IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 14, Issue 3 Ver. IV (Mar. 2015), PP 50-55
www.iosrjournals.org

Study of Effect of Serum Calcium Levels on Autonomic Nervous System in Pre-Menstrual Syndrome

Aruna Devisetty[1*], Chandrakala Kambar[2], Hanumanth N[3]
[1](Associate professor, Department of Physiology, RIMS, Srikakulam, AP,India
[2](Associate professor,Department of Pharmacology, Siddhartha Medical College, Vijayawada,AP,India)
[3](Lecturer in Statistics, Dr PSIMS & RF, Gannavaram, AP, India.)

Abstract: *Premenstrual syndrome (PMS) is defined as the cyclic recurrence of a constellation of non specific somatic, psychological or behavioural symptoms that are entrained with the luteal and premenstrual phases of the menstrual cycle and are of sufficient severity to result in deterioration of interpersonal relationships, interference with normal activities or both. The present study is an attempt to correlate the changes in serum calcium levels and changes in autonomic nervous system in PMS with an aim to derive a simple remedy to the much recurrent suffering of women like supplementation of calcium available plenty in many natural foods. This study included 100 women of reproductive age group, 50 with and 50 without PMS symptoms. In both groups blood pressure and heart rate were recorded by clinical methods as a function of autonomic nervous system and serum calcium levels were estimated by Ensure biotech O-Cresolphthalein complexone (OCPC) method during pre and post menstrual phases. Statistical methods were applied to compare the results and found significant variation in both autonomic function and serum calcium levels during luteal phase of PMS and a positive correlation with serum calcium and heart rate. It may be concluded from the present study that decrease in serum calcium levels during luteal phase in PMS may cause disturbance in autonomic nervous system, in PMS.*
Key words: *Heart rate, Blood pressure, Serum Calcium, pre menstrual phase, post menstrual phase*

I. Introduction

Indian women had a luxury of five days of absolute rest every menstrual period including relief from household duties and also of duties pertaining to her own children in olden days. They were provided with a special diet rich in calcium and iron and some sort of foods containing anti anxiety substances .[1]

Modern day women with increased demands and stresses, changes in nutrition and new careers that take them away from their natural cycle and their connection to the home, garden and nature, are particularly susceptible to PMS symptoms. [2] They are struggling to achieve high ambitions at the cost of both physical and mental health.

PMS is a major clinical entity affecting large segment of female population. PMS is a psychoneuro endocrine disorder with biological, psychological and social component along with stress as its major cause. PMS encomposes wide variety of cyclic, recurrent, physical, emotional, behavioural symptoms occurring during late luteal phase of menstrual cycle and abating shortly following beginning of menses. Stress disturbs the balance of sympathetic and parasympathetic nervous system.[2] Changes in heart rate and blood pressure are the most important physiological response following stress. [3]

Estrogens excess or deficiency or progesterone deficiency, estrogen-progesterone imbalance, abnormal androgen levels and gonadotropin abnormalities, thyroid dysfunction, excess production of aldosterone, antidiuretic hormone or both, and low levels of sex-hormone binding globulin, nutritional factors are all implicated in the etiology of PMS.[5]

About 200 symptoms have been associated with PMS. Most prominent being irritability, tension and dysphoria. Emotional and nonspecific symptoms include stress, anxiety, insomnia, headache, mood swings, increased emotional sensitivity, abdominal bloating, muscle cramps, breast tenderness. There is no definitive lab test or physical findings for the diagnosis. Diagnosis is based on ACOG (American Congress of Obstetricians and Gynaecologists) criteria. [2,7]

Calcium Calcium is an essential mineral with many biological roles. It is a major constituent in teeth and bones, crucial in muscle contractions and nerve conduction, as well as hormone regulation.

