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Study Of Correlation Of Serum Magnesium Levels With Autonomic Nervous System In Premenstrual Syndrome

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Abstract:
Premenstrual syndrome (PMS) is a psychological and somatic disorder known since centuries. Innumerable studies were and are being done. Many theories have been proposed in its etiology from gonadal hormones to neurotransmitters, micronutrients and many others. Autonomic nervous system disturbances have also been proposed to have an effect on the premenstrual symptomatology. Still there is no consensus on its definitive diagnosis or treatment, as there are no physical signs or symptoms or any laboratory test for the diagnosis. Present study is intended to correlate serum levels of magnesium, a micronutrient and heart rate and blood pressure as autonomic nervous system functions in PMS. Our study included 50 with and 50 without PMS, a total of 100 subjects,selected by judgement sampling . Serum magnesium levels were measured by the Calmagite method (Crest Biosystems). Heart rate and blood pressure were measured by clinical method using mercury sphygmomanometer and stethoscope. The results were subjected to statistical methods,spss v16. There was a significant decrease in serum levels of magnesium during premenstrual phase of PMS subjects and an increase in heart rate and blood pressure showing a correlation of decreased serum magnesium and autonomic function.

Key words: heart rate, systolic blood pressure, diastolic blood pressure, and serum magnesium.

I. INTRODUCTION

Premenstrual syndrome (PMS) is a psychosomatic disorder with a high incidence, yet of unknown etiology. There has been reluctance until recently to accept PMS as a serious condition, probably because of a failure to distinguish true premenstrual syndrome from the milder physiological premenstrual symptoms occurring in the normal menstrual cycle of the majority of women. [1]

Premenstrual syndrome is currently 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. [2]

The purpose of the present study is to assess the serum levels of magnesium and to correlate the results with the changes in heart rate and blood pressure in pre and post menstrual phases of PMS.

A. Magnesium

Magnesium is by far the least abundant serum electrolyte, yet it is extremely important in many body functions. Magnesium has been noted to fluctuate across the menstrual cycle and is involved in many cellular pathways and neuromuscular activities which effect PMS.

B. Autonomic Nervous System

Autonomic nervous system maintains the

homeostasis. Its two divisions the sympathetic and the parasympathetic work 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.

Stress disturbs the balance of sympathetic and parasympathetic nervous system and changes in the autonomic nervous system function plays a vital role in orchestrating the homeostatic disturbances during different phases of menstrual cycle. [3]

II. AIMS AND OBJECTIVES

To study the levels of serum magnesium and changes in heart rate and blood pressure in PMS.
To correlate the serum levels of magnesium with heart rate and blood pressure in women with PMS and without PMS.

III. MATERIALS AND METHODS

The present study was done at, Siddhartha Medical College and Government hospital, with Institutional ethical committee approval and informed consent, 100 healthy premenopausal women in the age group of 15-45 years, 50 with and 50 without PMS symptoms, were selected by Judgement sampling, using a self designed questionnaire based on American college of Obstetrics and Gynaecology guidelines and Moss distress questionnaire. All the subjects had regular cycles. Symptoms were prospectively documented. Serum magnesium was estimated by spectrophotometry and heart rate and blood pressure were recorded clinically during pre and post menstrual phases. General examination was done to rule out any physical illness clinically.

A. Inclusion Criteria

Healthy women in the reproductive age group of 15 to 45 years, having regular menstrual cycles in the last six months were included.

B. Exclusion Criteria

History of psychiatric disorders, ovarian dysfunction, other gynecological disorders, pregnancy or postpartum period, history of using oral contraceptives within last 3 months, serious physical illness or taking any medications such as psychoactive preparations or hormones are excluded.

C. Investigations:

Serum Magnesium was estimated by the Calmagite method (Crest Biosystems)

***Principle*:** Magnesium combines with Calmagite in an alkaline medium to form a red colored complex. Interference of Calcium and proteins is eliminated by the addition of specific chelating agents and detergents. Intensity of the colour formed is directly proportional to the amount of magnesium present in the sample.
Magnesium+ Calmagite (in alkaline medium) = Red colored complex.
Normal reference values:
Children-1.5-2.0 mEq/L, adults- 1.3-2.5mEq/L. (as per the kit)

IV. RESULTS

Subjects were divided into two groups, subjects with symptoms (Test group) and those without symptoms of PMS (Control group). Data was collected, compiled and analyzed using SPSS v16. Statistical tool applied were mean, SD, paired and unpaired t-test and correlation.

