Premenstrual Syndrome: Nutritional and Alternative Approaches

Kathleen A. Head, N.D.

Abstract

Since it was first identified in the 1930s, premenstrual syndrome (PMS) has presented the clinician with challenges from an etiological as well as treatment perspective. To know the cause is to know the cure. The cause of PMS appears to be a complicated interplay among hormones, neurotransmitters, nutrients and psychosocial factors. To complicate the picture further, the same imbalances are not present in every person suffering from PMS. This article is a review of the literature, citing numerous studies, sometimes with conflicting views, of the etiology and non-drug treatment for premenstrual syndrome. Specific nutrients and botanicals are discussed as they relate to particular neuroendocrine imbalances. In view of the fact that there appears not to be one particular deficiency or excess which can be identified in each case of PMS, the most reliable method of treatment involves a comprehensive approach which includes dietary changes, supplementation of specific nutrients and botanicals, and when indicated, use of identical to natural hormones such as progesterone.
(*Alt Med Rev* 1997;2(1):12-25)

Historical Perspective

Premenstrual syndrome (PMS) is a complex of physical and psychological symptoms appearing in the luteal phase of a woman's cycle, generally beginning seven to ten days prior to the onset of menses, increasing in severity as the menses approaches and ceasing with or slightly after the onset of menses. Hippocratic physicians made reference to physical and psychological symptoms in their writings[1] as early as the fourth century BC. It wasn't until 1931, however, that Robert Frank, an American physician, brought it to the attention of the New York Academy of Medicine and suggested that the cause was faulty ovarian function.[1] That same year, a psychoanalyst, Karen Horney, postulated that the syndrome was the result of suppressed sexual desire and power.[1]

Difficulties of Defining and Diagnosing PMS

The absence of any clear diagnostic criteria has made evaluation of this syndrome somewhat difficult. Much of the reporting has been dependent upon analysis of retrospective surveys which depend upon the patient's recall of symptoms and are not the most reliable means of evaluation. Studies employing both retrospective and prospective data indicate that retrospetive studies overestimate the prevalence of symptoms.[2] Whether a retrospective survey is used or a prospective symptom diary is kept, the subjectivity of the data is still an issue. The extent to

which a woman perceives premenstrual changes as a normal bodily function versus an illness has to do not only with the severity of the symptoms but cultural attitudes as well as the personality of the individual.

In the absence of any consistent organic or psychological pathology, the term PMS has come to encompass a wide variety of symptom complexes which differ greatly in nature and severity. Due to the inconsistencies which abound in defining premenstrual syndrome, estimates of the prevalence of the condition also vary widely. A survey reported upon by Abraham, conducted in the US from 1980-1982, found that 50% of women reported moderate to severe symptoms premenstrually.[3] A 1979 survey of French women indicated that 38% of French women suffered from PMS.[3] One author estimated the prevalence to be in the area of 2-8% where "once figures in excess of 70% were claimed".[4]

Possible Etiological Factors

No one consistent imbalance or deficiency has been identified which explains the complex interplay of neuroendocrine, chronobiological and psychosocial interactions which result in the syndrome we call PMS. A survey of the literature reveals at least 200 symptoms which have been reported to occur premenstrually.[5] Depending in part on which symptoms are being considered, etiological theories include; hormonal imbalance, psychological abnormalities, nutritional deficiency or excess, altered prostaglandin synthesis and neurotransmitter imbalance.[6] Although laboratory analysis demonstrates an excess or deficiency of certain hormones, neurotransmitters, or nutrients in some women, laboratory results from other women with symptoms of PMS may appear perfectly normal. In addition, an excess of a particular hormone may be implicated as causative in one group of women suffering from PMS, while an independent study identifies a deficiency of that same hormone as a causative factor.

In the early 1980s, Guy Abraham, a leading researcher in the field, in an attempt to bring some order to the confusing picture, proposed that PMS could be divided into four subcategories depending upon the symptoms. He proposed a different etiology for each group.[3,7,8] It should be noted that people often fall into more than one category.

PMT-A - the most common category, affects between 66-80% of PMS sufferers in the several surveys noted. The symptoms which predominate are anxiety, irritability, insomnia and general nervous tension. The proposed etiology of this type is an elevation of estrogen in relation to progesterone.

PMT-H - is the second most frequently seen constellation of symptoms, occurring in about 60-66% of patients. This category is characterized by weight gain, abdominal bloating, breast tenderness and engorgement and edema of the face, hands and feet and, in its most severe form, has been associated with aberrations in the renin-angiotensin-aldosterone axis. Deficient dopamine has also been implicated.

PMT-C - is characterized by a premenstrual appetite increase and a craving for sweets followed by symptoms of hypoglycemia including headaches, fainting, fatigue, dizziness, palpitations and trembling. Twenty-four per cent of patients in Abraham's surveys complain of these symptoms and abnormal glucose tolerance curves are often demonstrated on laboratory evaluation.

PMT-D - is the least common subgroup, estimated to affect 1.7-23% of patients with PMS depending upon whether it is in its pure form (1.7%) or combined with PMT-A (a larger group). Characterized by depression and suicidal tendencies, it has been associated

with an elevation of progesterone in relation to estrogen. High hair lead levels have been noted in some individuals in this category.

Among the other etiological theories are serotonin/tryptophan deficiency,[1] serotonin/tryptophan excess,[8,9] norepinephrine excess,[1,9] norepinephrine/tyrosine deficiency,[3] hypothyroidism,[10] androgen deficiency,[11] androgen excess,[12] GABA deficiency,[13] essential fatty acid deficiency resulting in abnormal prostaglandin synthesis,[1] possible genetic predisposition,[1] elevated prolactin,[1] pyridoxine deficiency,[1] magnesium deficiency,[14] social-psychological stress[1] and elevated melatonin.[1]

It is likely that an imbalance occurring at some point in the complicated interaction of hormones, essential nutrients and neurotransmitters combines with psycho-social stresses to cause the symptoms of PMS and that the imbalances may differ widely from person to person, and even from cycle to cycle within the same person. Rather than frank deficiencies, it has been postulated that PMS may instead be an abnormality in the way a woman adapts to the monthly hormone fluctuations. In the paragraphs below the mechanisms for these theories will be discussed in terms of specific hormone-neurotransmitter-nutrient interactions.

