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Research Article

STUDY OF SERUM CALCIUM AND MAGNESIUM LEVELS DURING PRE AND POST MENSTRUAL PHASES IN PRE MENSTRUAL SYNDROME COMPARED TO NORMAL SUBJECTS

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ABSTRACT
Pre Menstrual Syndrome (PMS) is a psychological and somatic disorder of unknown etiology. Most menstruating women exhibit some premenstrual symptomatology. There has been reluctance until recently to accept PMS as a serious condition. PMS is currently defined as the cyclic recurrence of a constellation of non specific somatic, psychological or behavioral 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 (Ginsburg).The present study was a comparative study done in Department of Physiology, Siddhartha Medical College, Vijayawada. The subjects were taken from two cities of Vijayawada and Eluru including 40 subjects of which 20 were with PMS and 20 were normal subjects in the age group of 15 to 45 years. Serum calcium and magnesium levels were estimated during pre and post menstrual phases and compared with premenstrual subjects and normal subjects. Serum calcium was measured by the Ensure biotech O-Cresol Phthalein Complexone (OCPC method) and Serum magnesium was by the Calmagite method (Crest Biosystems). This study showed a significant decrease in serum calcium during premenstrual phase in PMS subjects (chi-square value 4.91 and p value <0.05) when compared to normal subjects and also a significant decrease in serum magnesium levels during premenstrual phase in PMS subjects (chi-square value 5.01 and p value <0.05). This study showed that PMS is almost equally prevalent in all age groups and more prevalent in highly educated and working women. This study concluded that there is a significant association between lowered serum calcium and serum magnesium levels during premenstrual phase with the PMS.

Keywords: *PMS, Serum Calcium, Serum Magnesium, Luteal Phase*

INTRODUCTION
Historical aspects
The earliest references to menstrually related mood and physical disorders appear in writings of Hippocrates, although ancient Egyptian Papyrus' writings allude to similar ideas (Veith, 1965).
According to Hippocrates, such disorders were attributed to the hysteria, the disease of the wandering uterus (Rodin, 1992). Later, Pliny described the marked behavioral changes as follows: On approach of a woman in this state, grass withers away, garden plants are parched up, new wine becomes sour and the fruit will fall from the tree beneath which she sits (Mortola, 1992).
The idea that hysterical symptoms are related to the woman's sexuality and conformity to her prescribed role as a wife is a theme that runs through the history of the disease category of PMS (Veith, 1965).
Romans in the second century AD described the menses are about to appear when a woman feels uneasy on walking, some develop a torpor, yawning and pandiculation, while others develop nausea and a loss of appetite.
The first modern physician to delineate a set of symptoms related to menstruation as a clinical entity was Frank in 1931, who reported seizures, bronchial asthma and indescribable tension occurring in fifteen subjects from 7 to 10 days preceding menstruation.
The term PMS was first introduced by Dalton in 1953. In 1987 the term Late Luteal Phase Dysphoric Disorder (LLPDD) was introduced to provide a systematic set of diagnostic criteria for a premenstrual

disorder (Rapkin, 1992). This clinical entity was later renamed Premenstrual Dysphoric Disorder (PMDD) although there were few changes in the diagnostic criteria employed.

PMS

PMS is a recently described problem. Although the history of symptoms that occur around the menstrual cycle is ancient, it is likely that 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 such symptoms (Haas).

There are dozens of uncomfortable and painful symptoms of PMS and their appearance may occur from a few days before menstruation and disappear within a few days after the onset of menstruation. Some women with PMS tend to have relatively high levels of estrogen coupled with relatively low levels of progesterone (Dhaar, *et al.*, 1991; Sieppel, *et al.*, 1998). This estrogen-progesterone balance is critical to most of the health problems. Other factors associated with PMS are diet, obesity, vitamin and mineral deficiencies and an imbalance in hormone-like compounds called eicosanoids (Lurie *et al.*, 1990).