Table no. 1: Comparison of mean parameter between test and control.

Menstrual Phase	Parameter	Mean		SD		Independent t-value	p-value	Inference
		Test	Control	Test	Control			
Premenstrual	HR	72.20	76.55	5.67	6.88	3.09	<0.01	HS
	SBP	116.50	118.00	9.75	10.91	0.65	0.52	NS
	DBP	77.30	76.70	5.57	5.06	0.50	0.62	NS
	SeMg	2.08	2.32	0.35	0.34	3.07	<0.01	HS
Postmenstrual	HR	78.10	77.60	3.95	8.22	0.35	0.73	NS
	SBP	118.75	117.00	8.22	8.83	0.92	0.36	NS
	DBP	78.50	77.25	6.22	4.52	1.03	0.31	NS
	SeMg	2.31	2.08	0.34	0.36	2.98	<0.01	HS

In the present study, in premenstrual phase, Mean Heart rate was 76.55 in control group where as in test group it was 72.20 and it was highly statistically significant but not in postmenstrual phase. Mean Serum Magnesium was 2.32 in control group where as in test group it was 2.08 and it was highly statistically significant ($p<0.01$) in premenstrual phase as well as postmenstrual phase also with Mean Serum Magnesium was 2.08 in control group where as in test group it was 2.31

Table no. 2: Comparison of mean parameter between premenstrual and postmenstrual phases.

Menstrual Phase	Parameter	Mean		Paired t-value	p-value	Inference
		Premenstrual	Postmenstrual			
Test	HR	72.20	78.10	7.37	<0.01	HS
	SBP	116.50	118.75	1.46	0.15	NS
	DBP	77.30	78.50	1.01	0.32	NS
	SeMg	2.08	2.31	2.88	<0.01	HS
Control	HR	76.55	77.60	0.61	0.55	NS
	SBP	118.00	117.00	0.89	0.38	NS
	DBP	76.70	77.25	0.66	0.51	NS
	SeMg	2.32	2.08	3.33	<0.01	HS

HS: highly significant, NS: not significantIn the present study, In test group, Mean heart rate in postmenstrual phase was 78.10 where as in premenstrual phase it was 72.20 and it was highly statistically significant ($p<0.01$) but in control group it was not statistically significant. In test group, Mean Serum Magnesium in postmenstrual phase was 2.31 where as in premenstrual group it was 2.08 and it was highly statistically significant ($p<0.01$) and also in control group but Mean Serum Magnesium in postmenstrual phase was 2.08 where as in premenstrual group it was 2.32.

Table no. 3: Relation between SeMg with the ANS 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	-0.04	0.8	-0.15	0.35	-0.1	0.53	-0.16	0.33
SBP	-0.06	0.7	-0.11	0.51	0.07	0.64	0.19	0.24
DBP	0.4	**<0.05**	-0.4	**<0.01**	0.34	**<0.05**	-0.26	0.11

In test group, there was a negative correlation between Serum magnesium and DBP in postmenstrual phase with high statistical significance but in premenstrual phase it was correlated as positive with statistical significance where as in control group, there was a positive correlation in premenstrual phase with significance but in postmenstrual phase, negative relation found was not statistically significant.

