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Serum ion level and its relationship with the symptoms of premenstrual syndrome in young women

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Abstract

The aim of the study was to evaluate the serum ions level and its relationship with Premenstrual Syndrome (PMS) symptoms in young women.

Method: Ninety-three volunteers were monitored for three months. The nutritional status evaluation was based on BMI. Three “maps of daily symptoms” were used to investigate the frequency of the SPM symptoms. The biochemical evaluation was done in the first month in the luteal phase. The levels of sodium, potassium, calcium, magnesium were determined by colorimetric methods. The hemoglobin and hematocrit concentration were determined by conventional methods.

Results: The symptoms like anxiety (1,13; 0,81; 0,66), edema (0,99; 0,51; e 0,22), depression (0,58; 0,36; 0,20) and mastalgia (0,56; 0,35; 0,09) were the most evident in the menstrual than luteal and follicular phase. A small number of volunteers presented hypocalcemia (1,4%), hyponatremia (4,22%) and hypernatremia (7,04%). However, the higher number of the volunteers presented lower calcium level (83,09%). The frequency of anemic women was high (24%). Significant associations ($P < 0,05$) were observed between the anxiety symptom and sodium ($r = 0,2630$); and magnesium and depression ($r = 0,2508$) and nausea ($r = 2882$).

Conclusions: The anemia and hypocalcemia is an important nutritional problem. The regulation of the calcium serum level seems to be affected in the luteal phase of the menstrual cycle and the sodium and magnesium ions influence some psychological (anxiety and depression) and gastrointestinal (nausea and constipation) symptoms.

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Key words: Menstrual cycle. Premenstrual syndrome. Ions. Premenstrual symptoms.

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NIVEL DE IONES SÉRICA Y SU RELACIÓN CON LOS SÍNTOMAS DEL SÍNDROME PREMENSTRUAL EN MUJERES JÓVENES

Resumen

El objetivo del estudio fue evaluar el nivel de iones séricos y su relación con el síndrome premenstrual (PMS) Los síntomas en las mujeres jóvenes.

Método: Noventa y tres voluntarios fueron monitoreados durante tres meses. La evaluación del estado nutricional se basa en el índice de masa corporal. Tres “mapas de síntomas diarios” se utilizaron para investigar la frecuencia de los síntomas de SPM. La evaluación bioquímica se realizó en el primer mes de la fase lútea. Los niveles de sodio, de potasio, de calcio, de magnesio se determinaron por métodos colorimétricos. La concentración de hemoglobina y hematocrito se determinaron por métodos convencionales.

Resultados: Los síntomas como la ansiedad (1,13, 0,81, 0,66), edema (0,99, 0,51, 0,22 e), depresión (0,58, 0,36, 0,20) y la mastalgia (0,56; 0,35; 0,09) fueron los más evidentes en el ciclo menstrual de lútea y la fase folicular. Un pequeño número de voluntarios presentó hipocalcemia (1,4%), hiponatremia (4,22%) y la hipernatremia (7,04%). Sin embargo, el mayor número de los voluntarios presentó menor nivel de calcio (83,09%). La frecuencia de las mujeres anémicas fue alta (24%). Se encontraron asociaciones significativas ($P < 0,05$) entre el síntoma de ansiedad y sodio ($r = 0,2630$), y magnesio y la depresión ($r = 0,2508$) y náuseas ($r = 2,882$).

Conclusiones: La anemia y la hipocalcemia es un problema nutricional importante. La regulación de la concentración sérica de calcio parece ser afectada en la fase lútea del ciclo menstrual y el sodio y los iones de magnesio influir en algunos (ansiedad y depresión) psicológica y los síntomas gastrointestinales (náuseas y estreñimiento).

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Palabras clave: Ciclo menstrual. Síndrome premenstrual. Iones. Síntomas premenstruales.

Abbreviation list

PMS: Premenstrual Syndrome.

UFF: Federal Fluminense University.

BMI: Body Mass Index.

WHO: World Health Organization.

SISNEP: National Research Ethics System.

FAPERJ: Foundation for Research Support of the State of Rio de Janeiro.