Etiology and pathogenesis of PMS

The etiology and pathogenesis of PMS is not known. Historically, the earliest explanations of the mechanism of PMS attempted to implicate basal or other static reproductive hormone alterations. Estrogen excess or deficiency or progesterone deficiency, estrogen-progesterone imbalance, abnormal androgen levels and gonadotropin abnormalities have been implicated. However, studies of basal hormone levels in women who were defined as having PMS compared with control subjects have not shown consistent differences in levels of gonadotropins, gonadal steroids or their metabolites. Dynamic endocrine studies have also failed to show abnormal secretary patterns of these hormones in PMS patients (Strickler, 1987).

Other potential classic endocrine causes of PMS include prolactin excess, thyroid dysfunction, excess production of aldosterone, antidiuretic hormone or both, and low levels of sex-hormone binding globulin. Again studies have failed to find conclusive evidence for differences in basal hormone concentration between women with PMS and asymptomatic control women (Breckwoldt *et al.*, 2002).

Endogenous opiate withdrawal has been suggested as a mechanism for some symptoms of PMS , as many of the manifestations of PMS involve alterations of behavior, mood or both and that endogenous opiate peptides are important in the physiology and pathophysiology of both pain and mood changes. Also cyclic changes in endorphin activity throughout the menstrual cycle have been demonstrated (Breckwoldt *et al.*, 2002).

Another hypothesis is that progesterone induced GABA alterations could participate in the pathogenesis or relief of PMS symptoms. Evidence supports marked potentiation of GABA containing neuron transmission by progesterone metabolites through binding to the GABA receptor complex (Strickler, 1987).

Nutritional factors

The role of nutritional factors in PMS was described in 1944.Over the last few years, nutritional supplements have been widely used as treatments for PMS, based on the assumption that patients with PMS consume more refined sugar, refined carbohydrates and dairy products and less vitamins and minerals than do other women (Choung *et al.*, 1992).

Others implicate micronutrients like calcium, magnesium, zinc etc in the etiology of PMS.

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 (Thys-Jacobs *et al.*, 1998).

(Thys-Jacobs, 2000), in her study demonstrated that there is scientific evidence that support cyclic fluctuations of calcium and vitamin D during the menstrual cycle and may help explain some features of PMS. The study found that 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.

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 (Thys-Jacobs *et al.*, 1998). 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 then 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 calciotropic 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 PMS (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 estrogen 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 estrogen at the cellular level resulting in enhanced neuromuscular irritability and vascular reactivity (Thys-Jacobs *et al.*, 1999). Direct application of calcium chloride to hippo-campus 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 behavioral 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 behavioral effects of an excessive intake of dairy products. Aggressive behavior in girls consuming excess dairy products including calcium also has been observed (Thys-Jacobs *et al.*, 1998).

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

Magnesium is involved in over 300 metabolic reactions and is an essential mineral necessary for every major biological process. Magnesium is involved in the production of cellular energy and the synthesis of nucleic acids and proteins.

It is important for the electrical stability of cells, maintenance of membrane integrity, muscle contractions, nerve conduction and the regulation of vascular tone.

Magnesium is important for hormone production and transformation, as well as for the proper use of calcium and vitamin D (Johnson, 2001).

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 causes a specific depletion of brain dopamine without affecting brain serotonin and norepinephrine. Lower intracellular magnesium levels in patients with PMS compared with control subjects have been reported (Choung *et al.,* 1992). A craving for sweets, fatigue and sometimes the "shakes" are some of the common PMS symptoms. The explanation of these symptoms 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. This may be 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 PMS might be related to body changes responsible for fluid retention. 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 an increased pituitary and adrenal response to environmental stimuli with increased peripheral aldosterone.

The adrenal cortex is more responsive to psychological 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. Increasing magnesium intake seems to be the only way to break this cycle (Walker *et al.,* 1998).

Dairy products and calcium interfere with magnesium absorption. Excessive intake of dairy products was thought to result in a chronic magnesium deficiency and PMS (Choung *et al.,* 1992).