Disturbances in calcium regulation underlie the pathophysiologic characteristics of PMS. There is scientific evidence that support cyclic fluctuations of calcium and vitamin D during the menstrual cycle and ovarian hormones influence calcium, magnesium and vitamin D metabolism and it is estrogen that regulates calcium metabolism, intestinal calcium absorption and parathyroid gene expression and secretion, triggering fluctuations across the menstrual cycle. [7]

Autonomic nervous system (ANS) Sympathetic and parasympathetic divisions of the autonomic nervous system function antagonistically, complementarily, and/or harmoniously to play a crucial role in

dynamically controlling the response of the body to a range of external and internal stimuli, maintaining nearly every important homeostatic process in the body. [8]

Stress disturbs the balance of sympathetic and parasympathetic nervous system and changes in the heart rate and blood pressure are the most important physiological parameters of ANS. Changes in the autonomic nervous system function play a vital role in orchestrating the homeostatic disturbances during different phases of menstrual cycle.

Based on the above theory and data from various previous studies we made this study to be taken up in this area of south India to assess the variations in autonomic nervous system parameters in relation to serum calcium levels in PMS.

II. Objectives

To determine the effect of serum calcium levels, and changes in heartbeat and blood pressure in premenstrual and post menstrual phases of PMS patients and normal subjects.

To correlate the changes in serum calcium and changes in heart rate and blood pressure in pre and post menstrual phases in normal with those in PMS subjects

III. Materials And Methods

A sample of 50 healthy premenopausal women with premenstrual syndrome were taken as test group and sample of 50 healthy premenopausal women without premenstrual syndrome were taken as control group. This is a progressive observational study which was approved by the Institutional ethics committee, Siddhartha medical college, Vijayawada. Informed consent was obtained from all the subjects in the local language.

A self designed questionnaire was prepared based on relevant studies to collect the data from both the groups. Serum Calcium was estimated by spectrophotometry during premenstrual phase and postmenstrual phases of their cycles. Heart rate and blood pressure were recorded clinically during pre and post menstrual phases.

Healthy women in the reproductive age group of 15 to 45 years and women having regular menstrual cycles in the last six months were included in this study. Women with history of psychiatric disorders, ovarian dysfunction, other gynaecological disorders, pregnancy or postpartum period, using oral contraceptives within last 3 months, serious physical illness and history of taking any medications such as psychoactive preparations or hormones were excluded from the study.

The subjects belonged to all socio-economic strata, both educated and uneducated, employed and unemployed, married and unmarried. All the subjects had regular cycles. Symptoms were prospectively documented. General examination was done to rule out any physical illness clinically.

Investigations.

Serum calcium:

Serum Calcium was measured by the Ensure biotech OCPC method.

Principle: In an alkaline medium, Calcium reacts with O-Cresolphthalein complexone and forms a purple colored complex. Intensity of colour is measured at 570nm and this corresponds to Calcium concentration.

O-Cresolphthalein complexone+ 2 Ca^{++} = OCPC $(Ca^{++})_2$

Specimen: Fresh, Clear, Fasting Serum.

Calculations: Serum Calcium in mg/dl = Abs. of T X 10/Abs. of S.

Reference values of Serum Calcium: 8.7 – 10.5 mg/dl.

Statistics: Data was collected, compiled and analysed using SPSSv16. Statistical tools applied were Mean, SD, paired and unpaired t test and correlation coefficient.

Limitations of the Study:

Due to financial and technical constraints we have taken only 100 subjects, 50 with and 50 without PMS symptoms.

IV. Results

Subjects were divided into two groups, subjects with symptoms (Test group) and those without symptoms of PMS (Control group). Percentage of women married and unmarried, parous and nonparous, highly educated and uneducated or low educated and working or nonworking are determined in both the groups. Studies were conducted to co-relate levels of Serum calcium in relation to heart rate and blood pressure during pre and post menstrual phases. The results were subjected to Statistical Analysis and shown in tabular form separately.

The present study shows almost equal distribution of PMS in all age groups, parous and non-parous women, but a higher incidence in married, highly educated and employed women.

Table no. 1: Basic Parameters

Parameters		groups (in %)	
		Test	Control
Age	15-25	35	35
	26-35	30	55
	36-45	35	10
Marital Status	Married	60	70
	Unmarried	40	30
Parity	Parous	50	65
	Non parous	50	35
Occupation	Employed	70	30
	Unemployed	30	50
EducationalStatus	HighlyEducated	70	60
	Low/unEducated	30	40

The following data shows the variations in Systolic and diastolic blood pressures and Heart rate in control and test groups in both premenstrual phase and postmenstrual phases (in Fig no.s 1 and 2 respectively) where there is a rise in heart rate and blood pressure comparatively.