Pyridoxine/Pyridoxal-5-phosphate

Clinical Evidence: As early as the mid-1940s, Morton Biskind demonstrated an important role for the B vitamins in the metabolism of estrogen in the liver and further went on to demonstrate the effectiveness of B-complex in the treatment of PMS.[3] More recently, a number of studies have focused on the role of pyridoxine in the treatment of PMS. A retrospective survey of 630 women attending a PMS clinic was conducted. Good results (no residual complaints) were reported in 40% of patients taking 100-150 mg of pyridoxine daily and in 60% of those taking 160-200 mg daily.[15] A 1989 randomized crossover trial by Doll et al. found a significant benefit for the 36 women who completed the 7 month trial. The 50 mg daily dosage of B6 was observed to have a positive effect upon symptoms of depression, irritability and fatigue, but not on other symptoms.[16] A 1987 double-blind study by Kendall and Schnurr on 55 women found significant improvement in behavioral symptoms — sociability and performance — as well as in autonomic reactions such as dizziness but no significant effect on other symptoms.[17] Hagen et al. found no significant difference between 100 mg B6 and placebo in a group of 34 women with PMS.[18] In a larger sample of 434 patients receiving either 50 mg pyridoxine twice daily (with the option of increasing to 100 mg twice daily) or placebo, global assessment of symptoms after 3 cycles was significantly improved in patients receiving pyridoxine.[19] In this same study, no statistically significant difference was found when assessing individual symptoms. Barr reported effectiveness in a small scale double-blind crossover trial of 48 women prescribed 100 mg B6 daily or placebo.[20]

Mechanisms of Action: It has been proposed by some scientists that premenstrual symptoms are due in part to a pyridoxine deficiency. Stewart reports laboratory evidence of deficiencies of both B6 and magnesium in 11 women with PMS.[14] However, another trial comparing the pyridoxine and magnesium status of 9 women with PMS to 10 asymptomatic women found no differences in dietary intake of B6 in either group. Furthermore, both groups demonstrated adequate pyridoxine status as measured by plasma pyridoxal phosphate and erythrocyte aspartate aminotransferase stimulation.[21]

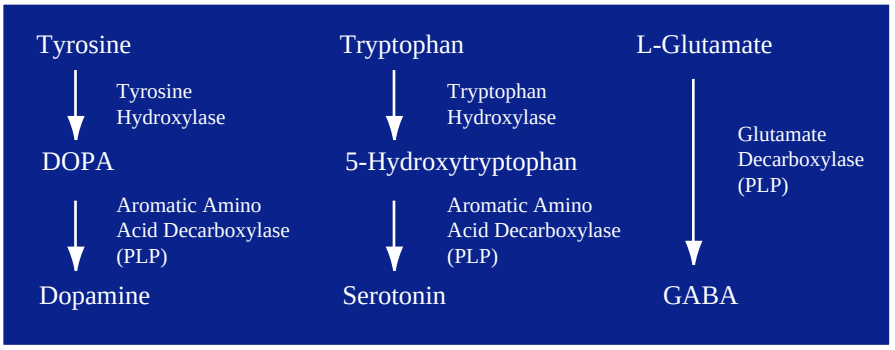
In evaluating the ubiquitous nature of pyridoxine in a multitude of biochemical pathways, indications for its use in PMS may be found no matter what etiological theory is embraced. At daily doses of 200-600 mg, B6 lowers serum estrogen and elevates serum progesterone levels.[3,22] This shift should benefit those patients who have an elevation of estrogen in relation to progesterone, which by some estimates is the largest group of PMS sufferers. High estrogen levels have also been implicated as a cause of depressed B6 levels.[1,23]

The active form of pyridoxine, pyridoxal-5-phosphate, is a co-factor in the formation of the following neurotransmitters; dopamine,[1,3] serotonin[1,3] and GABA (see figure 1).[14] Deficiencies of each of these neurotransmitters have been implicated in some symptoms of PMS, particularly depression. Additionally, dopamine has a dampening effect on aldosterone; a deficiency of dopamine thus will result in sodium absorption and subsequent water retention, a common symptom of PMT-H.[3] At doses of 600 mg, B6 is known to have an effect similar to the drug bromocriptine in suppressing aldosterone.[3] In addition, a dopamine deficiency may result in elevations of prolactin, also implicated in PMS.[1]

A deficiency of essential fatty acids leading to a decrease in the PGE1 series of prostaglandins has also been implicated as a cause of some premenstrual symptoms, particular those related to hypoglycemia. PGE1 inhibits glucose-induced insulin secretion.[24] In addition to niacin, vitamin C and zinc, pyridoxine is necessary for the conversion of linoleic to gamma linolenic acid which is ultimately converted to the PGE1 series of prostaglandins.[3]

