

## Review

# Micronutrients and the Premenstrual Syndrome: The Case for Calcium

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Premenstrual syndrome afflicts millions of premenopausal women and has been described as one of the most common disorders in women. Research over the past few years suggests that a variety of nutrients may have an important role in the phase related mood and behavioral disturbances of the premenstrual syndrome. There is scientific evidence, at least for a few of these micronutrients, specifically calcium and vitamin D, supporting cyclic fluctuations during the menstrual cycle that may help explain some features of PMS. Ovarian hormones influence calcium, magnesium and vitamin D metabolism. Estrogen regulates calcium metabolism, intestinal calcium absorption and parathyroid gene expression and secretion, triggering fluctuations across the menstrual cycle. Alterations in calcium homeostasis (hypocalcemia and hypercalcemia) have long been associated with many affective disturbances. PMS shares many features of depression, anxiety and the dysphoric states. The similarity between the symptoms of PMS and hypocalcemia is remarkable. Clinical trials in women with PMS have found that calcium supplementation effectively alleviates the majority of mood and somatic symptoms. Evidence to date indicates that women with luteal phase symptomatology have an underlying calcium dysregulation with a secondary hyperparathyroidism and vitamin D deficiency. This strongly suggests that PMS represents the clinical manifestation of a calcium deficiency state that is unmasked following the rise of ovarian steroid hormone concentrations during the menstrual cycle.

### Key teaching points:

- Calcium, magnesium, 1,25 dihydroxyvitamin D and other minerals are dynamically related to the menstrual cycle.
- Alterations in calcium homeostasis (hypocalcemia and hypercalcemia) have long been associated with many affective disturbances.
- PMS shares many of the features of depression, anxiety and the dysphoric states.
- Cyclical changes in calcium metabolism during the menstrual cycle may help explain some of the features of PMS.
- Recent evidence has demonstrated the efficacy of calcium in the treatment of PMS.

## INTRODUCTION AND BACKGROUND

Nearly 60 years ago, Frank described the premenstrual tension syndrome [1]. Premenstrual syndrome (PMS) is widely recognized as a recurrent, cyclical disorder related to the hormonal variations in the menstrual cycle, disrupting the emotional and physical well being of millions of women during their reproductive lives. The syndrome is characterized by a complex group of signs and symptoms that occur during the

luteal phase of the menstrual cycle, remitting soon after the onset of menses. Many women experience mild symptoms, and as many as 30% to 50% suffer from troublesome symptoms. Surveys indicate that approximately 5% of North American women consider their symptoms to be severe enough to have a substantially negative impact on their health and social well being. Symptoms vary among different individuals and may include depression, irritability, mood swings, bloating, breast tenderness and abdominal discomfort (Table 1). Because of the

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**Table 1.** Common Symptoms of Premenstrual Syndrome

<b>Affective</b>	<b>Fluid Balance</b>	<b>Behavioral</b>
depression	edema	decreased motivation
sadness	bloating	social isolation
anxiety		
irritability		
labile mood		
<b>Neurovegetative</b>	<b>Pain</b>	
fatigue	abdominal cramps	
lethargy	headache	
food cravings	generalized aches and pain	
insomnia		

number and diversity of symptoms, innumerable theories and mechanisms have been proposed to elucidate this syndrome with an array of therapeutic approaches offered [2,3]. The majority of these approaches have proved disappointing and scientifically unfounded. Current strategies now advocate the selective serotonin reuptake inhibitors, oral contraceptives, nonsteroidal anti-inflammatory agents and the gonadotropin releasing agonists in the management of women suffering with PMS.

Research over the past few years suggests that a variety of nutrients may have an important role in the phase related mood and behavioral disturbances of the premenstrual syndrome. In addition, there is scientific evidence, at least for a few of these micronutrients, supporting their cyclic fluctuations during the estrous and menstrual cycles. This review will summarize what is known pertaining to the physiology of the premenstrual syndrome, the efficacy of specific micronutrients in PMS and hypothesize as to why calcium may be the leading mineral of concern.

## PHYSIOLOGY

As the normal menstrual cycle is characterized by physiologic fluctuations of pituitary gonadotropins and ovarian steroid hormones, and because of the temporal occurrence of PMS within the menstrual cycle, attempts have been made to identify the hormonal and biochemical factors that could differentiate women with PMS from asymptomatic women [4,5]. However, these various investigations have not revealed a consistent difference in basal levels, pulsatility or patterns of ovarian steroid hormones and gonadotropins in women with PMS as compared to controls [6,7,8]. Estradiol, progesterone, follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin and cortisol have not been found to differ between groups [9,10,11].