Table no.2: Comparison between Test and control groups

Menstrual phase	Parameter	Mean		SD		Independent t-value	P-value	Inference
		Test	Control	Test	Control			
Pre	HR	72.40	75.20	5.45	7.72	1.33	0.19	NS
Post	HR	77.90	77.10	3.97	8.17	0.39	0.70	NS
Pre	SBP	116.00	117.00	9.95	10.81	0.30	0.76	NS
Post	SBP	117.50	116.50	8.51	9.33	0.35	0.73	NS
Pre	DBP	77.05	76.70	5.74	5.12	0.20	0.84	NS
Post	DBP	77.50	77.00	7.16	4.70	0.26	0.80	NS
Pre	Serum Calcium	7.88	9.04	0.83	0.68	4.80	<0.01	**HS**
Post	Serum Calcium	8.60	8.90	0.67	0.57	1.50	0.14	NS
NS- Not Significant HS- Highly Significant S- Significant								

In the present study, in premenstrual phase, Mean Serum Calcium was 9.04 in control group where as in test group it was 7.88 and it was statistically highly significant ($p<0.01$) but in postmenstrual phase it was not statistically significant.

Table no.3: Comparison between Premenstrual phases and Postmenstrual phases

Group	Parameter	Premenstrual phase	Postmenstrual phase	paired t-value	P-value	Inference
		Mean	Mean			
Test	HR	72.4	77.9	4.98	<0.01	HS
Control	HR	75.20	77.10	0.83	0.42	NS
Test	SBP	116	117.5	0.65	0.53	NS
Control	SBP	117.00	116.50	0.37	0.72	NS
Test	DBP	77.05	77.5	0.23	0.82	NS
Control	DBP	76.70	77.00	0.24	0.81	NS
Test	Se.Ca	7.88	8.6	3.35	<0.01	HS
Control	Se.Ca	9.04	8.90	0.81	0.43	NS
	NS- Not Significant HS- Highly Significant S- Significant					

In the present study, in test group, Mean heart rate in postmenstrual phase was 77.9 where as in premenstrual phase it was 72.4 and it was highly statistically significant ($p<0.01$) but in control group it was not statistically significant.

In test group, Mean Serum Calcium in postmenstrual phase was 8.90 where as in premenstrual group it was 9.04 and it was highly statistically significant ($p<0.01$) but in control group it was not statistically significant.

Table no. 4: Relation between Se.Ca with the following parameters in test and control groups

Parameter	Test group				Control group			
	Premenstrual phase		Postmenstrual phase		Premenstrual phase		Postmenstrual phase	
	r-value	p-value	r-value	p-value	r-value	p-value	r-value	p-value
HR	-0.085	0.721	0.401	0.08	-0.073	0.759	-0.252	0.284
SBP	-0.038	0.874	-0.027	0.911	-0.271	0.247	-0.409	0.073
DBP	0.05	0.834	-0.253	0.282	-0.226	0.339	-0.283	0.226

In test group, Positive correlation was found between Serum Calcium and Heart Rate in postmenstrual phase where as in premenstrual phase, it was negatively correlated but in control group correlation was negative in both the phases and it was not statistically significant.

In control group and test group, each parameter (HR, SBP, DBP) was negatively correlated with Serum Calcium in pre and postmenstrual phases except HR in postmenstrual phase & DBP in premenstrual phase, they were positively correlated with Serum Calcium but they were not statistically significant.