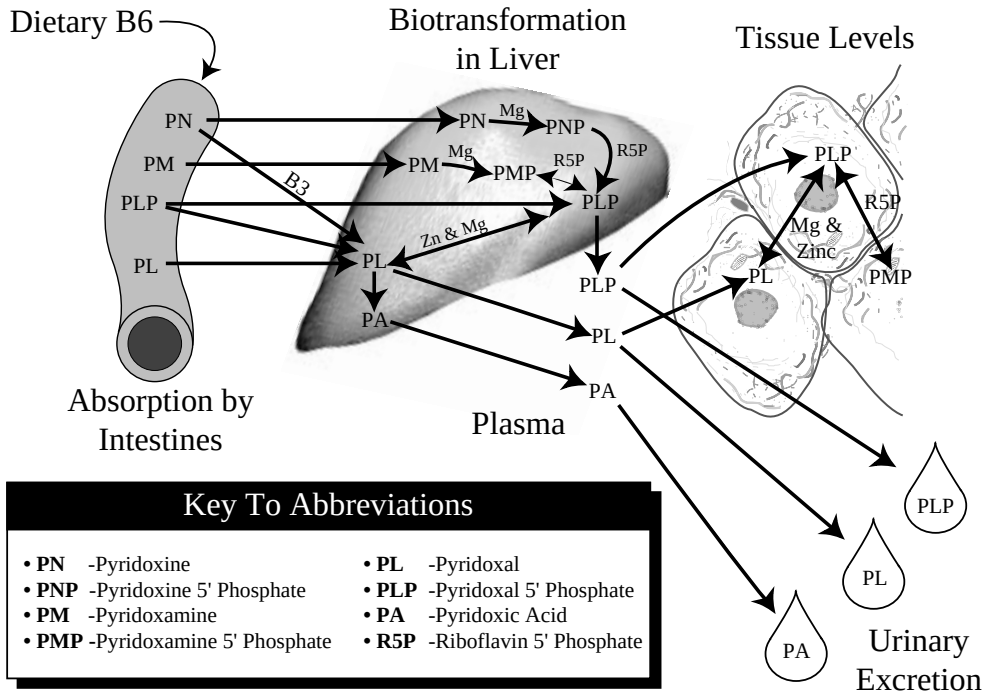
Toxicity of pyridoxine: There has been some concern about the possible toxicity of pyridoxine, even at low doses. Neurotoxicity, consisting of peripheral neuropathy, is the most commonly reported effect, generally occurring when B6 is administered in high doses. Katherine Dalton, well known for her advocacy of progesterone in the treatment of PMS, reported a significant number of cases of neurotoxicity at doses as low as 50 mg.[25] Brush et al., in their retrospective survey of 630 women, found no reports of symptoms consistent with peripheral neuropathy at doses of up to 200 mg daily.[15] Parry and Bredsen report that the use of doses as low as 200 mg daily for three years may result in sensory neuropathy.[26] Doses as low as 150 mg daily have been reported to cause gastrointestinal discomfort.[19] However, a controlled study of 434 patients reported no gastric discomfort in doses of 200 mg daily.[19]

FIGURE 1. Neurotransmitter Synthesis



Pyridoxal-5-phosphate (PLP): Studies reporting toxicity of B6 have been conducted using the inactive form, pyridoxine. Two enzymatic steps are required for the conversion in the liver of pyridoxine to its active

FIGURE 2. Pyridoxal 5' Phosphate Metabolism



form, pyridoxal phosphate. Pyridoxine must first be phosphorylated to pyridoxine phosphate, requiring magnesium. Secondly, pyridoxine phosphate must then be oxidized to pyridoxal phosphate. Riboflavin is necessary for this final step (see figure 2).[8] If a conditional deficiency of one of these co-factors exists, the conversion of pyridoxine to PLP may be inhibited. This may be an important factor in B6 toxicity.

Parry and Bredsen propose that the pyridoxine toxicity is caused by exceeding the liver's ability to phosphorylate pyridoxine to PLP, yielding high serum levels of pyridoxine which may be directly neurotoxic[26] or may compete with PLP for binding sites, resulting in a relative deficiency.[26] Since a deficiency of B6 causes a peripheral neuropathy similar to that experienced in toxicity reactions to pyridoxine, an inability to utilize pyridoxine as the active cofactor, may be the underlying mechanism in these individuals.

The use of supplemental PLP has not been associated with vitamin B6 toxicity and in addition might spare magnesium and riboflavin. Since preventing a magnesium deficiency is of particular relevance to PMS (see section on magnesium) and because the active forms of vitamins function as cofactors in biological enzymes, the use of PLP rather than pyridoxine may be preferable.

Magnesium

Clinical Evidence: Several studies point to the effectiveness of magnesium in the treatment of PMS. In 1973, in the First International Symposium on Magnesium Deficiency in Human Pathology, positive results were reported in 192 women treated with 4.5-6 grams daily of magnesium nitrate for one week premenstrually and for the first two days of menses. Nervous tension was relieved in 89%, mastalgia in 96%, weight gain in 95% and headache in 43%.[27] A Czechoslovakian study of 30 women found doses of .5 grams, given four times daily from 3-10 days prior to menses, helped one third of the women in this small sample.[28] In a recent double-blind, ran

domized trial of 32 women with PMS, magnesium pyrrolidone carboxylic acid (360 mg Mg), given from mid-cycle to menses, resulted in significant improvement in total Menstrual Distress questionnaire scores.[29] Two other studies utilizing a high potency multiple vitamin, with particularly high doses of magnesium and pyridoxine have yielded positive results in alleviating symptoms of PMS.[14,30]

Mechanism of Action: In some cases magnesium supplementation seems to be correcting a deficiency. Studies comparing the magnesium status of women with PMS to asymptomatic subjects have found no relationship between serum levels of magnesium and premenstrual symptoms[21,31,32] but have found a significant decrease in RBC magnesium levels in PMS patients.[21,31,32] One study also found a deficiency of mononuclear blood cell magnesium in the symptomatic group.[32]

A magnesium deficiency causes a depletion of brain dopamine.[33] A deficiency may also cause hyperplasia of the adrenal cortex, elevating aldosterone and contributing to fluid retention.[34] A vicious cycle results as the elevated aldosterone may in turn increase urinary excretion of magnesium.[35] A magnesium deficiency may also interfere with essential fatty acid metabolism, as magnesium is necessary for conversion of cis-linoleic to gamma linolenic acid. Magnesium may modulate possible hypoglycemic effects by reducing glucose-induced insulin secretion.[36]

Magnesium plays an integral part in all activities of pyridoxine, being necessary for its phosphorylation, the first step in conversion to PLP. A symbiotic relationship exists, as B6 enhances magnesium utilization and uptake by the cells.[3] In the rare cases where high lead levels have been implicated in PMS, magnesium provides benefit by blocking intestinal absorption of lead.[3]

Vitamin E

Clinical Evidence: The efficacy of vitamin E in the treatment of PMS has been studied most extensively by London et al. The research first focused upon the effect of vitamin E in alleviating breast symptoms. In a double-blind study there was a significant decrease in some symptoms.[37] In a later study doses of 150-300 IU D,L-alpha-tocopherol twice daily succeeded in significantly reducing symptoms in three of the four categories (as established by Abraham) of PMS.[38] London's previous trials were all among women with PMS and benign mammary dysplasia. Positive results were found in a subsequent double-blind study of women with PMS regardless of the existence of fibrocystic breast disease.[13]

Mechanism of Action: The physiological mechanisms for vitamin E in the treatment of PMS are not clearly understood. London found no relationship between alpha-tocopherol supplementation and levels of progesterone, estrogen, testosterone or DHEA-S.[11] Some evidence points to a role of vitamin E in the modulation of prostaglandin synthesis. Tocopherol reduces release of arachidonic acid from phospholipids,[39] resulting in a decrease in formation of PGE2, or inflammatory prostaglandins. Alpha-tocopherol, which crosses the blood-brain barrier, also has modulating effects on neurotransmitters. Supplementation of vitamin E, for instance, blocks arachidonic acid induced decreases in GABA.[13]

Essential Fatty Acids

Clinical Evidence: Several studies point to the importance of essential fatty acids in the treatment of PMS. Brush reported on 68 patients who received 1-2 grams evening primrose oil (EPO) daily from 3 days prior to the usual onset of symptoms until menses.

