

# Natural Interventions for Premenstrual Syndrome

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**ABSTRACT:** *Premenstrual syndrome (PMS) is a common disorder in women of reproductive age that is characterized by recurring physical, affective, and cognitive (or performance) symptoms in the latter half of the menstrual cycle. As many as 85% of menstruating women suffer from one or more PMS symptoms—with approximately 5% to 10% of women having symptoms severe enough to be debilitating. Although the precise etiology of PMS remains elusive, several physiologic mechanisms have been proposed. These theories mostly focus on sex hormones and their metabolites, as well as their interactions with neurotransmitters, their influences on kidney sodium regulation, and their ability to be metabolized in the liver.*

*The multifactorial nature of PMS has resulted in a variety of interventions, from the reversal of nutrient deficiencies to hormonal or neurotransmitter manipulation. A natural approach to managing PMS should begin with correcting possible nutrient deficiencies that have been associated with menstrually-related symptoms. Select, time-tested herbal remedies that have also attained scientific merit can support physiologic mechanisms associated with the menstrual cycle, such as hormonal and neurotransmitter activity, kidney function, and liver health. Dietary and lifestyle modifications may also play an important part in an intervention program for PMS.*

Premenstrual syndrome (PMS) is a common disorder in women of reproductive age that is characterized by the cyclic recurrence of physical, affective, and cognitive (or performance) symptoms. The symptoms occur in the latter half of the menstrual cycle, resolve after menses begins, and are absent during the early phase of the menstrual cycle. A diagnosis of PMS requires that symptoms are severe enough to negatively impact a woman's ability to function at home, in the workplace, or in personal relationships.

As many as 85% of menstruating women experience one or more symptoms of PMS. Approximately 5% to 10% of women have symptoms severe enough to be debilitating.<sup>1</sup> PMS affects women of all cultures and socioeconomic levels, but types of symptoms and levels of discomfort vary from woman to woman and may have cultural influence. More than 300 symptoms have been associated with PMS.<sup>2</sup> Among the most prominent and consistently described symptoms are irritability, tension, fluid retention, and a general unwell feeling (Table 1).<sup>3-5</sup>

## DIAGNOSIS

The signs and symptoms of PMS are not unique, and there are currently no laboratory tests to confirm a diagnosis. Because some health conditions manifest symptoms similar to PMS, it is imperative for healthcare practitioners to be knowledgeable of existing diagnostic criteria.

Patients presenting with symptoms consistent with PMS should undergo a thorough physical examination to rule out other underlying conditions. Disorders such as endometriosis, irritable bowel syndrome, chronic fatigue syndrome, hypothyroidism, and major depression should be excluded before a diagnosis of PMS is considered.<sup>6</sup>

Taking a detailed menstrual and gynecologic history, as well as a history of premenstrual symptoms and their impact on daily life, are key to accurate diagnoses. The diagnostic criteria for PMS are contingent on the timing and cyclic characteristics of symptoms. The applicable guidelines adapted are summarized as follows:<sup>7,8</sup>

1. Symptoms are consistent with PMS and occur reproducibly for at least two cycles.
2. Symptoms are present in the week or two before menses and resolve within several days after the onset of menses.
3. Severity of symptoms disrupt a woman's daily life (e.g., personal relationships, social activities, job performance).
4. Symptoms occur in the absence of hormone ingestion or pharmacologic therapy.
5. Symptoms are not merely an exacerbation of another condition (e.g., anemia, endometriosis, hypothyroidism, depression or anxiety disorders, diabetes, autoimmune disease, or cancer of the ovaries, uterus, cervix, or breast).