Although most women report swelling of some portion 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 PMS. The subjective symptoms of swelling and bloating are best reconciled by fluid shifts without sodium and water retention. Mechanisms for such fluid leaks need clarification (Strickler, 1987).

Clinical features

Over 150 nonspecific symptoms have been associated with PMS. Most often, patients complain of a combination of symptoms. The timing of appearance of the symptoms is important. Symptoms begin or considerably exacerbate either in the periovulatory phase of the cycle or later in the luteal phase, and then must either considerably improve or resolve by the onset of, or during menstruation (Ginsburg)

Commonly reported symptom groups in women with PMS are:

Psychological symptoms: Irritability, depression, crying/ tearfulness, anxiety, tension, mood swings, lack of concentration, confusion, forgetfulness, unsociable ness, restlessness, temper outbursts/anger, sadness / blues, loneliness. Pain symptoms: premenstrual mastalgia, bloatedness, Appetite symptoms, Behavioral symptoms, fatigue, dizziness, sleep/insomnia, decreased efficiency, accident prone, sexual interest changes, increased energy, and tiredness.

Irritability and aggression are among the most frequently reported psychological symptoms. Such symptoms may lead to an inability to tolerate the most trivial of social encounters, leading in turn to deterioration of interpersonal relationships, interference with normal activities or both (Shaughn *et al.*,).

Diagnosis

It is based on the ACOG (American Congress of Obstetricians and Gynaecologists) diagnostic criteria which

require reporting of at least any one affective and four somatic symptoms that should exist during the 5 days before menses at each of the three prior menstrual cycles and be relieved within 4 days of onset of menses
The diagnostic process begins with a detailed patient history. Important in this regard is the characterization of the patient's chief complaint, assessment of the timing of symptoms throughout the menstrual cycle, ranking of symptoms according to severity and assessment of the impact of PMS on lifestyle, daily routine, family and friends.
Establishing the age of onset of symptoms and the pattern or regularity of recurrence of symptoms each month should be attempted.
The Gynecological history should include assessment of the menstrual cycle with regard to length, regularity, amount and duration of blood loss, presence or absence of dysmenorrhoea and other molimina.
Current contraceptive practice should be determined.
A history of Gynecologic surgery should be elicited because PMS symptoms appear to be related to endocrine ovarian function and not to menstruation per se, as symptoms continue in women after hysterectomy but have ovaries preserved.
A detailed psychiatric history is also sought.
Information should be gathered on previous and current psychiatric symptoms, for example anxiety, depression, suicidal ideation or intent, paranoia, introversion, passivity, defense mechanisms, diagnosis, hospitalization and treatment. An analysis of the patient's marital and social interaction, the presence of stressful life events, including conflicts in marriage or other relationships, problems at work, difficulties with children and other concerns that might contribute to PMS, should be determined (Ginsburg).
Accordingly, it is clear that mere supplementation of calcium and magnesium can alleviate the much suffering and recurrent symptoms of PMS in women. Very few studies were done on this subject and there is paucity in reporting. Hence, based on this hypothesis, the present study was taken up.

MATERIALS AND METHODS

This was a comparative study. After obtaining ethical committee approval subjects were put to a detailed questionnaire and thoroughly examined to rule out any illness, pregnancy, diabetes, hypertension etc. With informed consent in local language blood samples within one week prior to periods and within one week after periods were collected under strict aseptic precautions from the normal subjects those with premenstrual symptoms satisfying ACOG diagnostic criteria.

Inclusion criteria

Healthy women in the reproductive age group of 15 to 45 years.
Having regular menstrual cycles in the last six months.

Exclusion criteria

History of Psychiatric disorders.
History of Ovarian dysfunction.
History other Gynaecological disorders.
Pregnancy or Postpartum period.
History of using oral contraceptives within last 3 months.
Serious physical illness.
History of taking any medications such as psychoactive preparations or hormones.

Sample selection

Using a self designed questionnaire basing on relevant studies was randomly asked to select both the test and control groups.

Sample size

Healthy premenopausal women with PMS in the age group of 15 to 45 years: 20 (Test group)
Healthy premenopausal women with out PMS in the 15 to 45 years age group: 20 (Control group). 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.