PROPI: Pro-Rectorate of Research, Graduate Studies and Innovation.

CNPq: National Council for Scientific and Technological Development.

Introduction

According to the *National Association for Premenstrual Syndrome*, 2000¹, more than 90% of menstruating women experience any premenstrual change. The premenstrual syndrome (PMS) is a chronic disorder that happens in the luteal phase of the menstrual cycle and disappears after the menstruation, characterized by the presence of physical symptoms, psychological and behavioral. Have been cataloged more than 150 symptoms attributed to it. These are not common in all women, they appear in different form and inconsistent making each person experiences one or more symptoms².

Among the various symptoms mentioned in the literature, the most observed are mastalgia, constipation, water retention, increase in body weight, mood swings (irritability, anxious and depression), insomnia, changes in appetite and in the feed behavior (compulsion), pain during ovulation and acne³. In addition of the great variability, stand out the intensity and the duration of the symptoms which will vary from cycle to cycle and can be influenced by others factors, such as stress and tiredness.

Most of the metabolic changes that occur during the menstrual cycle is associated with luteal phase, when progesterone levels are elevated, causing the increase of body temperature, hyperventilation and increase of the plasma volume⁴. Some authors claim that the increase of the basal metabolic rate increases the necessity for magnesium and oxidative enzymes, which are found in higher concentrations during this phase⁵.

Thys-Jacobs, 2000, emphasize that the ovarian steroid hormones, particularly the estrogen, influence actions of calcitropic hormones, such as the parathormone⁶. Other researchers have shown that hypercalcemia and hypocalcemia have been associated with many affective disorders. The hormonal changes that happen during the menstrual cycle also seem to influence the sodium ion and potassium. The progesterone has been considered responsible for liquid retention and sodium during the luteal phase, and thereby the presence of some physical symptoms during this phase⁴.

There is evidence in the literature showing that, even parameters related to iron are influenced by the menstrual cycle. During the menstrual bleeding there is increase of need for iron, reducing the hemoglobin and ferritin level with consequent elevation in intestinal absorption of this ion⁸.

The influence of different ions level on the PMS symptoms is not well known in Brazilian literature. Thus, this study aims to measure the serum level of ions during the luteal phase of the menstrual cycle of young women and observe possible associations with the symptoms of premenstrual syndrome.

This study intended to contribute to the advancement of scientific knowledge in this area, improving the nutritional approach to face issues that are part of the female physiology, contributing to improving the quality of life of young women without a diagnosis of the syndrome.

Methodology

This is an observational, longitudinal and randomized study which accompanied young women, college, living in the cities of Rio de Janeiro and Niterói and its surroundings for a period of three months. The selection criteria for participation in the study were to present a regular menstrual cycle –between 22 and 35 days–, minimum 20 years old and maximum 40 years old, absence of disease, not being a smoker and do not take nutritional supplements.

The recruitment of volunteers (n = 93) and the development of the study were conducted at the School of Nutrition in the Universidade Federal Fluminense (UFF), located in Niterói, during the year 2011. The activities were initiated only after approval of the study protocol by the Ethics Committee responsible for human studies at Hospital Antonio Pedro, UFF. After clarification of the purpose of the project and use of data under the guarantee of anonymity, the volunteers consented in writing the participation in the project. Once aware and according to the research proposal, the volunteers were interviewed for the characterization of the group and to obtain information about the lifestyle, age of menarche and beginning of sexual relations. This information was obtained according to standardized questionnaire, applied to the volunteers by the main researcher in the first approach due to the acceptance of the same in the study.

Anthropometric Assessment

The Anthropometric assessment of the volunteers involved the weight measurement (total body mass, kg) and height (meters). These measures were used to calculate the Body Mass Index (BMI) defined as body mass, in kg, divided by the height, in meters, squared. The anthropometric assessment was realized in two

moments: 1) in the luteal phase, between the 23° and 25° day of the cycle and 2) in the follicular phase, between the 10° and 12° day of the cycle, during 3 months.