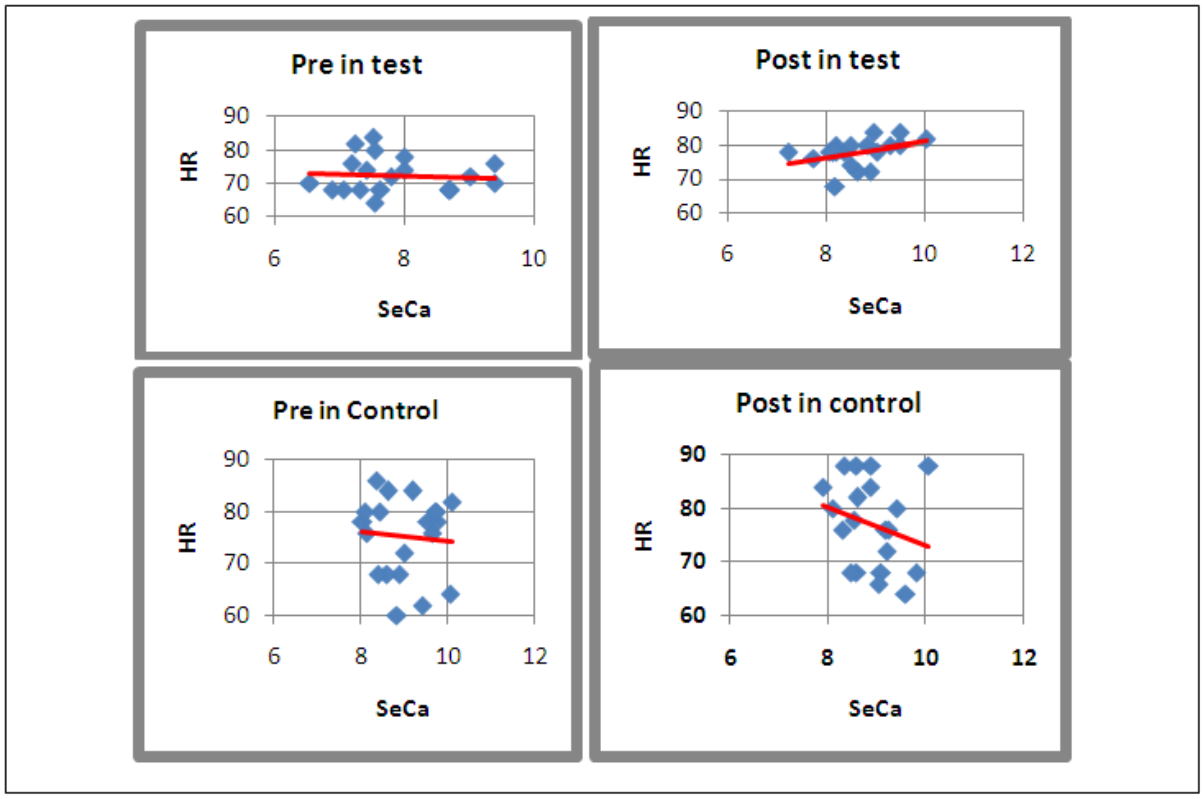

Fig no. 1: Scatter diagrams showing correlation between serum calcium and heart rate.

Scatter diagrams as in Fig no. 1 represents the relation between Serum Calcium (Se.Ca) with Heart Rate (HR) in pre and postmenstrual phases of test and control groups.

V. Discussion

Alterations in calcium homeostasis have long been associated with many affective disturbances and PMS shares many features of depression, anxiety and the dysphoric states. A causal link between disturbances in calcium and affective disorders of mood has been proposed for the past 50 years. Changes in the extracellular calcium concentration may affect the excitability of neuromuscular tissues involved in emotional regulation. Irritability, anxiety and mania have been associated with hypocalcaemia and increased calcium concentrations have been noted in some patients with depression. In addition, neuropsychiatric manifestations have been identified in a prototypical disorder of calcium homeostasis, primary hyperparathyroidism. As with primary hyperparathyroidism, the affective symptoms of PMS have been recently linked to monoamine metabolism and serotonergic dysregulation. Evidence exists that serotonin may be important in the pathophysiology of this syndrome. Fluoxetine, the selective serotonin reuptake inhibitor, has proved to be an effective treatment in some women with PMS. [9]

Calcium may ultimately affect the monoamine metabolism reversing the serotonergic dysregulation and providing a biochemical basis for the therapeutic effect.

The characteristic feature of PMS is its occurrence during the luteal phase of the menstrual cycle with symptomatology unmasked, and remitting with the onset of menses. The most likely explanation for this temporal occurrence is the relationship between the ovarian steroid hormones and the calciotropic hormones. Ovarian steroid hormones, estrogens in particular are known to influence the actions of the calcitropic hormones, specifically, parathyroid hormone. Estrogen lowers serum calcium and in its absence as seen at menopause serum calcium concentration rises.