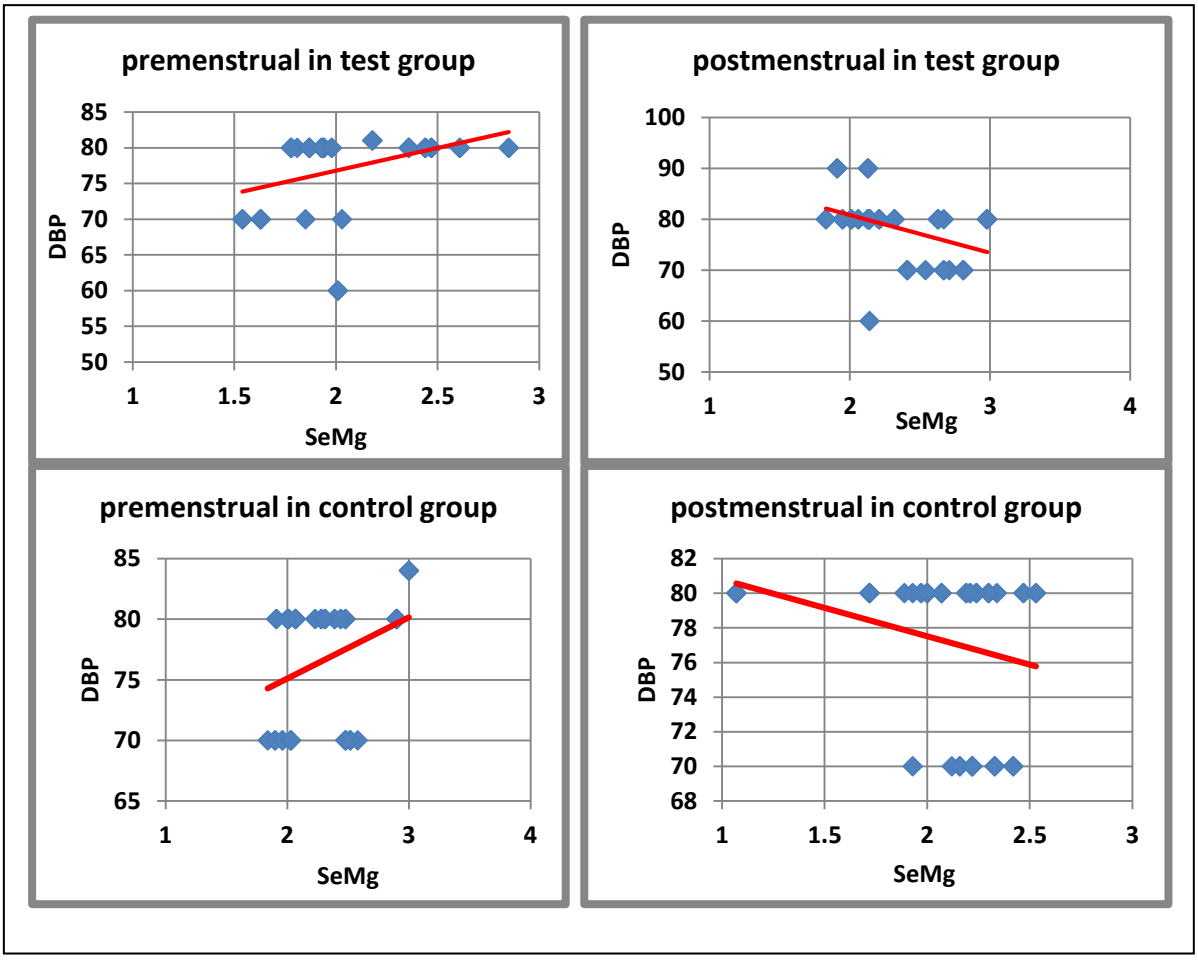

Fig no. 1: Scatter diagrams showing correlation between Se Mg and DBP in Both groups

The above scatter diagrams represent the relation between Serum Magnesium (SeMg) with DBP in pre and postmenstrual phases of test and control groups.

V. DISCUSSION

PMS is a common disorder occurring during luteal or premenstrual phase and abating after the onset of menses. Though the symptoms are recurrent, vary in severity from person to person and also from cycle to cycle in the same person. Important is the timing of its occurrence during the premenstrual phase abating with the onset of menstruation. The symptoms may be so severe to effect personal relationships and loss of work hours or mild.[4] Although physical discomfort

and mood changes related to menstruation have been known since Hippocrates times, it was Frank who proposed the concept of premenstrual tension in 1931 and in 1953 Greene and Dalton coined the term PMS.