The body mass measurement was performed at morning considering 12 hours fasting. For measurement of total body weight was used scales Tanita, Model TBF 350 – accuracy of 0,2 Kg of the Laboratory of Nutritional and Functional Assessment from UFF, supported on a flat surface and the stature was obtained using a stadiometer. To classify the nutritional status of the volunteers were adopted the World Health Organization's criteria (WHO), 2007⁹. Underweight BMI < 18,5; Normal weight BMI ≥ 18,5 and < 25,0; Overweight BMI ≥ 25,0 and < 30,0; Obesity BMI ≥ 30 kg/m².

Evaluation of the Premenstrual Syndrome Symptoms (PMS)

The evaluation of symptoms (anxiety, edema, depression, constipation, diarrhea, mastalgia and nausea) and its intensity was performed from the application of a adapted diary appropriate (Daily Symptom Report)¹⁰, where the volunteers reported daily symptoms identified: 1) in the luteal phase, between the 23° and 25° day of the cycle and 2) in the follicular phase, between the 10° and 12° day of the cycle, during 3 months. These symptoms have received a score on a five-point scale: 0 = absent; 1 = light (only slightly apparent to you); 2 = moderate (the symptom is perceptible, but does not alter the daily routine); 3 = intense (continuously bothered by the symptom and/or the symptom interfere the daily activities); 4 = serious (the symptom is more than can be controlled/supported and/or preclude the continuation of daily activity).

Biochemical Analysis

The Biochemical Analysis was realized only at the first month in the luteal phase of the menstrual cycle, between the 23° and 25° day of the cycle, due to non-compliance of the volunteers to donate blood samples more than once. Among 93 volunteers, only 71 have agreed to donate blood samples to the biochemical dosages. The blood collection was realized by a qualified technician, by venipuncture with disposable syringe, being watched the technical care on the sample gathering. Were collected 10 mL of blood after an overnight fast of 12 hours. The blood was immediately transferred to tubes containing heparin and used for the determination of hematocrit and hemoglobin. After, the blood was centrifuged at 3500 rpm for 15 minutes to obtain the plasma that was divided into aliquots and frozen at -76°C until analysis.

The hematocrit was analyzed in a standard procedure by microcentrifugation through the conventional

capillary technique, using a microcentrifuge Hemospin Model MICRO SPIN 1000. The hemoglobin level, calcium and magnesium were determined by colorimetric method, using commercial kit, in a spectrophotometer Model SP 220 in the following wavelengths: 540 nm, 578nm, 500nm, respectively. The determination of the ions level: sodium and potassium were realized by flame photometry, using photometer Model BFC – 300.

Statistical Analysis

It was used the GraphPad Instant version 3.01 to the realization of the analysis. The normality assumption (Gaussian distribution) of the data was checked using the Kurtosis and Skewness tests. The data with the normal distribution are presented from the descriptive statistics like average and standard deviation and the non-normal data like median and confidence interval. For the analysis of comparison of means between the three time periods studied it was used ANOVA with repeated measures and Tukey as post test. The Pearson's correlation analysis was used to check possible associations between the concentration of electrolytes and the symptoms of premenstrual syndrome. It was accepted a significance level of 5%.

The research protocol has fulfilled the ethical principles contained in the Declaration of Helsinki and the rules of resolution 196/96 of the National Board of Health and was approved by the Ethics in Research on humans at the University Hospital Antonio Pedro, approved in the National Information System on Ethics in Human Research (SISNEP) under the protocol number 0084 0 258 000-07.

Results

Characterization of the volunteers

Most of the volunteers (80.64%) were single college students, mean age 23 years old, menarche at 12 and first sexual intercourse at 18 years old. Only 34% of the volunteers reported regular physical activities in the gym (1.5 hours per week). The majority (65%) did not played any physical activity related to sport and leisure, only academic activities at the University.

About 53% of the volunteers used only the contraceptive hormonal method; 7.52% the barrier method (preservative); 17.20% used both methods and 21.50% weren't using any contraceptive method. The menstrual cycle, on average, had duration of 28 days, that may be considered normal¹¹ (Table I).