Despite these observations, there is convincing evidence that PMS is related to hormonal fluctuations of the menstrual cycle and occurs only in women with ovulatory cycles. PMS does not occur prepubertally or at menopause [12]. It is abolished by the administration of gonadotropin releasing hormone

agonists and following oophorectomy [13,14]. While differences in ovarian steroid hormones between symptomatic and asymptomatic women have not been observed consistently, suppression of ovarian hormone secretion results in marked attenuation of premenstrual symptomatology. In 1984, Muse *et al.* investigated the effect of a reversible medical ovariectomy with the administration of a gonadotropin releasing agonist during a six-month crossover trial in eight women with PMS [15]. The agonist induced-amenorrhea resulted in obliteration of normal pituitary and ovarian steroid hormone fluctuations and proved very effective in the reduction of luteal phase symptoms. However, the precise role of ovarian steroid hormones, although essential, was not yet clear in the pathophysiology of PMS. In 1998, Schmidt *et al.* demonstrated that administration of estradiol following gonadotropin releasing agonist (leuprolide) ablation of premenstrual symptoms resulted in a recurrence of symptoms in women with PMS, but not in normal asymptomatic controls [16]. The ovarian steroid hormones during the luteal phase of the menstrual cycle appeared to unmask a physiologic deficiency or abnormality inducing the mood and behavioral changes characteristic of PMS. Schmidt's study confirmed that the ovarian steroid hormones in susceptible women were essential in inducing the symptoms of PMS. The question remained what was the underlying biologic trigger in these women and why were symptoms only unmasked during the luteal phase of the menstrual cycle.

## CYCLICAL FLUCTUATIONS ACROSS THE MENSTRUAL CYCLE

Since ovarian activity is cyclical, variations in mineral metabolism may accompany the hormonal fluctuations during the normal menstrual cycle and may help explain some characteristics of PMS. Cyclical fluctuations during the estrous cycle have been demonstrated in a few animal investigations. Crescent and colleagues measured plasma levels of calcium, phosphorus, calcitonin, PTH and prolactin at hours 8, 13, and 17 during the four-day estrous cycle in Wistar rats [17]. Significant fluctuations in plasma calcium and calcitonin levels were noted. Calcium levels fell throughout the day during proestrous and estrous (ovulation) and rose during diestrous. Phosphorus levels fluctuated inconsistently. At all stages of the cycle, calcium declined between morning and evening. Similarly, calcitonin levels declined during estrous and increased during the diestrous phases of the cycle. There were no significant fluctuations noted in PTH concentrations during the estrous cycle. Although magnesium and zinc levels have not been reported in animal investigations to vary during the estrous cycle [18,19], vitamin D has been observed to fluctuate. Kenny and colleagues investigated vitamin D metabolism in the egg-laying Japanese quail [20]. They observed an enhanced synthesis of 1,25 dihydroxyvitamin D throughout the 24-hour

period following ovulation with a rise in estrogen concentrations. Tanaka *et al.* similarly noted the influence of the sex hormones on vitamin D metabolism in the Japanese quail when estradiol stimulated 1-hydroxylase activity and suppressed 24-hydroxylase activity resulting in elevations in 1,25 dihydroxyvitamin D concentrations [21]. Brommage *et al.* measured intestinal calcium absorption during the rat estrous cycle [22]. Both total and fractional intestinal calcium absorption as determined by a decrease in the ratio of <sup>47</sup>Ca to <sup>47</sup>Sc in feces relative to the diet were observed to vary. Both were highest during estrous and lowest during the second day of diestrous.