Serum calcium and magnesium were estimated by spectrophotometry during premenstrual phase and postmenstrual phases of their cycles.
General examination was done to rule out any physical illness clinically.

Statistical methods

Simple statistical methods like percentages, qualitative tests (Chi - Square) and quantitative test (paired t test) was done.

Limitation of the study

Due to technical and financial constraints, only forty samples were taken.

Biochemical investigations

Serum calcium: Serum calcium was measured by the Ensure biotech OCPC (O-Cresolphthalein complexone) 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.
Serum calcium in mg/dl = Abs. of T X 10/ Abs. Of S
Reference Values
Serum calcium: 8.7 – 10.5 mg/dl
Serum magnesium: Serum magnesium was 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.
Working reagent: For larger assays Working reagent may be prepared by mixing equal volumes of L1 (Buffer Reagent) and L2 (Colour Reagent). The working reagent is stable at 2-8^{o}C for at least one month. Keep tightly closed.
Calculations: Magnesium in mEq/L=Abs .T /Abs .S x 2

Aims and Objectives

Aim

To study the levels of serum calcium and magnesium in PMS subjects.

Objective

To compare the serum levels of calcium and magnesium in women with PMS and those without PMS during pre and postmenstrual phases.

RESULTS AND DISCUSSION

Subjects were divided into two groups, subjects with symptoms (Test group) and those with out symptoms of PMS (Control group.)
To determine the prevalence of PMS in relation to age, they were classified into 3 groups of 15 to 25, 26 to 35 and 36 to 45 years.
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 and Serum magnesium in relation to pre and post menstrual phases. The results were subjected to Statistical Analysis and shown in tabular form separately.
The present study show 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 as shown in table 1.
Figure1 shows the percentage of women with variation of Serum calcium levels in relation to pre and post menstrual phases i.e., those with premenstrual increase or decrease or post menstrual increase or decrease. In the test group 14 respondents have raised serum calcium levels (premenstrual values are deducted from the postmenstrual values) thus indicating lowered premenstrual serum calcium levels in the test group. The Chi-square value is 4.91 and at 1 degree of freedom the P value is less than 0.05, which is statistically

significant

Table 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
Educational Status	Highly Educated	70	60
	Low/un Educated	30	40

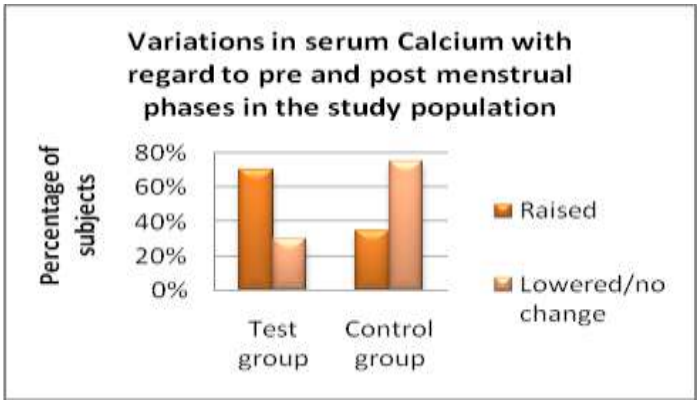

Figure 1: variation in serum calcium levels with regard to pre and post menstrual phases in the study population

Chi-square value is 4.91, p value at df 1 is <0.05. Hence significant.

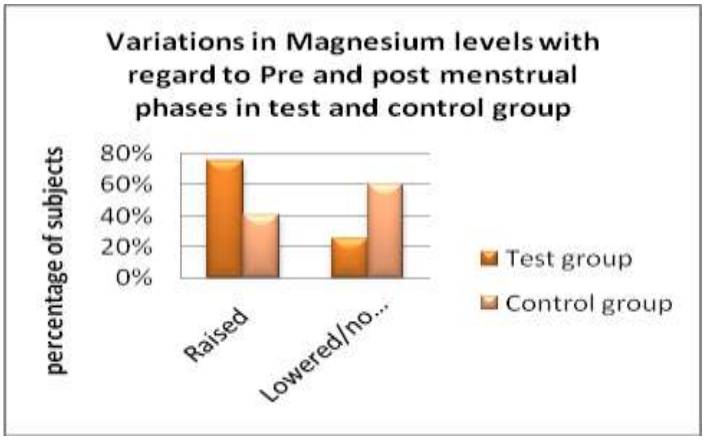

Figure2: variation in serum magnesium levels with regard to pre and post menstrual phases in the study population.