**Table 1. Common Symptoms Associated with Premenstrual Syndrome**

Physical Discomforts	Negative Affect	Impaired Cognitive Function or Performance
Fluid retention	Tension or anxiety	Difficulty concentrating
Weight gain	Increased appetite or food cravings	Distractibility
Breast tenderness (mastalgia)	Irritability	Forgetfulness
Headache	Depression or sadness	Confusion
Fatigue	Feelings of hopelessness	Mood swings
Nausea	Restlessness	Temper outbursts
Insomnia or excessive sleep	Tearfulness	Accident prone
Abdominal cramps	Anger	Poor motor coordination
Muscle, joint, or back pain	Feeling overwhelmed	Impulsivity

## UNDERSTANDING THE MENSTRUAL CYCLE

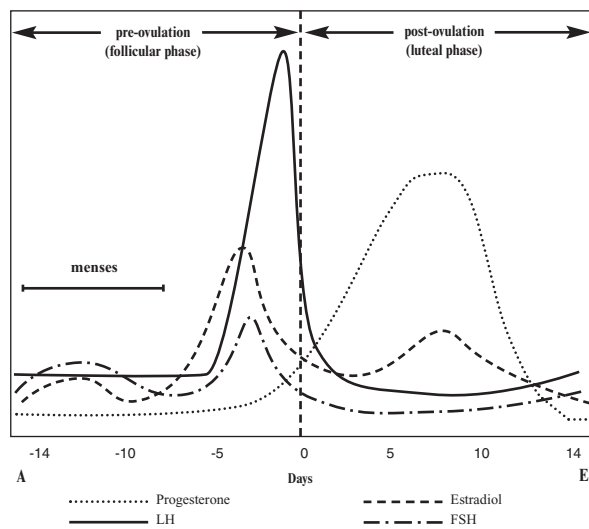
It has been hypothesized that hormonal fluctuations and other physiological mechanisms associated with the menstrual cycle may underlie menstrual symptoms; therefore understanding the normal pattern of the menstrual cycle is fundamentally helpful. A normal menstrual cycle in a woman of reproductive age can be divided into three distinct phases: follicular, ovulatory, and luteal (Figure 1).

**Follicular Phase**—The follicular phase, which initiates the development of an ovarian follicle, is characterized by a rise in estrogen and follicle-stimulating hormone (FSH). It begins when gonadotropin releasing hormone (GnRH) is secreted from neurons in the hypothalamus and transported to the anterior pituitary, stimulating the anterior pituitary to release FSH. FSH stimulates the development of an ovarian follicle. The rising FSH levels also activate aromatase and FSH receptors, resulting in a higher ratio of estrogens to androgens within the follicle. The rising estrogen levels trigger a negative feedback mechanism on the pituitary—inhibiting the pituitary production of FSH—while a positive feedback mechanism stimulates the pituitary to begin secreting luteinizing hormone (LH).

**Ovulatory Phase**—A peak in LH and estrogen levels predicts ovulation, taking place at the middle of the menstrual cycle. At this point, the follicle has acquired LH receptors and is responsive to LH, which induces the secretion of enzymes to rupture the follicular wall, releasing the egg into a fallopian tube. The rise in LH also allows the remaining follicular cells, which organize on the corpus luteum (a process known as luteinization), to secrete small amounts of progesterone.

**Luteal Phase**—The shift from estrogen dominance to progesterone dominance and the gradual reduction in LH and FSH levels characterize the luteal phase. This is the last part of the menstrual cycle in which premenstrual symptoms can begin, followed by their remittance during the beginning of the subsequent follicular phase. In the luteal phase, the egg travels through the fallopian tube, wherein fertilization can occur. The ruptured follicle, which has formed the corpus luteum, continues to release moderate amounts of estrogen and also starts to secrete progesterone. If the egg is fertilized, it will implant on the lining of the uterus, and if it is not fertilized the corpus luteum will disintegrate, stopping its production of estrogen and progesterone. This rapid fall in estrogen and progesterone causes the lining of the uterus to shed along with the unfertilized egg and blood, marking the beginning of menses and the end of the menstrual cycle.

