while 24 did not. No significant relationship was found between Phe levels and PMS symptoms ($p > 0.05$).

## 4. Discussion

This is the first questionnaire-based evaluation on menstrual cycle characteristics and PMS score of female patients with PKU. Evaluating menstrual cycle characteristics and PMS in PKU patients provides valuable insights for enhancing their overall health profile, personalizing treatment and management plans.

Menarche is a crucial transition in a woman's life, signifying the onset of puberty and the acquisition of reproductive capability [11]. Yücel et al. [11] reported that the mean age of menarche was 12.74 ± 1.03 years, the mean cycle duration was 28.1 ± 5.7 days, the mean duration of the period was 5.9 ± 1.4 days, and the mean number of pads used per day was 3.4 ± 1.3 in their study involving 2000 healthy females in Turkey. Our findings were consistent with this study. Similar to the results of this study, the mean age of menarche was 12.7 years in our study. Dysmenorrhea rate of 71.6 %, was observed as the most common menstrual problem, as it was similarly reported among adolescent females worldwide [11]. Menstrual disturbances, such as oligomenorrhea, amenorrhea, and polymenorrhea, occurred in 27 % of our patients. Primary and seconder amenorrhea was not reported in our patients. The results of our study indicate that some abnormalities of the menstrual cycle are observed in females with PKU but no statistically significant relationship was identified between these issues and metabolic control.

The dietary treatment for PKU should be continued throughout life [10]. There are many factors that affect dietary adherence. In this study, we investigated dietary adherence during the menstrual cycle. Sixty-eight percent of the patients had completely adhered to their diet throughout their menstrual cycles. Seven patients (9.4 %) were not adhering to their diet during the menstrual period, reporting a temporary pause in their dietary adherence during this specific time. Some females with inborn metabolic diseases experience symptoms of metabolic decompensation that correspond to their menstrual cycles. In females with PKU, fluctuations in plasma Phe levels can occur during the menstrual cycle, with elevated Phe levels typically observed in the late luteal phase [12]. Considering the challenges patients face in adhering to the diet and consuming the Phe-free protein substitute during the menstrual cycle, it is advisable to monitor blood Phe levels at the onset of menstruation and, if needed, subsequently.

PMS is one of the most widespread disorders in the reproductive age. Its diagnosis depends on PMS symptoms and relationship with the luteal phase since there is no objective chemical biomarker of PMS. Symptoms of PMS can vary in severity and impact daily life and well-being [5]. The rate of PMS has been found to be higher in individuals who smoke, consume alcohol, and are exposed to passive smoking. Additionally, studies have reported a higher level of PMS in individuals who consume

excessive amounts of coffee [13]. In our study, we did not observe a statistically significant difference between PMS and age, BMI, marital status, smoking, caffeine intake, physical activity and PMS in the family. Seedhom et al. [13] reported a significant association between premenstrual symptoms and a maternal history of PMS, unlike to our study. PKU patients in the study group, following a special dietary regimen differing from their families, might have resulted in this divergent outcome.

Scientific evidence suggests a significant correlation between the presence and severity of PMS symptoms and variations in BMI, with an increase in BMI demonstrating a proportional escalation in the number and intensity of PMS symptoms [14]. In a study by Bertone-Johnson et al. [15] that investigated the association between body fatness and PMS in women, it was observed that women with a BMI ≥27.5 had a notably higher prevalence of PMS compared to women with a BMI <20. In our study group 30 % of PKU patients were overweight or obese, and no significant difference was observed regarding the presence or absence of PMS compared to those without obesity. In a study conducted in the United Kingdom, the prevalence of overweight and obesity in PKU females was not statistically significantly different from that in healthy individuals. Additionally, it was observed that as the average blood Phe concentration increased in women, a corresponding increase in their BMI was observed [16].

In our study, nearly half of the participants (48.6 %) engaged in some degree of physical activity. Our findings are consistent with the research conducted by Jani et al., where they utilized a self-reported evaluation through the International Physical Activity Questionnaire. In their study, the majority of PKU patients, precisely 85 %, reported being physically active. Moreover, 54 % of these patients indicated involvement in light to moderate physical activities [17]. Veena et al. [3] reported that premenstrual symptoms were also significantly high in girls who did not do regular physical activity. In our study, no significant correlation was observed between physical activity and the presence of premenstrual symptoms.

Diet-related factors can also influence PMS symptoms. According to studies, the consumption of fast food, high-calorie, fatty, fried foods, and excessive consumption of sweets/salty snacks increase the incidence of PMS. It has been observed that women who do not consume enough fruits and vegetables have a higher level of PMS compared to individuals who consume a higher amount of fruits and vegetables [13]. In a study conducted among fertile women aged 15–49 years in Turkey, PMS was reported at 72.2 % [18]. PMS prevalence was 39.1 % in our study. Low frequency of PMS in PKU patients may be attributed to be due to their Phe-restricted diet, which is based on fruits and vegetables. Further research and data are needed to determine the impact of a low Phe diet on PMS.

## 5. Conclusions

The findings of the study revealed that PMS prevalence was 39.1 % among PKU women. Awareness about this syndrome, will improve the quality of life in females with PKU by evaluating and taking measures for PMS. In conclusion, these data do not support the hypothesis that there is an association with the presence or severity of PMS symptoms among females with PKU and Phe levels. While these conditions are fundamentally different in their etiology and primary effects, they share a common feature of affecting the individuals' overall well-being and quality of life. However, individual experiences can vary widely, and some individuals with PKU may report changes in their symptoms or well-being during their menstrual cycle. This study highlights the need for further investigations to evaluate potential interactions or influences between PKU and PMS.

PMS: Premenstrual syndrome; BMI: Body mass index.

## Ethics approval

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional) and with the Helsinki Declaration of 1975, as revised in 2000. The study was approved by the Ethics Committee of the Istanbul University, Turkey (IRB study protocol: 28.04.2023–1,736,005). Informed consent was obtained from all patients for being included in the study.

## A patient consent statement

The patients and patient's parents gave their informed consent for the publication.

## CRediT authorship contribution statement

**Arzu Selamioğlu:** Writing – original draft, Supervision, Methodology, Investigation, Data curation. **Zelal Tandoğan:** Methodology, Data curation. **Mehmet Cihan Balcı:** Methodology, Formal analysis. **Meryem Karaca:** Investigation. **Tuğba Kozanoğlu:** Formal analysis, Data curation. **Alihan Yesil:** Data curation. **Gülden Gökçay:** Writing – review & editing, Validation, Supervision.

## Declaration of competing interest

The authors declare no conflict of interest.

## Data availability

All data generated or analyzed during this study are included in this. Further enquiries can be directed to the corresponding author.

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