Sixty-one per cent reported full relief of symptoms and 23% partial relief with the greatest impact on mastodynia.[40] Two other studies indicated statistically significant improvement particularly with the symptoms of depression and irritability.[41,42]

Mechanism of Action: Since PGE1 inhibits glucose induced insulin secretion, a deficiency, occurring either as a result of an inadequate intake of essential fatty acids in the form of cis-linoleic acid or problems with conversion to GLA, could result in symptoms of hypoglycemia, cravings for sweets and increase in appetite reported by many PMS patients.[24] Previously discussed nutrients, magnesium and B6 (as well as zinc, niacin and vitamin C), are important for the conversion of cis-linoleic acid to

PGE1. Since it is known that PGE1 modulates prolactin levels, another mechanism which has been suggested is that essential fatty acids act to decrease tissue sensitivity to prolactin.[41] An alpha-linolenic acid deficient diet in rats resulted in a 40-75% decrease in dopamine in the frontal cortex.[43] If this effect can be extrapolated to humans this would have further implications for PMS, particularly in regard to dysphoric symptoms.

Other Nutrients

Vitamin A: A couple of European studies have shown high doses of vitamin A (50,000 IU twice daily in one study and 200,000-300,000 IU daily in another study) to be helpful for the treatment of PMS, particularly for premenstrual headaches.[44,45] Doses as low as 40,000 IU daily over a period of years may be toxic.[46] Since recent evidence suggests that administering more than 10,000 IU of supplemental vitamin A per day may increase the risk of teratogenicity, until more is known, dosages above 10,000 IU per day should be avoided in all women capable of conception.[47]

Zinc: Zinc may be important, as it influences the binding of progesterone to human endometrium.[14] Zinc is also involved with B6 in the synthesis of GABA[14] and is necessary for the formation of PGE1 from linoleic acid. Furthermore, zinc is necessary for the mobilization of vitamin A from the liver, so supplementation may decrease the necessary therapeutic dose of vitamin A .[8] At doses of 50 mg daily, zinc may inhibit prolactin levels, an elevation of which may result in depressed progesterone.[8]

Calcium, Vitamin D and Manganese: In a double-blind trial, calcium was found to significantly decrease pain and water retention during the luteal and menstrual phase.[48] In a very small trial, two women were treated with calcium and vitamin D. Both women cited major reductions in menstrual migraines and other premenstrual symptoms after two months of therapy.[49] A group of 10 women was studied in a controlled setting. Those on a high calcium (1336 mg compared to 587 mg) diet had fewer premenstrual symptoms related to mood, concentration and behavior while a low manganese diet (1 mg as opposed to 5.6 mg) seemed to correlate with an increase in premenstrual symptomatology.[50]

Flavonoids: In rat studies naringenin, a bioflavonoid from grapefruit, exhibited weakly anti-estrogenic activity on uterine tissue.[51] In vitro, it also exhibited an anti-estrogenic effect on MCF-7 human breast cancer cells.[51]

One hundred sixty-five women were treated with Endotelon, a standardized grape seed oligomeric proanthocyanidin (OPC). Significant improvement was noted in some symptoms of PMS, particularly those of vascular origin. After two cycles there was a

60.8% improvement and after four cycles, a 78.8% improvement in abdominal swelling, mammary symptoms, pelvic pain, weight fluctuations and venous problems of the legs.[52]

Flavonoids such as apigenin and quercetin inhibit the synthesis of human estrogen in vitro and may do so in vivo by competing with estrogen substrates.[53]

Botanical Influences on PMS

Considering the prevalence of the use of botanical formulas in the treatment of PMS to enhance liver function, modulate hormones and relieve specific symptoms such as water retention, constipation, anxiety and depression, there is a surprising paucity of good, reliable studies. This article is by no means meant as a comprehensive discussion of the use of botanicals in the treatment of PMS but rather as a reporting of some of the studies available on the subject. The lack of available research serves to demonstrate the need for further study in this area.

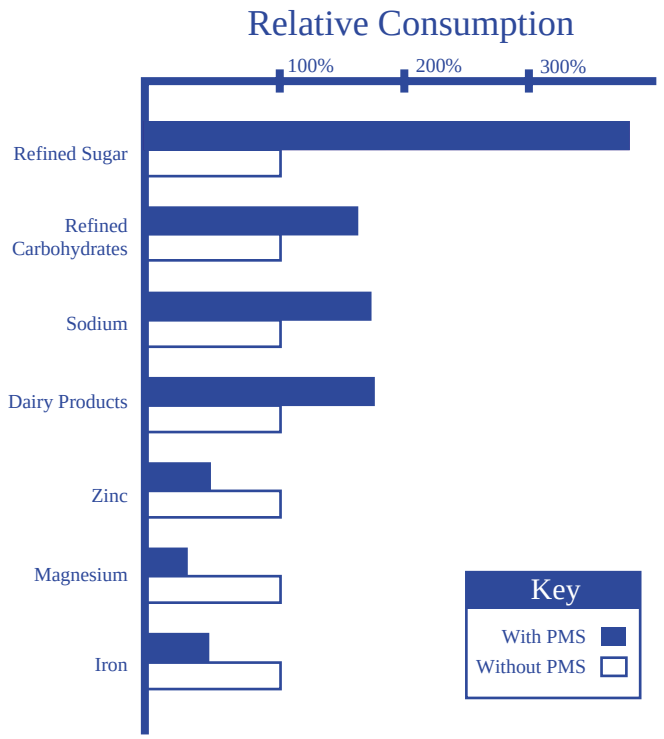
The efficacy of a standardized extract of Gingko biloba was evaluated in a group of 165 women in a double-blind study. Women received either 80 mg (24% gingkoflavoneglycoside content) twice daily or placebo from day 16 of their cycle until day 5 of the next cycle. Statistically significant improvement was noted for congestive, particularly breast, symptoms as well as neuropsychological symptoms.[54] Gingko extracts have been reported to exert monoamine oxidase (MAO) inhibiting activity.[55] This inhibition may be underlying the anxiolytic activities of gingko.