The assessment of nutritional status of the volunteers in the luteal and follicular phases of the menstrual cycle was based on average values of BMI of the three months follow up. The average BMI of the volunteers during the luteal phase was 22.74 ± 3.75 kg/m² and on

Table I
General characteristics of the volunteers studied

Characteristic	Average \pm SD	Min-Max.
Age (years)	23,36 \pm 4,15	18-40
Menarche (years)	12,30 \pm 1,28	10-15
Onset of sexual activity (years)	18,14 \pm 2,28	11-25
Physical Activity (hours /week)	1,57 \pm 2,63	0-12
Menstrual cycle duration (days)	28,51 \pm 1,84	22-31

the follicular phase were $22.88 \pm 4.21\text{kg/m}^2$. It was found that the most (>78%) of the volunteers were eutrophic with no significant changes in the nutritional status throughout the study between the two phases of the cycle. It was observed low frequency of underweight women (4.28% and 4.68%), in both phases, and 15.71% and 17.18% were overweight and/or obesity in the luteal and follicular phases, respectively.

The perception of the intensity of the symptoms related to PMS was assessed during the luteal, menstrual and follicular phases of the menstrual cycle and categorized according to the map of symptoms at levels ranging from 0 to 4 (Fig. 1). The values shown represent the mean of three months studied. It was observed that on the menstrual phase these symptoms were more intense than on the luteal and follicular phases. The anxiety was the most perceived symptom ($p < 0.0001$) on the menstrual (1.13) and luteal (0.81) phase. However, this symptom decreased in the follicular phase (0.66). The edema (0.99; 0.51; 0.22); depression (0.58; 0.36; 0.20) and mastalgia (0.56; 0.35; 0.09) were the most perceived ($p < 0.0001$) by the volunteers in the menstrual and luteal phases than in follicular phase, respectively. Being the gastrointestinal symptoms perceived in a milder form, with no statistical difference for constipation and nausea. However, the manifestation of diarrhea was significantly higher in the menstrual phase ($p < 0.03$).

It was observed associations between serum level of electrolytes and the intensity of symptoms related to the PMS. The anxiety symptom was negatively associated with sodium ($r = -0.26$); and magnesium positively with depression ($r = 0.25$) and nausea ($r = 0.29$) symptoms. For both correlations was considered $p < 0.05$.

The table II shows the frequency of the volunteers in function of the perception of the intensity of the symptoms anxiety, edema, mastalgia and depression. It can be observed that most of the volunteers presented symptoms in the category absent or light. However, the frequency of volunteers who showed these symptoms with moderate and intense intensity was higher in the menstrual phase (50.72%; 39.13%; 21.74%; 24.64%) and luteal (37.68; 17.39%; 11.59%; 10.14%) than in the follicular phase (21.74%; 5.80%; 2.90%; 4.35%), respectively. However, a small number of volunteers (1.45%) perceived the symptom edema with serious intensity, only, on the menstrual phase.

The serum level of sodium, potassium, calcium and magnesium during the luteal phase is showed on the table III. The sodium (139.13 mEq/L) is found within the range considered normal, however there were hyponatremia (4.22%) and hypernatremia (7.04%) cases in some volunteers. The potassium level was 4.09 mEq/L and most of the volunteers (98.59%) were within acceptable limits. In relation to calcium, it was observed the serum level of 7.93 Mg/dL and could be perceived that the majority (83.09%) of the volunteers had values below of the normality. Unlike calcium, the magnesium level was 1.89 Mg/dL. Eighty percent of the volunteers were within normal limits, only 14% had concentrations below the normality range and 5.63% above this.

In the present study, the volunteers had hematocrit and hemoglobin value within the normal range ($39.46 \pm 2.56\%$; $12.98 \pm 1.22\text{ g/dL}$), respectively. However, about 24% of the women studied had low hemoglobin concentration, characterizing anemia.