The syndrome is a complex condition that includes about 200 symptoms, most frequent being irritability, breast tenderness, bloating and dysphoria.

Symptoms of PMS are multidimensional and affect different physiological systems. Many ideological factors have been implicated including reproductive hormones and imbalance between estrogens and progesterones, neurotransmitters, micronutrients etc.

Autonomic nervous system may also play a crucial role in controlling body response to external and internal stimuli, and maintain homeostatic process. Classical studies have shown lower parasympathetic activity in PMS during luteal phase compared to follicular phase, shown by decrease in venous oxygenation index. Also there is elevated norepinephrine and total peripheral resistance at rest during mental stressors. These were observed in both follicular and luteal phases. Hence instability or slight disequilibrium of the ANS may induce premenstrual symptoms. [5]

Magnesium is involved in over 300 metabolic reactions and is an essential mineral necessary for every major biological process as in the production of cellular energy and the synthesis of nucleic acids, and proteins, hormone production and transformation. It is important for the electrical stability of cells, maintenance of membrane integrity, muscle contractions, nerve conduction and the regulation of vascular tone and also for the proper use of Calcium and vitamin D. [6]

Magnesium deficiencies have been noted in women with PMS. Chocolate especially dark chocolate is a natural source of magnesium and that may be the root of chocolate cravings in women with PMS.

Lower-brain neurotransmitters, such as dopamine, have been implicated in the etiology of PMS. Magnesium deficiency as reported in patients with PMS, causes a specific depletion of brain dopamine without affecting brain serotonin and norepinephrine. [7]

A craving for sweets, fatigue and sometimes the "shakes" are some of the common PMS symptoms. It might be that the affected woman's cells have an increased capacity to bind insulin during the luteal phase, resulting in an increased effect of insulin during the luteal phase. In addition, Prostaglandin E inhibits glucose-induced insulin secretion in vivo in humans. Neuroendocrine responses to insulin-induced hypoglycemia are potentiated by sodiumsalicylate, a prostaglandin inhibitor. Magnesium is required for the enzymatic conversion of cis-linoleic acid to gamma-linolenic acid, the rate limiting step in Prostaglandin E1 synthesis from cislinoleic acid. Magnesium modulates glucose-induced insulin secretion by the pancreas. Increasing the magnesium to calcium ratio decreases the insulin response to glucose, another mechanism by which magnesium deficiency increases the insulin response to a glucose load that is independent of the prostaglandin E1 effect.

It has long been suggested that premenstrual weight gain was thought to occur due to salt and water retention. The most potent sodium-retaining hormone is aldosterone, secreted by the adrenal cortex. The hormonal factors that control aldosterone secretion are corticotrophin, secreted by the pituitary gland under the influence of stress, serotonin and angiotensin II. Because magnesium is known to increase the threshold for stressful stimuli, magnesium deficiency could promote and increase pituitary and adrenal response to environmental stimuli with increased peripheral aldosterone.

The adrenal cortex is more responsive to psychologic stress during the premenstrual phase. Aldosterone increases the urinary excretion of magnesium and if there is no compensatory mechanism to conserve magnesium, then magnesium deficiency may be worsened by its effect on aldosterone secretion and increasing magnesium intake seem to be the treatment. [8]

Dairy products and calcium interfere with magnesium absorption. Excessive intake of dairy products was thought to result in a chronic magnesium deficiency and PMS. [7]

Although most women report swelling of some portions of the body in the premenstruum,

increased weight is not observed in either asymptomatic or PMS women. Aldosterone rises in the luteal phase, but the plasma level is the same for PMS and control women. The kidney can metabolize progesterone to deoxycorticosterone. Thus, the natriuretic effect of progesterone seems balanced by appropriate changes in hormones that conserve body sodium. There is no evidence that this system is unbalanced in women with Premenstrual Syndrome. The subjective symptoms of swelling and bloating are best reconciled by fluid shifts without sodium and water retention.[9]

ABRAHAM[10] in 1983, in his classic randomized, double blind study on nutrition and PMS associated PMS-H, a premenstrual condition characterized by fluid retention, weight gain, swelling and bloating, with a synergistic imbalance causing magnesium deficiency and elevated aldosterone levels, have shown that many women with this type of PMS may benefit from magnesium supplementation, which can alleviate symptoms such as mood swings and fluid retention.