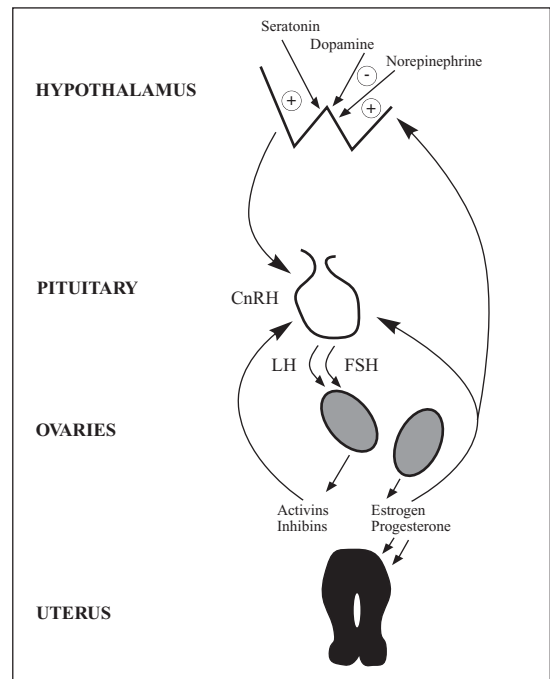
Figure 1. A normal ovulatory menstrual cycle



## Continuous Interplay of Hormones and Neurotransmitters

A normal ovulatory menstrual cycle relies on the coordinated activity of the hypothalamus, pituitary, ovary, and endometrial lining of the uterus, which is subject to modulation by certain hormones and neurotransmitters.<sup>9</sup> Throughout the menstrual cycle, GnRH is secreted from neurons in the hypothalamus in a pulsatile manner under the control of serotonin, norepinephrine, and other neurotransmitters. GnRH controls the release of FSH and LH, which stimulate the ovaries to secrete the hormones estrogen, progesterone, activin, and inhibin. Estrogen and progesterone feed back on the hypothalamus and pituitary to regulate the release of GnRH and LH, and activin and inhibin feed back on the pituitary to modulate the secretion of FSH.<sup>10</sup> Throughout the cycle, estrogen, progesterone, and progesterone metabolites can also exert effects on neurotransmitters (Figure 2).<sup>2,11,12</sup>

Figure 2. The coordinated activity of the hypothalamus, pituitary, ovaries, and uterus are influenced by certain neurotransmitters and sex hormones during a normal ovulatory menstrual cycle.



## ETIOLOGY

Although the basic physiology and symptomatology of the menstrual cycle are well understood, the exact etiology of PMS has not been fully elucidated and may be complex and multifactorial. Several physiologic mechanisms that underlie PMS have been proposed. These theories focus mostly on sex hormones and their metabolites, as well as their interactions between neurotransmitters (e.g., serotonin), their influences on kidney sodium regulation, and their ability to be metabolized in the liver.<sup>2</sup>

### Estrogen and Progesterone Fluctuations

Much of the early research has focused on sex hormone levels and their fluctuations during the menstrual cycle.<sup>2</sup> There are obvious links between the rise and fall of sex hormones associated with ovulatory cycles and PMS symptomatology. The fact that the most severe PMS symptoms occur during the luteal phase as progesterone levels decline, coupled with the discovery of progesterone's anxiolytic (or anti-anxiety) effects has led some researchers to hypothesize that PMS symptoms such as irritability, tension, and anxiety may originate from progesterone deficiency.<sup>7</sup>

In support of this theory, PMS does not occur premenarchally or in postmenopausal women refraining from hormone replacement therapy (HRT); whereas an induction of symptoms has been observed in postmenopausal women on HRT with the addition of progestin, especially in women with a history of PMS.<sup>14</sup> These observations and the cyclicity of symptoms indirectly suggest that sex hormones may, at least in part, play a role in PMS.<sup>2,14</sup>

Early pharmacologic interventions have thus included progestin supplementation and ovulation suppression. However, this mode of treatment has not consistently proven efficacious over time. It has been postulated that some progestins might actually contribute to symptoms, while some other natural progesterone metabolites might have a positive effect due to their neuroactive properties.<sup>2</sup> Nevertheless, equivocal data on the efficacy of various progesterone interventions has led researchers to explore other possible etiologic factors, such as the role of certain neurotransmitters and their complex interactions with sex hormones.