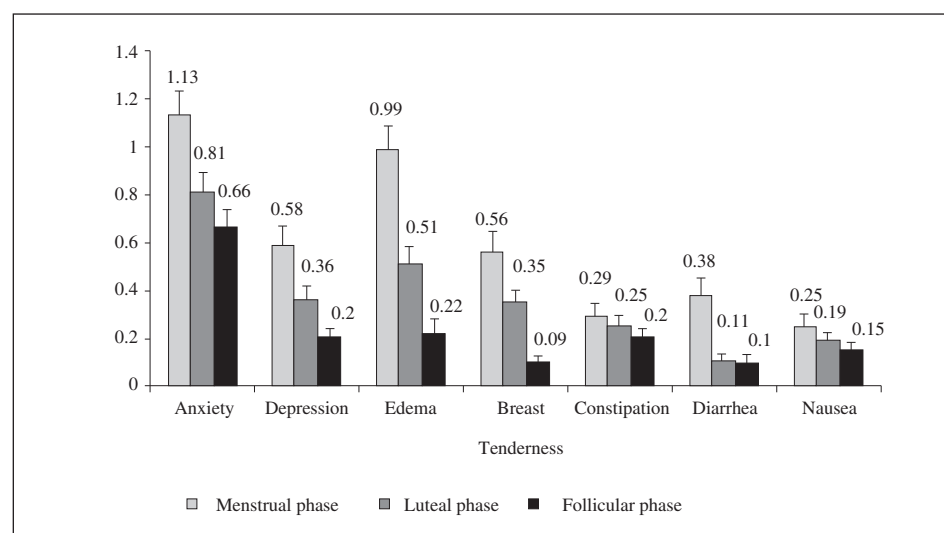


Fig. 1.—Intensity of symptoms related to Premenstrual Syndrome during the menstrual, luteal and follicular phases of the menstrual cycle.

Table II
Frequency of volunteers according to the intensity of anxiety, edema, mastalgia and depression symptoms

Symptoms	Menstrual cycle phases		
	Menstrual	Luteal	Follicular
Anxiety			
Absent (0)	10,14%	7,25%	14,49%
Light (1)	39,13%	55,07%	63,77%
Moderate (2)	34,78%	33,33%	17,39%
Intense(3)	15,94%	4,35%	4,35%
Edema			
Absent (0)	15,94%	26,09%	49,28%
Light (1)	43,48%	56,52%	44,93%
Moderate (2)	28,99%	14,49%	4,35%
Intense (3)	10,14%	2,90%	1,45%
Serious (4)	1,45%	0,00%	0,00%
Mastalgia			
Absent (0)	26,09%	30,43%	63,77%
Light (1)	52,17%	57,97%	33,33%
Moderate (2)	18,84%	11,59%	1,45%
Intense (3)	2,90%	0,00%	1,45%
Depression			
Absent (0)	39,13%	28,99%	46,38%
Light (1)	36,23%	60,87%	49,28%
Moderate(2)	20,29%	10,14%	4,35%
Intense (3)	4,35%	0,00%	0,00%

Discussion

For some women the menstrual cycle can bring emotional, behavioral, physical and cognitive changes. While for others persons this events go unnoticed. In general, the literature shows the changes in behavior, during the menstrual cycle, only women with premenstrual syndrome¹². In Brazil, there is little available information about these changes during the menstrual cycle of women with and without the syndrome.

The role of changes in female sex hormones is considered to be of central importance in premenstrual symptoms¹³. The metabolism of calcium suffers hormonal influences and these are able of causing fluctuations in its concentration throughout the menstrual cycle⁶. The present study found low serum calcium level in most of volunteers studied, corroborating result found by another study with adult women with PMS symptom, in New York. Other researchers, studying the levels of serum calcium in young women, during all phases of the menstrual cycle, showed low level of serum calcium on the luteal phase¹⁴. This may be explained by the fact that estrogen inhibits the action of the PTH and stimulate the release of calcitonin. Thereby, it can influence the serum concentration of calcium and its regulation by inhibiting bone resorption, suppressing the mesenchymal process involved in the bone remodeling⁶.

As the extracellular calcium is the source of the intracellular calcium, the reduction of their serum level results in abnormalities in the synthesis and release of neurotransmitters¹⁵. This event can affect the excitability of neuromuscular tissues involved in emotional regulation. Symptoms related to the PMS, such as irritability and anxiety have been associated with hypocalcemia. On the other hand, the increase in calcium concentration has been noted in some patients with depression⁷.