Evidence supports cyclical changes in mineral metabolism involving healthy premenopausal women during the menstrual cycle. In Pitkin's study of seven healthy premenopausal women, the concentration of PTH progressively increased through the follicular phase of the cycle [23]. It peaked 30% to 35% above earlier follicular and late luteal phase concentrations in association with reduced ionized calcium concentrations. Total calcium, magnesium and phosphorus concentrations exhibited no particular pattern. Similar midcycle fluctuations were observed for 1,25-dihydroxyvitamin D levels with a near doubling of its concentration as compared to early follicular levels. In 1982, Gray and colleagues measured the circulating concentrations of calcium and 1,25-dihydroxyvitamin D in seven normal women on Days 1, 8, 15 and 22 of their menstrual cycles [24]. Concentrations of 1,25-dihydroxyvitamin D on Day 15 were double the concentrations noted on Days 1 and 8. There was no detectable change in the total serum calcium level. Similarly, Tjellesen found a near doubling of this biologically active vitamin D metabolite at the time of ovulation in five young premenopausal women [25]. Fasting serum calcium, alkaline phosphatase activity, urinary calcium and hydroxyproline did not significantly vary across the cycle. In 1997, Das and Chowdhury measured plasma concentrations of metallic ions in normally menstruating women [26]. The concentrations of magnesium, zinc, selenium and manganese were highest during menses and lowest at the ovulatory phase. There was a rise in ionic levels of magnesium and selenium, with a fall in zinc and manganese during the luteal phase. Muneyyirci-Delale and colleagues noted a significant increase in the serum of Ca<sup>2+</sup>/Mg<sup>2+</sup> ratio at both the ovulatory and luteal phases in healthy cycling women [27]. Thus, variations in mineral metabolism, specifically calcium and the calciotropic hormones, have been observed during both the menstrual and estrous cycles, and these cyclical changes may help explain some of the features of PMS.

## CLINICAL TRIALS ON THE MICRONUTRIENTS

A variety of micronutrients have been investigated in the therapeutic approach to PMS. The majority of these clinical trials have been small trials, with methodologic shortcomings

in both design and diagnosis. The evidence of efficacy is not convincing for vitamin E [28], vitamin B6 [29], evening primrose oil (a rich source of gamma-linolenic acid) [30,31] or potassium [32].

## MAGNESIUM AND PMS

Magnesium has been noted to fluctuate across the menstrual cycle and is involved in many cellular pathways and neuromuscular activities which effect PMS. The clinical evidence, however, on magnesium supplementation, while promising, remains limited in scope. A double blind, randomized study in 1991 examined the effect of magnesium (360 mg per day) for two cycles compared to placebo [33]. Magnesium was administered during the luteal phase of the menstrual cycle until the onset of menstrual flow. Although 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. Walker and colleagues also investigated the benefit of magnesium supplementation in PMS in a double blind crossover trial over four menstrual cycles [34]. A daily supplement of 200 mg of magnesium was provided to forty-one women with PMS for two cycles. Of the six categories of symptoms investigated (anxiety, craving, depression, hydration, other and total symptoms) only the hydration (bloating) group was significantly effected compared to placebo. There was no effect on depression, anxiety or global symptoms.

## CALCIUM AND PMS

The similarity between the symptoms of PMS and hypocalcemia is striking, and it is not surprising that the beneficial response demonstrated with calcium in the treatment of PMS has proven efficacy (Table 2).

A. Three calcium trials have demonstrated the efficacy of calcium treatment. In 1989, a randomized, double blind crossover trial was conducted to assess the effectiveness of calcium in women with PMS [35]. Thirty-three women received three

**Table 2.** Clinical Features of Hypocalcemia

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Fatigue
Anxiety
Depression
Impaired memory
Impaired intellectual capacity
Personality disturbances
Neuromuscular irritability
Muscle cramps
Paresthesias
Tetany