### The Serotonergic System

The serotonergic system modulates mood, sleep, and appetite and is thought to influence behavioral and physiologic functioning. This system is a network of nerves that communicates to the rest of the brain via a chemical messenger known as serotonin. Dysfunction of the serotonergic system on the basis of decreased serotonin concentrations and diminished serotonin reuptake has also been postulated as a potential cause of PMS.<sup>15,16</sup> This theory is supported by studies using antidepressant medications in the management of premenstrual dysphoric disorder—the most severe, debilitating form of PMS characterized by mood symptoms that seriously impact relationships and interfere with daily functioning.<sup>17</sup>

It has been postulated that some antidepressants may help with symptoms of PMS by enhancing the central serotonergic tone; however, augmentation of serotonergic transmission alone cannot fully explain their effects in PMS. Because all the symptoms of PMS are maximal in the late luteal phase, it is also speculated that a deficiency of progesterone metabolites influencing the anxiolytic neurotransmitter gamma aminobutyric acid (GABA) might account for many of the mood-related symptoms of PMS. This hypothesis, in combination with previous theories about progesterone, has stimulated an interest in investigating the possible relationship between the progesterone metabolite allopregnanolone and neurotransmitter activity in PMS.<sup>16</sup>

### Progesterone's Neuroactive Metabolites

Allopregnanolone, an A-ring-reduced metabolite of progesterone, can rapidly alter the excitability of the nervous system by interacting with GABA<sub>A</sub> receptors, suggesting it may play an important role in PMS.<sup>18</sup> It possesses a high affinity for binding to GABA<sub>A</sub> receptors and increases sensitivity to GABA—an inhibitory neurotransmitter that controls depression, pain perception, and anxiety—indicating it can be anxiolytic, and at high doses, anesthetic.<sup>19,20</sup> Decreased allopregnanolone levels may therefore contribute to the inability to enhance GABA when the central nervous system is susceptible to excitatory triggers, stress, or rapid hormonal fluctuations, as may occur during the menstrual cycle.<sup>21,23</sup> An impaired GABA<sub>A</sub>-mediated response may therefore play a role in explaining various mood, behavioral, and cognitive symptoms occurring with PMS.<sup>11</sup>

Data on the potential relationship between allopregnanolone and PMS are equivocal. Some research has shown no correlation between circulating allopregnanolone levels and severity of mood and behavioral symptoms.<sup>21</sup> Conversely, the results of several human studies have demonstrated an inverse relationship between levels of allopregnanolone and severity of PMS distress during the symptomatic luteal phase, suggesting allopregnanolone deficiency may, in part, explain PMS and the severity of distressing symptoms.<sup>11,22</sup>

### Influence of Estrogen on Neurotransmitters

In contrast with progesterone, estrogen appears to have an excitatory response on neurotransmitters.<sup>19</sup> It interacts with some of the key neurotransmitters involved in regulating a variety of behaviors that may change during the menstrual cycle in women with PMS, such as mood, impulsivity, cognition, appetite, and sleep.<sup>12</sup>

Among its influences, estrogen enhances monoamine activity, increasing the postsynaptic responsiveness of the excitatory neurotransmitter serotonin. It also increases the synthesis of serotonin, the number of serotonergic receptors, and the transport and uptake of neurotransmitters. Cumulatively functioning as a potent serotonin agonist, estrogen may indirectly stimulate nervous tension, drowsiness, fluid retention, and difficulty concentrating.<sup>2</sup>