It has become popular to prescribe Prozac or one of the other serotonin re-uptake inhibitor drugs such as Paxil, Effexor or Zoloft for the treatment of dysphoric symptoms associated with PMS (see discussion below). Over 25 double-blind studies have demonstrated the effectiveness of standardized extracts of Hypericum in the treatment of depression, comparable to standard antidepressant drugs. A recent study demonstrated a 50% inhibition of serotonin uptake at 6.2 mcg/ml.[56] The exact manner in which Hypericum exerts this inhibition is still not known. A favorable effect of Agnus castus for premenstrual water retention has been reported.[57]

General Dietary Considerations

PMS patients consume 275% more refined sugar, 62% more refined carbohydrates, 78% more sodium, 79% more dairy products, 52% less zinc, 77% less magnesium and 53% less iron than women without PMS

FIGURE 3. Comparison of Selected Food Groups and Nutrient Intakes in Women With PMS and in Women Without PMS.[58]



has been noted between saturated, but not unsaturated, fats in the diet and blood estrogen levels.[8] Furthermore, women who derive approximately 20% of their calories from fat have significantly lower blood estrogen levels than women who consumed 40% of their calories as fat.[8] Women who consume large amounts of caffeine are more likely to suffer from PMS.[60] Sodium, in addition to contributing to fluid retention, enhances glucose absorption, contributing to a more exaggerated insulin response.[61] Refined sugar, in addition to contributing to hypoglycemic symptoms, increases the urinary excretion of magnesium, thus contributing to a magnesium deficiency.[62]

Other Lifestyle Considerations

PMS patients should be questioned about alcohol consumption. There are over 2 million alcoholic women in the reproductive age group in the US. Sixty-seven per cent of alcoholic women relate their drinking to the menstrual cycle,[8] with bouts of heavy consumption often occurring during the premenstrual period as an attempt to relieve anxiety and depression.

A Finnish study of 748 female university students found that women who participated in sports experienced much less premenstrual anxiety than non-athletic women.[63] Possible mechanisms include improved circulation, stimulation of endorphins, and a decrease in fat resulting in a decrease in circulating estrogens. The improvement of depression with regular aerobic exercise has been well documented.[64]

Reflexology has been found to alleviate many symptoms of PMS. Thirty-five women with PMS were randomly assigned to receive ear, hand and foot reflexology or placebo. They kept a daily diary of thirty-eight symptoms for two months prior to treatment, for the two months of treatment which consisted of one 30 minute treatment a week and for two months following treatment. There was a significantly greater decrease in PMS symptomatology in women given true reflexology over those receiving sham treatments. [65]

The Progesterone Controversy

Studies attempting to definitely connect PMS to a deficiency of progesterone or a relative increase in estrogen in relation to progesterone have been fraught with inconsistency and controversy. As early as 1938, Israel proposed that PMS was caused by unopposed estrogen during the luteal phase.[1] Dalton and Green continued to further this theory in the 1950s. Dalton has been one of the leading proponents of progesterone therapy, having treated thousands of patients for decades with progesterone injections (25-100 mg daily), suppositories (400-1600 mg daily) and subcutaneous pellets (500-1600 mg every 3-12 months).[63] Others have used nasal sprays, dermal patches and buccal tablets.[63] Dalton reported complete relief of symptoms in 83% of a group of 86 women with PMS.[63]

More recently, Lee has become a leading proponent of the use of transdermal creams for the treatment of PMS and reports significant success in his clinical practice.[66] Martorano et al. reported successful use of progesterone in clinical practice with doses of 300 mg oral micronized progesterone daily or 3cc rectal solution twice daily.[67] They emphasized the difference between progesterone, synthesized from yam or soy beans, and progestogen, such as is in birth control pills, Provera and other "progesterone" therapies. Progestogen may actually result in lowering serum progesterone levels.[67]

In Abraham's categorization of PMS, he reports a low progesterone:estrogen ratio as the etiology for PMT-A, his largest sub-

group.[3,8] He hypothesizes that the abnormal ratio is due not only to low progesterone but to an excess of estrogen caused by several possible factors — excess secretion from a tumor or ovarian cyst, increased aromatization of androgens from adipose tissue, decreased hepatic clearance of estrogens or decreased intestinal clearance.[8] Dietary and supplement programs which have successfully treated PMS often result in a decrease in serum estradiol and an increase in progesterone.[8]

A much smaller segment of the population, in Abraham's opinion, suffers from the reverse — low estrogen in relation to progesterone during the luteal phase.[3,8] In 1977, Steiner and Carroll also suggested that one sub-group of PMS sufferers, those with anxiety, irritability and hostility demonstrated a high estrogen to progesterone ratio, while those suffering depression seemed to have low estrogen to progesterone ratios.[68] This would be consistent with Abraham's PMT-D category.

On the other hand, there are numerous studies pointing to a lack of efficacy of progesterone in the treatment of PMS. In 1977 Sampson reported in a double-blind study that progesterone was no more effective than placebo.[69] Freeman et al. also found oral micronized progesterone to be no better than placebo in the treatment of severe premenstrual syndrome and premenstrual dysphoric disorder (PDD).[70] This same research group had found progesterone suppositories ineffective in a previous 1990 trial.[71] Reporting on these studies in *The Lancet*, van Leusden hypothesized the PMS symptoms to be caused by the rise of progesterone during the luteal phase, which, once in motion, could not be stopped. Thus, he proposed the most effective treatment is to prevent ovulation with medication or castration, thus stemming the incoming tide of progesterone.[72]

An epidemiological report by Cowan et al. found that women with a progesterone deficiency causing infertility had 5.4 times the risk of premenopausal breast cancer and a 10 fold increase in deaths from all malignant neoplasms. They found no relationship between progesterone levels and the incidence of postmenopausal breast cancer.[73] As physicians, perhaps we need to consider a history of premenstrual syndrome as a possible risk factor for premenopausal breast cancer, assuming that progesterone plays a significant role in PMS in at least some patients.