Chi-square value is 5.01, p value at df 1 is <0.05. Hence significant.

Figure 2 shows the percentage of women with variation of Serum magnesium levels in relation to pre and post menstrual phases i.e., those with premenstrual increase or decrease or post menstrual increase or decrease. In the test group out of 20 respondents 8 have raised serum magnesium levels i.e. they have lowered serum magnesium levels in the premenstrual phase (premenstrual values were deducted from those of the postmenstrual values). The Chi-square value is 5.01 and at 1 degree of freedom the P value is less than 0.05, which is statistically significant

DISCUSSION

The results of the present study show the prevalence of PMS to be almost equal in all age groups of the women in the reproductive age. These findings are consistent with other studies (Golub *et al.*, 1976; Widholm, 1985; Kutner *et al.*, 1972; Halbreich, 2004). These studies found no relation of PMS with age. PMS was thought to be more common in women in their 30s and 40s than in those of teenage years. Other factors associated with an increased likelihood of PMS problems include marital status, parity, exercise, use of birth-control pills, pre-eclamptic toxemia, emotional stress, nutritional habits leading to certain deficiencies or excesses. Premenstrual changes are commonly reported beginning at the menarche and studies show approximately the same percentage reporting severe symptoms in teenagers as among older people, though the symptoms differ qualitatively.

In an another study, it was found that no difference in the occurrence of PMS by age, but difference by age group in the distribution of symptoms subtypes is seen (Keep, 1981).

The results also show no significant relation to marital status and parity in this study. The association between the age and parity makes it difficult to distinguish between the effects of each. Parous women reported more symptoms than nulliparous and associated with the onset of PMS to post pregnancy period (Keep, 1981; Dalton, 1984). It may be due to women in their 30s have better access to health care or are more likely to seek treatment than younger women with the same symptoms (Hargroove, 1987).

Though the results are statistically insignificant in relation to the education and occupation in our study, there is an increased incidence among highly educated and working women due to the fact that the women's level of education affected PMS more and stress plays a major role in the etiology of PMS (26Marvan, 1998).

Modern day women with increased demands and stresses, changes in nutrition and new careers and high ambitions that take them away from their natural cycle and their connection to the home, garden and nature are particularly susceptible to symptoms of PMS (Rapkin, 1992). In their study, Hourani *et al.*, 2004, 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.

However, an observation that lends evidence to the possibility that a biological mechanism may be responsible for PMS symptoms involves a study of twins. The concordance of PMS diagnosis was significantly higher in monozygotic twins (94%) than in either dizygotic twins (44%) or members of control population (Ginsburg).

The percentage of women with premenstrual decrease of serum calcium levels in this study is statistically significant ($P < 0.05$). Penland et al., in 1993, in their study examined the pattern of calcitropic hormone cyclicity in women with PMS compared to asymptomatic controls. Fasting blood samples were drawn at six points throughout the ovulatory cycle. In both the asymptomatic and PMS groups of women, total and ionized calcium varied across the menstrual cycle and declined significantly at midcycle with the increase of estradiol. In the women with PMS peak midcycle parathyroid hormone was significantly elevated by approximately 30% compared with early follicular levels. Significant differences between groups were found for total calcium, 25-hydroxy vitamin D and 1, 25 dihydroxy vitamin D.

In the women with PMS, 25 hydroxy vitamin D concentrations were significantly lower across the menstrual cycle compared to asymptomatic controls.