Similarly, estrogen increases the activity of norepinephrine—an excitatory neurotransmitter that can trigger irritability and hostility—facilitating its turnover and possibly decreasing its reuptake and metabolism. It also appears to decrease receptor sensitivity to dopamine, an inhibitory neurotransmitter that relaxes nerves. It has therefore been speculated that increased fluctuations in estrogen levels during the luteal phase of the menstrual cycle may play a role in PMS symptomatology. However, estrogen also fluctuates in the asymptomatic follicular phase of the menstrual cycle, suggesting additional factors are involved.<sup>2</sup>

### Estrogen, Progesterone, and Kidney Function

Estrogen and progesterone influence kidney sodium regulation by interacting with the renin-angiotensin-aldosterone system (RAAS), a system that influences electrolyte and fluid balance. The RAAS involves a series of steps, beginning with the conversion of angiotensinogen to angiotensin I, which is then converted into angiotensin II—a potent vasoconstrictor that stimulates the adrenal cortex to release aldosterone. Aldosterone, a mineralocorticoid hormone, stimulates the conservation of sodium in extracellular fluid and the excretion of potassium in the urine, thereby increasing sodium and water retention. Estrogen may stimulate the RAAS by inducing angiotensinogen synthesis in the liver; this effect has been postulated to underlie menstrual symptoms such as bloating and weight gain.<sup>2</sup>

Conversely, progesterone exhibits anti-mineralocorticoid activity by competing with aldosterone at the receptor level; this may favorably impact menstrually related bloating and weight gain. These effects are mediated by endogenous progesterone; most synthetic progestins do not possess anti-mineralocorticoid activity.<sup>2</sup>

### Imbalance in Estrogen-to-Progesterone Ratio: Implications of Liver Function

While progesterone deficiency in relation to PMS has not proven consistent, it is generally thought that an imbalance between the activity of estrogen and progesterone (in which estrogen is dominant) may be at least partially to blame.<sup>23</sup> In fact, some research studies have demonstrated an association between excess estrogen levels and a higher intensity of PMS symptoms.<sup>23-26</sup>

High estrogen-to-progesterone activity can be due to various factors. A principle factor contributing to estrogen excess is decreased metabolic clearance of estrogens, which has been observed in women with PMS.<sup>23,26</sup> Estrogens are metabolized primarily in the liver, wherein they are conjugated and rendered water soluble and inactive. The conjugated estrogens are then cleared by the kidneys, and subsequently excreted in the urine. Compromised liver function can therefore result in decreased estrogen excretion and increased estrogen activity, suggesting that maintaining liver health is essential to maintaining a balanced estrogen-to-progesterone ratio.<sup>23</sup> (For more information on estrogen metabolism, please refer to the Applied Nutritional Science Report entitled *Nutritional Influences on Estrogen Metabolism* by Douglas C. Hall, MD.)

## NUTRITIONAL STRATEGIES FOR INTERVENTION

The multifactorial nature of PMS has resulted in a variety of interventions, from the reversal of nutrient deficiencies to hormonal or neurotransmitter manipulation.<sup>2</sup> Successful management of PMS should begin with correcting possible nutrient deficiencies that can exacerbate symptoms.

### Multivitamin/Mineral

Scientific investigations suggest a role of nutritional deficiencies in PMS symptomatology, suggesting that reversing any possible nutrient deficiencies should be the first step in PMS management.<sup>27-29</sup> This is of particular importance due to the fact that women with PMS have been reported to consume more refined sugar, refined carbohydrates, and dairy products that may lack adequate quantities of vitamins and minerals.<sup>28,30</sup>

In a double-blind, placebo-controlled study, high doses of a multivitamin/mineral supplement was shown to correct laboratory analyzed nutrient deficiencies, as well as significantly improve symptoms of premenstrual tension over the 4-month study period. The most significant deficiencies detected prior to supplementation included vitamin B<sub>6</sub> and magnesium, although deficiencies of vitamins E, B<sub>1</sub>, B<sub>2</sub>, and the minerals zinc and chromium were also noted.<sup>28</sup>