Estrogen is believed to lower serum calcium through an inhibition of bone resorption by suppressing the mesenchymal process involved in bone remodeling and promoting bone mineralization. Parathyroid hormone appears to act in an exactly opposite manner. Recent evidence suggests that estrogen has calcium antagonistic properties, inhibiting calcium currents and decreasing calcium entry into vascular smooth muscle. During the menstrual cycle, estradiol has two peaks, one immediately before the LH surge and ovulation and the second during the luteal phase. Increasing estrogen levels would result in falling calcium concentration with compensatory rises in parathyroid hormone preventing marked degrees of hypocalcaemia. Therefore, it may be hypothesized that women with an already underlying calcium disturbance, such as those suffering with premenstrual syndrome (lower calcium concentration, lower 25-hydroxyvitamin D levels and higher parathyroid hormone concentration), would be subjected to further decrements in calcium concentration on exposure to increasing oestrogen levels during the luteal phase of the menstrual cycle.

Since extracellular calcium is the ultimate source of intracellular calcium, intracellular calcium may be perturbed resulting in abnormalities of neurotransmitter synthesis and release. During this particular phase of the menstrual cycle, progesterone which is the predominant ovarian steroid hormone and is an antiestrogen, may modify the action of oestrogen at the cellular level resulting in enhanced neuromuscular irritability and vascular reactivity. [10]

Direct application of calcium chloride to the hippocampus of laboratory animals decreases their learning ability compared with that in control animals. It is possible that excess brain calcium interferes with intellectual performance and causes behavioural problems.

Because the brain uses glucose as its sole source of energy, interference with glucose breakdown by excess calcium (an effect of calcium on glycolytic enzymes) could be one mechanism that explains the behavioural effects of an excessive intake of dairy products. Aggressive behaviour in girls consuming excess dairy products including calcium also has been observed. [7]

The present study was an extension of our previous study which studied serum calcium and magnesium levels in PMS in both premenstrual and postmenstrual phases where there was a significant variation of serum calcium and magnesium levels in PMS. [2]

PALMERO et.al.,1991,[11] in their study, resting heart rate in women with and without premenstrual symptoms, reported that in the premenstrual phase, PMS group showed significantly higher resting heart rate levels than non PMS group. With regard to resting heart rate levels across the four phases studied, significant differences within PMS group were observed.

LANDEN M et.al., 2004 [12] measured heart rate variability as a measure of autonomic regulation of the heart and found two variables reflecting vagal activity in the time domain, the root mean square of differences of successive normal RR intervals (gamma MSSD) and standard deviation of normal RR intervals (SDNN) were lower in PMS patients, but this difference was statistically significant in the follicular phase only.

The most important vagal measure in the frequency domain, supine high frequency (HF), also appeared lower in PMS subjects during the follicular phase. It is suggested that PMS may be associated with reduced vagal tone compared to controls and that this difference is most apparent in the non-symptomatic follicular phase of the menstrual cycle.

HOURANI LL et.al. 2004 ,[13]in their study on premenstrual symptoms among a large, population-based sample of reproductive age, active-duty women, concluded that the greatest risk factor was a high level of job stress, with an almost 3-fold increase in risk relative to those without symptoms.

Significantly higher heart rate, systolic and diastolic BP in basal condition, in premenstrual phase is because of higher sympathetic activity due to premenstrual stress. Changes in the autonomic function may be responsible for some of the symptoms produced through endorphins and have been held responsible for behavioural changes. Increased blood pressure due to premenstrual stress is due to increase in peripheral resistance mediated by adrenocortical stimulation causing precapillary resistance. This could be due to increasing sympathetic activity or elevation of circulating catecholamine while other active hormone like renin angiotensin aldosterone system also contributes. Rise in blood pressure due to stress leads to increased epinephrine secretion. Rise in blood pressure is an important sympatho-adrenal response to physiological stressful experience caused by premenstrual stress.