These data suggest that women with PMS have perturbations in calcium homeostasis characterized by a secondary hyperparathyroidism. Calcium supplementation of 1200-1600mg/day, unless contraindicated,

should be considered a sound treatment option in women who experience PMS (Ward, 1999).

Susan Thys-Jacobs et al., 2000, reported that disturbances in calcium regulation underlie the pathophysiologic characteristics of PMS and calcium supplementation may be an effective therapeutic approach. In their study involving women between the ages of 18 and 45 years, who suffered with moderate to severe premenstrual symptoms, were randomly assigned to receive 1200mg elemental calcium per day in the form of calcium carbonate or placebo, for three menstrual cycles. Routine chemistry, complete blood cell count and urinalysis were obtained on all participants. Daily documentation of symptoms, adverse effects and compliance with medications were monitored. During the luteal phase of the treatment cycle, a significantly lower mean symptom complex score was observed in the calcium treated group for both the second and third treatment cycle.

The results show the percentage of women with PMS in this study have a statistically significant lower serum magnesium levels ($P < 0.05$) during premenstrual phase. PMS-H a premenstrual condition is characterized by fluid retention, weight gain, swelling and bloating with a synergistic imbalance causing magnesium deficiency and elevated aldosterone levels (Simon, 2004; Walker, 1998; Das,1997).

The paired t test shows significant lowering of serum calcium and serum magnesium during pre menstrual phase even in the control group. However the decrease is highly significant in the test group. There is evidence that support cyclic fluctuations of calcium, magnesium and vitamin-D during the menstrual cycle and that woman with an already underlying calcium disturbance such as those suffering from PMS would be subjected to further decrements in calcium concentration on exposure to increasing estrogen levels during the luteal phase of the menstrual cycle (Thys-Jacobs, 1998).

Randomized, double-blind studies have shown that many women with PMS may benefit from supplementation of 200mg. of magnesium per day reported a significant reduction of several symptoms related to PMS like mood swings, fluid retention, swelling of extremities, breast tenderness, and abdominal bloating (Sherwood, 1986).

Posaci *et al.*, 1994, reported that the mean magnesium levels and the Zn/Cu ratio were significantly lower in PMS patients than in the control group. Plasma magnesium and Zinc levels were diminished significantly during the luteal phase compared to the follicular phase in PMS group. In a study measured blood magnesium across the menstrual cycle in women with PMS and control women and concluded lower magnesium concentration in PMS patients at each sampling time (Rosenstein, 1994).

Muneyvirci-delale et al., 1998, in their study reported that healthy women of reproductive age demonstrate recurring cycling of ionized magnesium and cyclic alterations in the ionized calcium to magnesium ratio in their serum.

The changes in serum concentrations of these important physiologically active cations in the range at which they occur can affect such entities as the vasculature, synaptic transmission and excitation- secretion coupling and then can produce the well-known PMS, during the luteal phase in women who are somewhat deficient in magnesium or in those who have an unusually increased calcium to magnesium ratio. In a randomized, double blind, placebo-controlled, cross-over study it is, found that magnesium supplementation alleviates premenstrual symptoms of fluid retention. The study investigated the effect of a daily supplement of 200mg of magnesium as magnesium oxide, for two menstrual cycles on the severity of premenstrual symptoms. An analysis of 38 women showed no effect of magnesium supplementation compared with placebo in any category in the first month of supplementation. However, in the second month there was a greater reduction of symptoms of PMS –H group (weight gain, swelling of extremities, breast tenderness, abdominal bloating) with magnesium supplementation compared with placebo (Walker, 1998).

De souza *et al.*, in 2000, tested the single and combined effects of daily dietary supplementation with 50 mg. of vitamin B6 and 200mg of magnesium (as magnesium oxide) for one cycle for the relief of mild PMS symptoms. The study demonstrated a significant effect on reducing anxiety-related premenstrual symptoms (nervous tension, mood swings, irritability or anxiety) when 200mg. /day magnesium+50 mg. /day of vitamin B6 was consumed. The study concluded that there was synergistic effect of a daily dietary supplementation when a combination of magnesium and vitamin B6 was administered.