### Vitamin B<sub>6</sub>

Vitamin B<sub>6</sub>, or pyridoxine, has been studied as a possible intervention for PMS for over two decades. An important cofactor for enzymes involved in the synthesis of neurotransmitters, vitamin B<sub>6</sub> deficiency has been associated with decreased levels of serotonin and GABA, as well as increased central nervous system irritability.<sup>30-32</sup> Since these neurotransmitters are crucial for control of depression, pain perception, and anxiety, pyridoxine deficiency may exacerbate premenstrual dysphoria, whereas adequate pyridoxine status has a favorable impact on affect.<sup>30,31</sup>

Vitamin B<sub>6</sub> is postulated to influence neurotransmitters by regulating monoamine metabolism, perhaps by altering the metabolism of tryptophan or 5-hydroxytryptophan (5-HTP), which function as indirect and direct precursors of serotonin, respectively.<sup>31,33</sup> It is further postulated that imbalances in levels of sex hormones contribute to vitamin B<sub>6</sub> deficiency. In this respect, it has been shown that women taking oral contraceptives have abnormal tryptophan metabolism, and vitamin B<sub>6</sub> has been shown to attenuate depressive symptoms in oral contraceptive users.<sup>33,34</sup>

With respect to PMS, administration of vitamin B<sub>6</sub> has yielded promising results in the management of premenstrual depression and irritability, although many studies have been poorly controlled.<sup>28,33,35-37</sup> In a study of 32 women with moderate to severe PMS, vitamin B<sub>6</sub> given at a low dose of 50 mg/day for 7 months was shown to provide a significant beneficial effect on symptoms—such as depression, irritability, and fatigue—during the premenstrual period. In fact, these symptoms were approximately halved in the treatment months when compared to the placebo months.<sup>33</sup> In support of these findings, a double-blind, cross-over study performed on 21 women with PMS receiving vitamin B<sub>6</sub> 500 mg/day for three consecutive menstrual cycles showed significant clinical benefit.<sup>35</sup> Additionally, a review of nine published trials representing 940 subjects with premenstrual syndrome indicated that vitamin B<sub>6</sub>, when given at doses up to 100 mg/day, is likely to be of benefit in the treatment of premenstrual symptoms.<sup>36</sup>

Note: High doses of vitamin B<sub>6</sub> (200 mg/day) taken for long periods of time may cause neurological symptoms that are reversible with temporary discontinuation of this vitamin. Women with PMS have experienced relief of premenstrual symptoms from taking lower dosages ranging from 50 to 100 mg/day.<sup>32,36</sup>

## Magnesium and Calcium

Magnesium is an essential cofactor in over 300 enzymatic actions and plays a role in the maintenance of cell membrane electrical potential and electrolyte balance.<sup>38</sup> A deficiency of magnesium can present with a wide variety of neuropsychological symptoms, including depression, agitation, personality changes, and memory and concentration difficulties, as well as physical complaints surrounding fluid balance.<sup>38,39</sup> It has therefore been postulated that magnesium deficiency may exacerbate certain PMS symptoms.<sup>27</sup>

Indeed, studies have demonstrated significantly lower magnesium concentrations in women with PMS than that of control groups, and magnesium administration has been shown to reduce premenstrual symptoms.<sup>27,28,38,39</sup> In a double-blind, randomized study, 32 women with PMS were given supplemental magnesium (360 mg 3 times per day) or placebo. As assessed by the Menstrual Distress Questionnaire, the subjects noted significant improvements in "negative affect" scores after 2 months.<sup>40</sup> In another study, women with mild premenstrual symptoms receiving supplemental magnesium of 200 mg/day for 2 cycles demonstrated a reduction in premenstrual symptoms, such as weight gain, swelling of extremities, breast tenderness, and abdominal bloating, compared to placebo.<sup>38</sup> Additionally, a small synergistic effect of magnesium (200 mg/day) and vitamin B<sub>6</sub> (50 mg/day) in reducing mild premenstrual anxiety-related symptoms has also been noted in a one-month double-blind study.<sup>41</sup>