Therefore, some researchers^{6,16} suggest that PMS and its symptoms can be a reflection of the deregulation of calcium balance due to the hormone fluctuations responsible for its homeostasis. Thus, the restoration of the calcium balance can help to relieve the symptoms of PMS¹⁶.

Research conducted in India¹⁴ with women suffering from PMS, observed that during the luteal phase, serum level of magnesium, also, have been implicated in the etiology and symptomatology of the PMS. In the present study, it was observed low magnesium level in fourteen percent of the volunteers studied and the literature shows that magnesium deficiency during the

Table III
Serum concentration and frequency of inadequacy of the ions studied

Indicator	Reference Value	Average ± SD	% adequation
Sodium (mEq/L)	135-145	139,13 ± 3,4	Below: 4,22% Adequate: 88,73% Above: 7,04%
Potassium (mEq/L)	3,6-5,6	4,09 ± 0,29	Below: 1,40% Adequate: 98,59%
Calcium (mg/dl)	8,8-11,0	7,93 ± 0,90	Below: 83,09% Adequate: 16,90%
Magnesium (mg/dl)	1,6-2,4	1,89 ± 0,33	Below: 14,08% Adequate: 80,28% Above: 5,63%

luteal phase can influence the symptoms of the PMS for several metabolic pathways in healthy women. It is important emphasize that magnesium is involved in the activity of serotonin and other neurotransmitters, in the neuromuscular function and stability of the membrane cell⁶. Thus, the cyclic changes in the calcium and magnesium level can then produce the well-known psychological symptoms of PMS, during the luteal phase in women with low serum magnésio^{6, 17}. Our results corroborate those from the literature, showing a positive significant association of magnesium with depression and nausea symptoms. Current studies suggest that supplementation of calcium and magnesium seems to minimize these sintomas^{6,7,18}.

Oscillations in the sodium level and its implications on PMS symptoms have been documented by some researchers^{5,19,20} and in this study. Some possible causes for the changes in serum sodium, in the luteal phase, include the increase in the concentration of antidiuretic hormone and the progesterone antagonistic effect in the aldosterone system. So, it can affect the expression of some symptoms, such as edema¹⁹. It must be emphasized the multiplicity of phenomena interacting on the serum ions level and the importance of several hormones acting on its control. Although in the present study there was no observed relationship between the sodium level on the edema symptom, this was the ion which had important association with the anxiety symptom. It shows the importance of its regulation and problems that the overconsumption can cause.

A study realized by Santos et al, 2011²¹, shows that the women in the luteal phase tend to increase the consumption of food high in sodium and fat, due to the increase of "food desire" symptom, which is directly related to the psychological aspect of anxiety.

In general, the anemia in developed countries is rare. Unlike in the Brazil, the anemia is still considered a public health problem^{22,23}. Studies with teenager²⁴ and adult women²⁵, independent of the menstrual cycle, show similar frequency of anemia observed in this study. However, a research conducted in women of developed country, shows different results of those reported here, showing normal hemoglobin values during the luteal phase, with concentration slightly lower only in women during the period of bleeding²⁶.

The presence of those symptoms, above cited, is a characteristic and important fact for the determination of PMS. The somatic, emotional, cognitive and behavioral factors depend on its intensity and it can interfere of many ways on women's life²⁷. This study found that the volunteers presented the symptoms more intense during the menstrual cycle, followed by the luteal and follicular phases. Among all the symptoms analyzed, the edema, depression and mastalgia were the most perceived by the volunteers. Some researchers claim for the existence of metabolic changes and changes in electrolyte balance during the luteal phase. So, the hormonal changes that occur during this process can affect physiological and biochemical processes^{4,6}.

Conclusion

These results suggest that although the volunteers, mostly presenting appropriate anthropometric nutritional status, we found high frequency of anemia and hypocalcemia. The regulation of serum calcium concentration seems to be affected in the luteal phase of the menstrual cycle. Sodium and magnesium ions influence some psychological and gastrointestinal symptoms.

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