Simon *et al.*, 2002, in their study observed very low levels of magnesium and high levels of calcium during

the premenstrual phase. Some experts hypothesize then that deficiencies in magnesium may be responsible for triggering symptoms. The effects are likely to be more complicated than this, however, since taking calcium supplements appears to reduce PMS symptoms in some women, while taking magnesium seems to have no effect.

Calcium and magnesium help nerve cells to communicate and blood vessels to widen and narrow. Female hormones, including estrogen, regulate calcium and magnesium. Hormonal swings during the premenstrual phase then also cause variations in these important minerals. Some researchers believe that imbalances in these minerals may contribute to PMS. Vitamin D which is essential for calcium absorption may also be deficient in women with PMS.

Summary and Conclusion

Forty healthy women in the reproductive age group of 15-45 years, with regular menstrual cycles were chosen for the present study. Among these 40 women, 20 are with PMS symptoms (test group) and 20 are without PMS symptoms (control group). Thorough history was taken and clinical examination was done for diagnosis and to rule out other physical illness clinically. Serum levels of calcium and magnesium were estimated by Spectrophotometry. The results were statistically analyzed.

PMS was almost equally prevalent in all age groups. Incidence of PMS was more in the highly educated and working women. There was no significant relation to marital status and parity to PMS. There was a significant association between lowered serum calcium and serum magnesium levels in the premenstrual phase and PMS.

These findings were consistent with other studies showing a relationship between micronutrients and PMS.

Changing life style, reducing stress, healthy food habits, can have a therapeutic effect on PMS. Calcium and magnesium supplementation also play a significant therapeutic role in PMS.

REFERENCES

Andrea J Rapkin (1992). *Clinical Obstetrics and Gynaecology* **35**(3). ISSN 0009-9201-

Breckwoldt M and Keck CH. (2002). PMS. *Therapeutische Umschau* **59**(4) 183-7.

Dalton K (1984). *The PMS and Progesterone Therapy* (William Heinman Medical Books Ltd., London).

Das K and Chowdhury AR (1997). Metallic ions during Menstrual cycle in normally menstruating women. *Indian Journal of Medical Sciences* **51** 52-4.

De Souza MC and Walker AF (2000). A synergistic effect of a daily supplement for one month of 200 gm Mg. plus 50 mg Vit.B6 for the relief of anxiety – related premenstrual symptoms: a randomized double-blind crossover study. *Journal of Women's Health and Gender-Based Medicine* **9**(2) 131-9.

Dhaar V and Murphy BE (1991). The PMS and its treatment. *The Journal of Steroid Biochemistry and Molecular Biology* **39**(2) 275-81.

Elson M. Haas MD (No Date). Nutritional Program for PMS, excerpted from staying healthy with Nutrition, Celestial Arts.

Golub S (1976). The magnitude of premenstrual anxiety and depression. *Psychosomatic Medicine* **38** 4-14.

Halbreich U (2004). The diagnosis of PMSs and premenstrual dysphoric disorder-clinical procedures and research perspectives. *Gynecological Endocrinology* **19**(6) 320-35.

Hargroove JT and Abraham GE (1987). The incidence of premenstrual tension in a gynaecologic clinic. *The Journal of Reproductive Medicine* **27** 721-724.

Harvey Simon MD (2004). *Premenstrual Syndrome –Review* (University of Maryland Medical Center).

Hourani LL, Yuan H and Bray RM (2004). Psychosocial and lifestyle correlates of Premenstrual Symptoms among military women. *Journal of Women's Health (larchmt)* **13**(7) 812-21.

Ilza Veith I (1965). *Hysteria: The History of a Disease* (Chicago, University of Chicago Press).

James Chuong C and Earl B Dawson (1992). Critical evaluation of nutritional factors in the pathophysiology and Treatment of PMS. *Clinical Obstetrics and Gynaecology* **35**(3) 679-92.