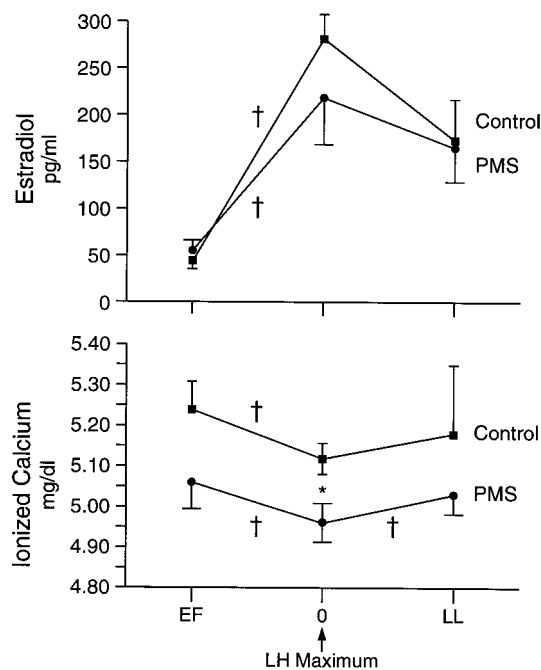
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months of daily calcium supplementation (1000 mg of elemental calcium in the form of calcium carbonate) and three months of placebo. At the end of the trial, 73% of the women cited global improvement of symptomatology on calcium compared to placebo. Elemental calcium was found to significantly result in an overall 50% reduction in PMS symptomatology. In 1993, Penland *et al.* conducted a metabolic study of calcium and manganese nutrition in ten women with premenstrual and menstrual distress symptomatology [36]. Women were assigned in a double blind manner to one of four dietary periods of either 587 mg or 1336 mg of calcium with 1.0 mg or 5.6 mg of manganese per day. The high dietary calcium intake in the amount of 1336 mg per day was found to benefit mood, behavior, pain and water retention symptoms significantly during the menstrual cycle. In 1998, a prospective, multicenter, randomized double blind placebo controlled parallel-group, clinical trial was conducted in women with moderate to severe PMS to determine the efficacy of calcium in symptom reduction [37]. Subjects were randomly assigned to receive 1200 mg of elemental calcium per day in the form of calcium carbonate or placebo for three menstrual cycles. Approximately two thousand women were prescreened, seven hundred and twenty women were screened prospectively with a daily rating scale for two menstrual cycles, four hundred ninety-seven women were enrolled, and 95% completed the trial. By the third treatment cycle, calcium effectively resulted in an overall 48% reduction in total symptom scores. Calcium was found to be effective on all four core symptom factors of PMS representative of this syndrome (negative affect, water retention, food cravings and pain) as well as on 15 of the 17 individual symptoms.

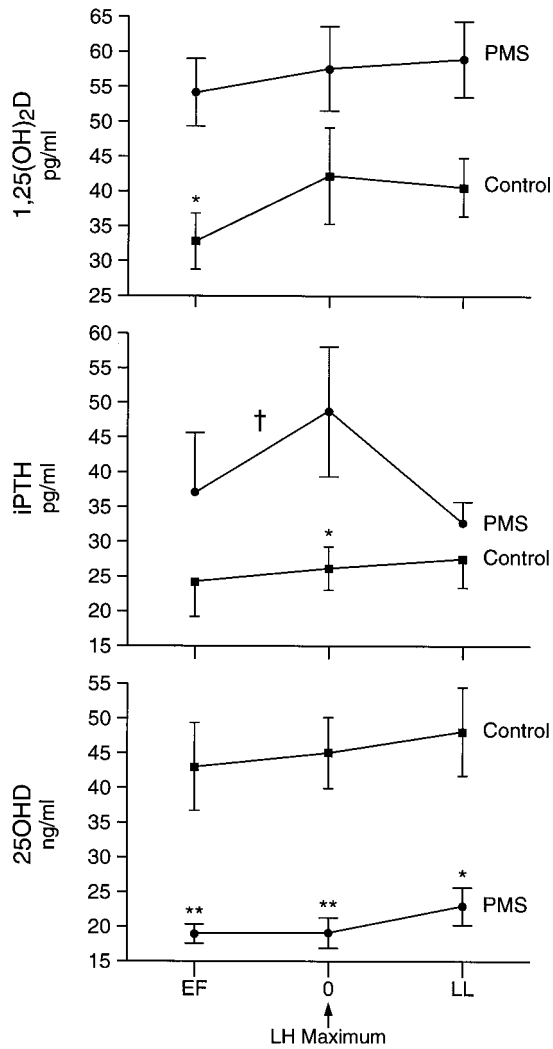
**B.** Two investigations have identified a relationship between PMS and bone loss, further promoting a derangement in calcium metabolism in PMS as a potential biologic trigger. In 1994, Lee and Kanis examined the relationship of premenstrual and postmenopausal symptoms with vertebral osteoporosis by means of a retrospective case control questionnaire [38]. Seventy-five postmenopausal women with vertebral osteoporosis were age matched to seventy-seven controls. The risk of vertebral osteoporosis was significantly greater in women with a history of PMS (RR 1.86), oligomenorrhea (RR 3.08) or vasomotor symptoms (RR 1.35). In 1995, a prospective, cross sectional survey prospectively examined the relationship between bone mass and PMS symptomatology [39]. Twenty-six women with PMS were compared to twenty age matched controls. Controls and women with PMS had similar age, race, body mass index, physical activity, history of smoking and oral contraceptive use. Bone mass measurements were performed with dual photon absorptiometry at two sites, the lumbar vertebrae and proximal femur. Compared to controls, women with PMS had significantly lower vertebral bone mass measurements at the lumbar vertebrae (L2-4) and at Ward's triangle in the femur. The data suggested that the presence of PMS might

be associated with abnormalities in bone metabolism and reduced bone mass measurements.