SHERWOOD et. al. in 1986[11], in a double-blind trial using 200mg. of magnesium per day reported a significant reduction for several symptoms related to PMS like fluid retention, swelling of extremities, breast tenderness, and abdominal bloating.

Stress intensifies release of catecholamines and corticosteroids that increase survival of normal animals when their lives are threatened, "fight or flight syndrome". When magnesium (Mg) deficiency exists, stress paradoxically increases risk of cardiovascular damage including hypertension, cerebrovascular and coronary constriction and occlusion, arrhythmias and sudden cardiac death (SCD). Dietary imbalances such as high intakes of fat and/or calcium (Ca) can Mg inadequacy, especially under conditions of stress. Adrenergic stimulation of lipolysis can intensify its deficiency by complexing Mg with liberated fatty acids (FA), A low Mg/Ca ratio increases release of catecholamines, which lowers tissue (i.e. myocardial) Mg levels and also favors excess release or formation of vasoconstrictive and platelet aggregating factors. A high Ca/Mg ratio also directly favors blood coagulation, which is also favored by excess fat and its mobilization during adrenergic lipolysis. Auto-oxidation of catecholamines yields free radicals, enhancing the protective effect of Mg by anti-oxidant nutrients against cardiac damage caused by beta-catecholamines. Thus, stress, whether physical or emotional and dyspnea as in asthma increases need for Mg. Genetic differences in Mg utilization may account for differences in vulnerability to Mg deficiency and differences in body responses to stress. [12]

PALMERO et.al.,1991,[13] in his study 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.

FACCHINETTI F et.al. in 1991,[14] study, examined the effect of Magnesium (360 mg/day) for two cycles compared to placebo and showed that magnesium was found to reduce total symptom scores and the negative affect group of symptoms, baseline symptom scores between treatment groups was significantly different and the expected placebo effect was lacking in this trial.

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 behavioral changes. Increased blood pressure due to premenstrual stress is due to increase in peripheral resistance and mediated by adrenocortical stimulation causing precapillary resistance. This could be due to increasing sympathetic activity or elevation of circulating catecholamine while other active harmone like rennin angiotensin aldosterone system also contribute. Rise in blood pressure due to stress leads to increased epinephrine secretion, 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 PMS 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 behavioral symptoms appearing premenstrualy.[15]

Magnesium affects limbic-hypothalamus-pituitary-adrenocortical axis. Magnesium has the property to suppress -hippocampal kindling, to reduce the release of adrenocorticotrophic hormone (ACTH) and to affect adrenocortical sensitivity to ACTH. magnesium acts in the central nervous system via the *N*-methyl-d-aspartate-antagonistic, γ-aminobutyric acid$_A$-agonistic or a angiotensin II-antagonistic property of this ion. A direct impact of magnesium on the function of the transport protein p-glycoprotein at the level of the blood-brain barrier has also been demonstrated, possibly influencing the access of corticosteroids to the brain. Furthermore, magnesium dampens the calciumion-proteinkinase C related neurotransmission and stimulates the Na-K-ATPase. All these systems have been reported to be involved in the pathophysiology of depression. Despite the antagonism of lithium to magnesium in some cell-based experimental systems, similarities exist on the functional level, i.e. with respect to kindling, sleep-EEG and endocrine effects. Controlled clinical trials examining the effect of Mg in affective disorder are warranted.[16]

VI. CONCLUSION

Magnesium, micronutrient available in natural foods, plays an important role in the body functions. Its deficiency is shown to cause disturbances in autonomic nervous system in PMS and many studies have shown supplementation with magnesium alleviate the PMS symptoms. Nutritional deficiency of magnesium is not common but some foods interfere with magnesium utilization in the body. Modern day lifestyle is becoming more and more stressful and stress is shown to be one of the major causes of PMS. Our study concludes that change in lifestyle and change in food habits may alleviate many of the symptoms of PMS.

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