Johnson S (2001). The multifaceted and Widespread Pathology of magnesium deficiency. *Medical Hypotheses* **56**(2) 163-70.

Kenneth A Ginsburg (No Date). PMS. *Text Book of Gynaecology* 684-694.

Kutner SJ and Andersch (1972). Types of oral contraceptives, depression and premenstrual symptoms. *The Journal of Nervous and Mental Disease* **155**(3) 153.
Lurie S and Borenstein R (1990). The PMS. *Obstetrical and Gynecological Survey* **45**(4) 220-8.
Mari Rodin (1992). The Social Construction of PMS. *Social Science and Medicine* **35**(1) 49-56.
Marvan ML(1998). Premenstrual symptoms in Mexican women with different educational levels. *The Journal of Psychology* **132**(5) 517-26.
Morgan M and Rapkin A (2002). Cognitive flexibility, reaction time and attention in women with PMDD. *The Journal of Gender Specific Medicine* **5**(3) 28-36.
Mortola JF (1992). Issues in the Diagnosis and Research of PMS. *Clinical Obstetrics and Gynaecology* **35**(3) 587.
Muneyvirci – Delale O (1998). Sex-Steroid hormones modulate Serum Ionized magnesium and Calcium levels. *Fertility and Sterility* **69**(5) 958-62.
Penland JG and Johnson PE (1993). Dietary Calcium and Manganese Effects on Menstrual cycle symptoms *American Journal of Obstetrics and Gynecology* **168**(5) 1417-23.
Posaci C (1994). Plasma copper, Zinc, and magnesium levels in patients with Premenstrual tension Syndrome. *Acta Obstetricia et Gynecologica Scandinavica* **73**(6) 452-5.
Ronald C Strickler (1987). M.D. Endocrine Hypotheses for the etiology of PMS. *Clinical Obstetrics and Gynaecology* **30**(2) 377.
Rosenstein DL (1994). Magnesium measures across the menstrual cycle in PMS. *Biological Psychiatry* **35**(8) 557-61.
Shaughn PM and O'Brein. PMS, Text book of Gynaecology, edited by Robert.W.Shaw et.al., 401-413. PMS and Idiopathic odema. 447-457 Text book of gynaecology. Edited by Jay J.Gold et.al. 4th edition.
Sherwood RA and Rocks BF (1986). Magnesium and the PMS. *Annals of Clinical Biochemistry* 667-70.
Sieppel L and Backstrom T (1998). Luteal Phase estradiol relates to symptom severity in patients with PMS. *The Journal of Clinical Endocrinology and Metabolism* **83**(6) 1988-92.
Thys-Jacobs S and Alvir M (1999). Calcium –Regulating hormones across the Menstrual cycle: evidence of a secondary hyperparathyroidism in women with PMS. *The Journal of Clinical Endocrinology and Metabolism* **80** 2227-32.
Thys-Jacobs S (2000). Micronutrients and the PMS: the case for Calcium. *The Journal of the American College of Nutrition* **19**(2) 220-7.
Thys-Jacobs S, Starkey P, Bernstein D and Tian J (1998). Calcium carbonate and the PMS: Effects on premenstrual and menstrual symptoms. PMS study Group. *American Journal of Obstetrics and Gynecology* **179**(2) 444-52.
Van Keep PA and Lehert P (1981). The PMS- an epidemiological exercise. In: *The PMS, Lancaster*, edited by van Keep PA and Utian WH (Eng. MTP press Ltd) 31-42.
Walker AF and De souza (1998) Magnesium supplemantation alleviates Premenstrual Symptoms of Fluid Retention. *Journal of Women's Health* **7**(9) 1157-65.
Ward MW and Holimon TD (1999). Calcium Treatment for PMS. *Annals of Pharmacotherapy* **33**(12) 1356-8.
Widholm O (1985). Epidemiology of premenstrual tension syndrome and primary dysmenorrhea**.** In: *Premenstrual Syndrome and Dysmenorrhea* edited by Dawood MY, McGuire JL, Demers LM (Baltimore: Urban and Schwarzenberg) 3–12