The Serotonin Connection

There is some disagreement in the scientific community regarding the effects of serotonin in the pathogenesis of PMS. Abraham made references in an article published in 1987 to the negative effect of high levels of serotonin on symptoms related to PMS.[8] Serotonin at high levels may cause nervous tension, drowsiness, palpitations, difficulty with concentration and water retention.[9] More recently, studies have focused on low serotonin levels contributing to premenstrual symptoms, particularly depression. In fact, to facilitate the discussion, a sub-category of PMS, premenstrual dysphoric disorder (PDD), has been identified. Symptoms include depression, anxiety, lability of affect and decreased interest in life.[72]

The use of serotonin uptake inhibitor drugs such as fluoxetine (Prozac) have been used widely to treat this condition. Steiner et al. found that 52% of women diagnosed with PDD improved 50% with fluoxetine versus 22% in the placebo group. The improvement dropped to 37% after three cycles. There was a 42% drop out rate due to side effects, especially at higher doses.[74] A small scale trial of fluoxetine found 15 of 16 women experienced complete remission of symptoms of PMS,

however ten women reported side-effects and 3 dropped out of the trial as a result of drug effects which included insomnia, GI upset, menstrual disturbances and sweating.[75]

Although a study by Veeninga and Westenberg does not support a role for serotonin in the pathophysiology of late luteal phase dysphoric disorder (LLPDD),[76] Rapkin reported whole blood serotonin levels to be lower 10 days prior to menses in PMS patients when compared to controls who experienced a mid-luteal rise in serotonin levels.[77] Furthermore, he found tryptophan loading to consistently increase serotonin levels in controls but not PMS patients.[77] A review article which looked at over 170 articles on PMS concluded that the only generalizations that could be made were that a fall in levels of gonadal hormones during late luteal phase resulted in a decrease in serotoninergic activity.[78]

As noted above, tryptophan loading in at least one study did not result in an increase in serotonin levels in PMS patients. According to some studies however, tryptophan administration does seem to play a positive role in PMS symptomatology. Brzezinski reported in *The Lancet* on an unpublished trial of tryptophan for PMS. One gram daily significantly improved symptoms of anxiety, depression and irritability in women with PDD.[79] He goes on to report that the study was discontinued when the FDA sounded the alarm about tryptophan. The drug d-fenfluramine was used instead of tryptophan in later studies.[79] Another study found L-tryptophan at 6 grams daily to significantly ameliorate symptoms of PDD, with only mild side-effects.[80] Menkes et al. found that a diet designed to provide acute tryptophan depletion resulted in the aggravation of premenstrual symptoms, particularly irritability, in a small group of 16 women.[81]

While the evidence regarding the connection between serotonin and PMS continues to be inconclusive, it appears that, in some cases at least, patients have benefited from increasing serotonin levels. Due to the potential side effects of various serotonin re-uptake inhibitor drugs, it is this author's opinion that other methods of enhancing serotonin levels should be employed. Magnesium is necessary for the activation of pyridoxine to pyridoxal phosphate, which in turn is necessary for conversion of tryptophan to serotonin. And, as mentioned previously, the botanical, Hypericum, appears to exert its anti-depressant effects, at least in part, by inhibiting the re-uptake of serotonin.[56] As I examined the literature on this topic, I found it interesting that serotonin was either not mentioned or mentioned in a negative light in regard to PMS in most of the studies prior to 1990. During the last several years there has been a rash of studies on the need to enhance serotonin levels in order to treat PMS. These studies appear to coincide with the introduction of various serotonin re-uptake inhibitor drugs.

Conclusions:

After a review of the literature, it is difficult to draw any absolute conclusions regarding the etiology of PMS. It appears to be caused by the interactions of cyclic changes in various gonadal hormones, particularly estrogen and progesterone, with other hormone and neurotransmitter systems. In addition, psycho-social factors play an important role. It seems clear that no single deficiency or excess of a particular nutrient, hormone or neurotransmitter can explain all cases of premenstrual syndrome. Because of the complexities involved, drug treatment which depends on a single-etiology/one-treatment mentality has not met with consistent success. An approach which combines diet and lifestyle changes, along with the administration of specific nutrients and botanicals, has the ability to affect

several systems in the body simultaneously and is the logical and most effective way to approach the treatment of PMS.