Women with greater degree of premenstrual distress possess higher sympathetic activity in late luteal phase than women with less symptoms. Change in physiological response in premenstrual syndrome group is

because of increased sympathetic activity resulting from modulation of neurotransmitter due to hormonal fluctuation.

Altered functioning of autonomic nervous system in the late luteal phase could be associated with diverse psychosomatic or behavioural symptoms appearing premenstrually. Relaxation techniques were recommended as an adjuvant therapy to tilt the autonomic balance to parasympathetic dominance to get relieved from premenstrual symptoms. [4]

Calcium and vitamin D3 supplementation plays a very effective role in controlling hypertension of various etiology. [14]

VI. Conclusion

PMS is a psychoneuro endocrine disease with a myriad of symptomatology and with stress as an important underlying factor. Many theories have been proposed with no consensus on definitive etiology. The results of the present study indicate a correlation with the decreased serum calcium levels and depressed vagal activity during premenstrual phase in subjects with PMS. Hence changes in lifestyle and supplementation of calcium may be a simple remedy for alleviation of premenstrual symptomatology. Calcium is available in plenty in natural and traditional economical foods.

References

[1]. KENNETH A. Ginsburg, PMS. Text book of Gynaecology 684-694.
[2]. Devisetty Aruna, Chandrakala Kambar and Chowdeswari, Study of serum calcium and magnesium levels during pre and post menstrual phases in pre menstrual syndrome compared to normal subjects. International Journal of Basic and Applied Medical Sciences ISSN: 2277-2103 (Online) An Open Access, Online International Journal Available at http://www.cibtech.org/jms.htm 2014 Vol. 4 (1) January-April, pp.116-126/Aruna et al.
[3]. Elson M.Haas MD, Nutritional Program for PMS, excerpted from Staying healthy with Nutrition, Celestial Arts.
[4]. M.V. Rode, P. Kamble, M.S. Phatak, P. Jadhao and P. Tayde ., Effect of premenstrual stress on autonomic function Annals of Neurosciences, Volume 17, Number 3, July 2010.
[5]. Ronald C. Strickler (1987). M.D. Endocrine Hypotheses for the etiology of PMS Clinical Obstetrics and Gynaecology Vol.30 No.2, June, 377.[4]
[6]. Freeman ew., halberich u. 1998 premenstrual syndromes, psychopharmacol bull. 1998;34(3):291-5.
[7]. Thys-Jacobs S (2000). Micronutrients and the PMS: the case for Calcium. J Am Coll Nutr. April; **19**(2):220-7
[8]. Tamaki Matsumoto, 1 Takahisa Ushiroyama,2 Tetsuya Kimura,3 Tatsuya Hayashi,3 and Toshio Moritani3) Altered autonomic nervous system activity as a potential etiological factor of premenstrual syndrome and premenstrual dysphoric disorder, Biopsychosoc Med. 2007; 1: 24. Published online Dec 20, 2007. doi: 10.1186/1751-0759-1-24PMCID: PMC2253548
[9]. Thys-Jacobs S, Starkley P, Bernstein D, Tian J. Calcium carbonate and the Premenstrual syndrome: effects on premenstrual and menstrual symptoms. Premenstrual study group. Am J Obstet Gynaecol. 1998Aug;179(2):444-52.
[10]. Thys-Jacobs S and Alvir M (1999) Calcium-Regulating across the menstrual cycle:evidence of a secondary hypoparathyroidism in women PMS. The Journal of Clinical Endocrinology and Metabolism 80 2227-32.
[11]. Palmero F, Choliz M. Resting heart rate in women with and without premenstrual syndrome, J Behav Med. 1991 Apr;14(2):125-39
[12]. Landen M, et. al. heart rate variability in premenstrual dysphoric disorder.Psychoneuroendocrinology, 2004,Jul;(6):733-40.
[13]. Hourani LL,Yuan H, Bray RM. Psychosocial and lifestyle correlates of Premenstrual Symptoms among military women. J Womens Health (larchmt). 2004 Sep;13 (7):812-21.
[14]. Pfeifer M1, Begerow B, Minne HW, Nachtigall D, Hansen C., Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. J Clin Endocrinol Metab. 2001 Apr; 86(4):1633-7.