**C.** Previous investigations in calcium metabolism had reported on the cyclicity of the calcium regulating hormones across the menstrual cycle, with some authorities suggesting cyclic fluctuations of parathyroid hormone (PTH), 1,25 dihydroxyvitamin D and calcium. One study in 1995 examined the pattern of calciotropic hormone cyclicity in women with PMS compared to asymptomatic controls [40]. 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 (Fig. 1). In the women with PMS, peak midcycle PTH was significantly elevated by approximately 30% compared with early follicular levels (Fig. 2). Significant differences between groups were found for total calcium, 25 hydroxyvitamin D and 1,25 dihydroxyvitamin D. In the women with PMS, 25 hydroxyvitamin D concentrations were significantly lower across the menstrual cycle compared to asymptomatic controls. The data suggested that women with PMS have perturbations in calcium homeostasis characterized by a secondary hyperparathyroidism.



**Fig. 1.** Mean concentrations of estradiol and ionized calcium across the menstrual cycle. Data are presented as means ( $\pm$ SE). The PMS group is represented by circles; the asymptomatic group by squares. EF denotes early follicular phase; LL denotes late luteal phase of the menstrual cycle. The asterisk indicates  $p < 0.05$  for the change from EF to Day 0 or from Day 0 to LL.



**Fig. 2.** Mean concentrations of 25OHD, iPTH and 1,25(OH)<sub>2</sub>D across the menstrual cycle. Data are presented as means ( $\pm$ SE). The PMS group is represented by circles; the asymptomatic group by squares. EF denotes early follicular phase; LL denotes late luteal phase of the menstrual cycle. The asterisk indicates  $p < 0.05$  for the change from EF to Day 0 or from Day 0 to LL. 25OHD represents 25 hydroxyvitamin D; iPTH represents intact parathyroid hormone; 1,25(OH)<sub>2</sub>D represents 1,25 dihydroxyvitamin D. The asterisk indicates  $p < 0.05$  for controls vs. PMS. The double asterisk indicates  $p < 0.01$  for controls vs. PMS. The dagger refers to  $p < 0.01$  for the change from EF to Day 0.

### CALCIUM AND DEPRESSION

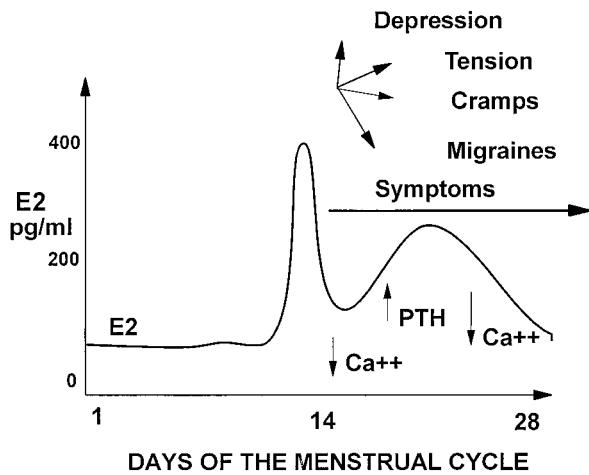
A causal link between disturbances in cellular calcium and affective disorders in mood have been proposed for the past 50 years [41]. Changes in the extracellular calcium concentration may affect the excitability of neuromuscular tissues involved in emotional regulation [42]. Irritability, anxiety and mania have been associated with hypocalcemia; increased calcium concentrations have been noted in some patients with depression [43]. In addition, neuropsychiatric manifestations have been identified in a prototypical disorder of calcium homeostasis, primary