References

1. Clarke A. Premenstrual syndrome: Single or multiple causes? *Can J Psychiatry* 1985; 30:474-482.
2. Rubinow D, Hoban C, Roy-Byrne P, et al. Premenstrual syndromes: Past and future research strategies. *Can J Psychiatry* 1985;30:469-473.
3. Abraham GE. Nutrition and the premenstrual tension syndromes. *J Appl Nutr* 1984;36(2): 103-117.
4. Clare AW. Hormones, behaviour and the menstrual cycle. *J Psychosom Res* 1985;29(3): 225-233.
5. Halbreich U, Endicott J, Lesser J. The clinical diagnosis and classification of premenstrual changes. *Can J Psychiatry* 1985;30:489-497.
6. True BL, Goodner SM, Burns EA. Review of the etiology and treatment of premenstrual syndrome. *Drug Intell Clin Pharm* 1985; 19(10):714-722.
7. Abraham GE. Premenstrual Tension. *Problems in Obstet & Gynecol* 1980;3(12):1-39.
8. Abraham GE. Role of nutrition in managing the premenstrual tension syndromes. *J Reprod Med* 1987;32(6):405-422.
9. Schildkraut JJ, Kety SS. Biogenic amines and emotion. *Science* 1967;156:21-30.
10. Girdler SS, Pedersen CA, Light KC. Thyroid axis function during the menstrual cycle in women with premenstrual syndrome. *Psychoneuroendocrinol* 1995;20:395-403.
11. London RS, Sundaram G, Manimekalai S, et al. The effect of alpha-tocopherol on premenstrual symptomatology: A double-blind study.II.Endocrine correlates. *J Am Coll Nutr* 1984;3:351-356.
12. Eriksson E, Sundblad C, Lisjo P, et al. Serum levels of androgens are higher in women with premenstrual irritability and dysphoria than in controls. *Psychoneuroimmunology* 1992;17(2-3):195-204.
13. London RS, Murphy L, Kitlowski KE, Reynolds MA. Efficacy of alpha-tocopherol in the treatment of the premenstrual syndrome. *J Reprod Med* 1987;32(6):400-404.
14. Stewart A. Clinical and biochemical effects of nutritional supplementation on the premenstrual syndrome. *J Reprod Med* 1987;32(6): 435-441.
15. Brush MG, Bennett T, Hansen K. Pyridoxine in the treatment of premenstrual syndrome: a retrospective survey in 630 patients. *Br J Clin Pract* 1988;42(11):448-452.
16. Doll H, Brown S, Thurston A, Vessey M. Pyridoxine (vitamin B6) and the premenstrual syndrome: a randomized crossover trial. *J R Coll Gen Pract* 1989;39(326):364-368.
17. Kendall KE, Schnurr PP. The effects of vitamin B6 supplementation on premenstrual symptoms. *Obstet Gynecol* 1987;70:145-149.
18. Hagen I, Nesheim BI, Tuntland T. No effect of vitamin B6 against premenstrual tension. A controlled clinical study. *Acta Obstet Gynecol Scand* 1985;64:667-670.
19. Williams MJ, Harris RI, Dean BC. Controlled trial of pyridoxine in the premenstrual syndrome. *J Int Med Res* 1985;13:174-179.
20. Barr W. Pyridoxine supplements in the premenstrual syndrome. *Practitioner* 1984;228(1390):425-427.
21. Gallant MP, Bowering J, Short SH, et al. Pyridoxine and magnesium status in women with premenstrual syndrome. *Nutr Res* 1987;7:243-252.
22. Hargrove JT, Abraham GE. Effect of vitamin B6 on infertility in women with the premenstrual tension syndrome. *Infert* 1979;2:315.
23. Winston F. Oral contraceptives, pyridoxine and depression. *Am J Psychiatry* 1973;130:1217-1221.
24. Gugliano D, Torrela R. Prostaglandin E1 inhibits glucose-induced insulin secretion in man. *Prostaglandins Med* 1979;48:302.
25. Dalton K. Pyridoxine overdose in premenstrual syndrome. *Lancet* 1985;1:1168.
26. Parry GI, Bredesen DE. Sensory neuropathy with low-dose pyridoxine. *Neurology* 1985;35:1466-1468.
27. Nichols A. Traitement du syndrome prementruel et de la dysmeorrhea par l'ion magnesium. In: Durlach, J. *First Int Sympos on Magnesium Deficiency in Human Pathology* . Paris, Springer, Verlag; 1973:261-263.
28. Hronek J, Kolomaznik M. Oganicke soli magnezia v lecbe premenstrualni tenze. *Cs Psychiat* 1985;5:301-306.

29. Facchinetti F, Borella P, Sances G, et al. Oral magnesium successfully relieves premenstrual mood changes. *Obstet Gynecol* 1991;78(2): 177-181.
30. Goei GS, Abraham GE. Effect of a nutritional supplement, Optivite, on symptoms of premenstrual tension. *J Reprod Med* 1983; 28(8):527-531.
31. Abraham GE, Lubran MD. Serum and red cell magnesium levels in patients with premenstrual tension. *Am J Clin Nutr* 1981;34:1264-1266.
32. Rosenstein DL, et al. Magnesium measures across the menstrual cycle in premenstrual syndrome. *Biol Psychiatr* 1994;35:557-561.
33. Barbeau A, et al. Deficience en magnesium et dopamine cerebrale. In: Durlach J. *First Int. Sym on Magnesium Deficiency in Human Pathology*. Paris, Vittel; 1973:149.
34. Cantin M. Hyperaldosteronisme secondaire au cours do la carence en magnesium. In: Durlach J. *First Int Sympos on Mansesium Deficiency in Human Pathology*. Paris, F. Vittel; 1973:461.
35. Horton R, Biglieri EG. Effect of aldosterone on the metabolism of magnesium. *J Clin Endocrinol* 1962;22:1187.
36. Curry DL, et al. Magnesium modulation of glucose-induced insulin secretion by the perfused rat pancreas. *Endocrinology* 1977;101:203.
37. London RS, Sundaram GS, Murphy L, Goldstein PJ. Evaluation and treatment of breast symptoms in patients with the premenstrual syndrome. *J Reprod Med* 1983;28(8): 503.
38. London RS, Sundaram G, Manimekalai S, et al. The effect of alpha-tocopherol on premenstrual symptomatology: A double-blind trial. *J Am Coll Nutr* 1983;2:115-122.
39. Panganamala RV, Cornwall DG. The effects of vitamin E on arachidonic acid metabolism. Vitamin E: Biochemical, hematological, and clinical aspects. *Ann NY Acad Sci* 1982;396: 376.
40. Brush MG. Evening primrose oil in the treatment of the premenstrual syndrome. In: Horrobin DF, Ed. *Clinical Uses of Essential Fatty Acids*. Montreal: Eden Press; 1982:155-162.
41. Horrobin DF. The role of essential fatty acids and prostaglandins in the premenstrual syndrome. *J Reprod Med* 1983;28(7):465-468.
42. Puolakka J, et al. Biochemical and clinical effects of treating the premenstrual syndrome with prostaglandin synthesis precursors. *J Reprod Med* 1985;39(3):149-153.
43. Delion S, Chalon S, Guilloteau D, et al. Alpha-linolenic acid dietary deficiency alters age-related changes of dopaminergic and serotoninergic neurotransmission in the rat frontal cortex. *J Neurochem* 1996;66(4):1582-1591.
44. Block E. The use of vitamin A in the premenstrual tension. *Acta Obst Gynec Scand* 1960;39:586-592.
45. Kleine HO. Vitamin A therapie bei pra menstruellen nervosen Beschwerden. *Dtsch Med Wschr* 1954;79:879-880.
46. Farris WA, Erdman JW. Protracted hypervitaminosis A following long-term, low-level intake. *JAMA* 1982;247:1317.
47. Rothman KJ, Moore LL, Singer MR, et al. Teratogenicity of high vitamin A intake. *N Engl J Med* 1995;333:1369-1373.
48. Alvir JM, Thys-Jacob S. Premenstrual and menstrual symptom clusters and response to calcium treatment. *Psychoparmacol Bull* 1991;27(2):145-148.
49. Thys-Jacob S. Vitamin D and calcium in menstrual migraine. *Headache* 1994;34(9): 544-546.
50. Penland JG, Johnson PE. Dietary calcium and manganese effect on menstrual cyle symptoms. *Am J Obstet Gynecol* 1993;168(5):1417-1423.
51. Ruh MF, Zacharewski T, Connor K, et al. Naringenin: a weakly estrogenic bioflavonoid that exhibits antiestrogenic activity. *Biochem Pharmacol* 1995;50(9):1485-1493.
52. Amsellem M, et al. Endotelon in the treatment of venolymphatic problems in premenstrual syndrome; Multicenter study on 165 patients. *Tempo Medical* 1987;282.
53. Kellis Jr JT, Vickery LE. Inhibition of human estrogen synthetase (aromatase) by flavones. *Science* 1984;255:1032-1034.
54. Tamborini A, Taurelle R. Value of standardized Gingko biloba extract (EGb 761) in the management of congestive symptoms of premenstrual syndrome. *Rev Fr Gynecol Obstet* 1993;88:447-457.
55. White HL, Scates PW, Cooper BR. Extracts of Gingko biloba leaves inhibit monoamine oxidase. *Life Sci* 1996;58:1315-1321.