hyperparathyroidism [44]. Symptoms described include mild personality changes, anxiety, confusion and depression similar to the negative affective features associated with PMS [45]. Fatiguability, concentration difficulties, tension, sadness and failing memory are a few of the psychiatric symptoms that have been reported to improve following treatment with parathyroid surgery [46]. Several studies have identified patients with primary hyperparathyroidism manifesting psychosis, paranoia, obsessive-compulsive behavior and organic brain syndrome. Disturbances in either parathyroid hormone or the intracellular regulation of calcium in the central nervous system have been implicated to explain the psychiatric symptoms in primary hyperparathyroidism [47]. Monoamine metabolism in the central nervous system has been considered of additional importance in accounting for the psychiatric disturbances. A recent investigation by Joborn and colleagues measured the monoamine metabolites, 5-hydroxyindole acetic acid, homovanillic acid, and 3 methoxy-4-hydroxy-phenyl-glycol in the cerebrospinal fluid (CSF) of patients with primary hyperparathyroidism [47]. Their patients had pronounced psychiatric symptomatology, which was mainly affective in nature. The majority of patients had low CSF concentrations of monoamine metabolites and those with the most severe psychiatric symptoms had low values for 5-hydroxyindole acetic acid. Following parathyroid surgery, the patients had an improvement in psychiatric symptomatology with an increase in CSF 5-hydroxyindole acetic acid and homovanillic acid. The low CSF levels of monoamine metabolites in primary hyperparathyroidism were similar to those observed in patients with endogenous depression and suicidal behavior [48,49]. These investigators concluded that hyperparathyroidism influences both the serotonergic and dopaminergic mechanisms in the brain, resulting in a variety of psychiatric disturbances.

Altered intracellular calcium regulation, as well, may help to explain the affective nature of PMS. As with primary hyperparathyroidism, the affective symptoms of PMS have recently been linked to monoamine metabolism and serotonergic dysregulation. Evidence exists that serotonin may be important in the pathophysiology of this syndrome [50]. Fluoxetine, the selective serotonin reuptake inhibitor, has proved to be an effective treatment in some women with PMS [51]. Calcium may ultimately affect the monoamine metabolism reversing the serotonergic dysregulation and providing a biochemical basis for the therapeutic effect.

### HYPOTHESIS

The characteristic feature of PMS is its occurrence during the luteal phase of the menstrual cycle with symptomatology unmasked, 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 calcitropic hormones. Ovarian steroid hormones, estrogens in particular,



**Fig. 3.** Estradiol influences calcium and vitamin D metabolism across the menstrual cycle inducing fluctuations in calcium concentrations and triggering luteal phase symptoms. E2 represents estradiol; PTH—parathyroid hormone; Ca++—ionized calcium.

are known to influence the actions of the calcitropic hormones, specifically calcium and PTH [52]. Estrogen lowers serum calcium, and in its absence as seen at menopause, serum calcium concentrations rise [53]. 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 [54]. Parathyroid hormone appears to act in an exactly opposite manner. Estrogen treatment in patients with mild primary hyperparathyroidism has been shown to lower serum and urinary calcium levels. Recent evidence suggests that estrogen has calcium antagonistic properties, inhibiting calcium currents and decreasing calcium entry into vascular smooth muscle [55]. During the menstrual cycle, estradiol has two peaks, one immediately before the LH surge and ovulation, and the second during the luteal phase (Fig. 3). Increasing estrogen levels would result in falling calcium concentrations with compensatory rises in parathyroid hormone preventing marked degrees of hypocalcemia. Therefore, it may be hypothesized that women with an already underlying calcium disturbance, such as those suffering with PMS (lower calcium concentrations, lower 25 hydroxyvitamin D levels and higher PTH concentrations), would be subjected to further decrements in calcium concentrations 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 actions of estrogen at the cellular level resulting in enhanced neuromuscular irritability and vascular reactivity.

## CONCLUSION

Historically, alterations in calcium homeostasis have long been associated with many affective disturbances. PMS shares many of the features of depression, anxiety and the dysphoric states. Recent evidence has suggested that PMS may be associated with a perturbation in calcium homeostasis and parathyroid hormone dysregulation. Indeed, calcium supplementation has been demonstrated to relieve many of the symptoms such as irritability, depression, anxiety, social withdrawal, headache, and cramps of the premenstrual syndrome. Exaggerated fluctuations of the calcium regulating hormones across the menstrual cycle in women with PMS support the hypothesis that disordered calcitropic hormone regulation is a major provocative factor in PMS. The calcium dysregulation may be intensified at the times of increasing ovarian steroid concentrations (midcycle and luteal phase occurrences), resulting in falling calcium concentrations with compensatory rises in parathyroid hormone contributing to both the psychiatric and somatic features of the syndrome. In addition to the abnormalities in calcitropic hormones and the clinical response observed on calcium supplementation in PMS, a relationship between PMS and bone loss has been identified, further supporting a derangement in calcium metabolism in PMS. A clinical entity such as PMS could be a reflection of an important physiological disruption in calcium regulation, while adequate treatment of PMS could help restore bone mineral homeostasis and reverse the associated neuropsychiatric disturbances.

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