56. Perovic S, Muller WEG. Pharmacological profile of hypericum extract. Effect of serotonin uptake by postsynaptic receptors. *Arzneim Forsch* 1995;45:1145-1148.
57. Amann W. Premenstrual water retention. Favorable effect of Agnus castus (Agnolyt) on premenstrual water retention. *Z Allgemeinmed* 1971;47(7):360-362.
58. Abraham GE. Nutritional factors in the etiology of the premenstrual tension syndromes. *J Reprod Med* 1983;28:446-363.
59. Goldin BR, et al. Estrogen excretion patterns and plasma levels in vegetarian and omnivorous women. *N Engl J Med*1982;307:1542-1547.
60. Rossignol AM. Caffeine-containing beverages and premenstrual syndrome in young women. *Am J Public Health* 1985;75(11):1335-1337.
61. Ferrannini E, et al. Sodium elevates the plasma glucose response to glucose ingestion in man. *J Clin Endocrinol Metabol* 1982;54:455.
62. Seelig M. Human requirements of magnesium: Factors that increase needs. In: Durlach J, Ed. *First Int Sympos on Magnesium Deficiency in Human Pathology*. Paris, Springer, Verlag; 1971:11.
63. Keye WR Jr. Medical treatment of premenstrual syndrome. *Can J Psychiatry* 1985;30: 483-487.
64. McCann L, Holmes DS. Influence of aerobic exercise on depression. *J Pers Soc Psychol* 1984;46:1142-1147.
65. Oleson T, Flocco W. Randomized controlled study of premenstrual symptoms treated with ear, hand and foot reflexology. *Obstet Gynecol* 1993;82(6):906-911.
66. Lee J. *Natural Progesterone: The Multiple Roles of a Remarkable Hormone.* Sebastopol, CA: BLL Publishing; 1995:50-52.
67. Martorano JT, Ahlgrimm M, Myers D. Differentiating between natural progesterone and synthetic progestogens: Clinical implications for premenstrual syndrome management. *Compr Ther* 1993;19(3):96-98.
68. Steiner M, Carroll BJ. The psychobiology of premenstrual dysphoria: review of theories and treatments. *Psychoneuroendocrinol* 1977;2: 321-325.
69. Sampson G. Premenstrual syndrome: a double-blind controlled trial of progesterone and placebo. *Br J Psychiatry* 1979;135:209.
70. Freeman EW, Rickels K, Sondheimer SJ, Polansky M. A double-blind trial of oral progesterone, alprazolam, and placebo in treatment of severe premenstrual syndrome. *JAMA* 1995;274:51-57.
71. Freeman EW, Rickels K, Sonheimer SJ, Polansky M. Ineffectiveness of progesterone suppository treatment for premenstrual syndrome. *JAMA* 1990;264:349-353.
72. van Leusden H. Premenstrual syndrome no progesterone; premenstrual dysphoric disorder no serotonin deficiency. *Lancet* 1995;346: 1443-1444.
73. Cowan L, Gordis L, Tonascia J, Seegar Jones G. Breast cancer risk in women with progesterone deficiency. *Am J Epidemiol* 1981: 114:209-217.
74. Steiner M, Steinberg S, Stewart D, et al. Fluoxetine in the treatment of premenstrual dysphoria. *N Engl J Med* 1995;332(23):1529-1534.
75. Menkes DB, Taghavi E, Mason PA, Howard RC. Fluoxetine's spectrum of action in premenstrual syndrome. *Int Clin Psychopharmacol* 1993;8(2):95-102.
76. Veeninga AT, Westenberg HG. Serotonergic function and late luteal phase dysphoric disorder. *Psychopharmacology (Berl)* 1992;108(1-2):153-158.
77. Rapkin AJ. The role of serotonin in premenstrual syndrome. *Clin Obstet Gynecol* 1992;35(3):629-636.
78. Halbreich U, Tworek H. Altered serotonergic activity in women with dysphoric premenstrual syndromes. *Int J Psychiatry Med* 1993;23(1):1-27.
79. Brezezinski A. Serotonin and premenstrual dysphoric disorder. *Lancet* 1996;347:470-471.
80. Steinberg S, Abbable L, Young SN, Belanger MC. Tryptophan in the treatment of late luteal phase dysphoric disorder: a pilot study. *J Psychiatry Neurosci* 1994:19(2):114-119.
81. Menkes DB, Coates DC, Fawcett JP. Acute tryptophan depletion aggravates premenstrual syndrome. *J Affect Disord* 1994;32(1):37-44.