Calcium deficiency has also been associated with PMS, and supplemental calcium has been associated with significant improvements in a variety of symptoms that are representative of PMS, including negative affect, water retention, food cravings, and pain.<sup>29,42,43</sup> The ratio of calcium to magnesium in ovulatory women has also been investigated.<sup>27,43</sup> In one study, serum mineral concentrations assessed throughout the menstrual cycle showed decreases in serum magnesium and increases in serum calcium during the luteal phase of the menstrual cycle, demonstrating significant increases in the calcium-to-magnesium ratio.<sup>27</sup> The researchers postulated these changes in serum mineral balance may affect synaptic transmission and other entities underlying PMS.

## HERBAL APPROACHES TO MANAGEMENT

A variety of herbal approaches have successfully been used to help manage PMS symptoms, many with a history of use dating back centuries. Recently, some of these herbal approaches have attained scientific merit that supports their traditional uses in gynecological practice, further validating their history of safety and efficacy. These natural interventions include herbs that support hormonal balance, neurotransmitter activity, fluid balance, and liver health (Table 2).

### Chasteberry

Native to the Mediterranean, chasteberry (*Vitex agnus castus*) has been used for centuries in the management of gynecological complaints. Traditionally used as a tea (containing 1 tsp of the ripe berries, the equivalent to 1.5 g to 2 g of the crude herb), the greatest use of chasteberry has been in disorders associated with hormone function such as premenstrual distress and dysmenorrhoea.<sup>44</sup> Evidence on its effectiveness has led to its approval by the German Commission E as an intervention for premenstrual complaints, cyclical breast tenderness, and menstrual cycle irregularities.<sup>45</sup> Today, chasteberry is among the most popular herbs to help relieve a broad spectrum of PMS symptoms, such as breast tenderness, weight gain, abdominal cramps, depression, and mood swings.

Human studies support the noted efficacy of chasteberry in reducing the severity of premenstrual symptoms. In a double-blind, placebo-controlled study, 170 women diagnosed with PMS taking 20 mg/day of a chasteberry fruit 6-12:1 extract reported significant improvements in overall premenstrual symptoms compared to the placebo group after 3 consecutive

cycles.<sup>46</sup> The responder rates were 52% and 24% for active and placebo, respectively. In another double-blind study, women with cyclical breast pain given chasteberry (30 drops twice per day) reported a significant reduction in pain compared to the placebo group after 3 months.<sup>47</sup> Further support of the efficacy of chasteberry (20 mg/day) was demonstrated in two other human studies, in which women with premenstrual complaints reported considerable symptomatic relief. Overall, chasteberry has been shown to be well tolerated.<sup>48,49</sup>

Although the mode of action of chasteberry is not completely understood, various mechanisms related to the menstrual cycle have been demonstrated. Chasteberry has been shown to be a dopamine agonist, possessing the ability to decrease prolactin via binding at pituitary dopamine-D2 receptors.<sup>47-50</sup> Elevated prolactin levels are thought to be associated with PMS and may play a role in complaints of cyclical breast tenderness.<sup>47,50</sup> Chasteberry also appears to contain constituents that influence mood by acting via opioid receptors or the GABA-system. Regardless of its mode of action, chasteberry's clinical efficacy and tolerability is well documented.<sup>44-50</sup>

### Serotonergic Herbs

**St. John's Wort**—St. John's wort (*Hypericum perforatum*) has been popularly used for decades in the management of mild to moderate depression, and recently has been a topic of scientific investigation. Many clinical trials have demonstrated the efficacy of St. John's wort in reducing depressive symptoms versus placebo and in comparison with some conventional approaches.<sup>51-57</sup> With its extensive history, St. John's wort has been approved by the German Commission E health authorities for the management of depressive moods, anxiety, and nervous unrest.<sup>45</sup> In a recent pilot study, St. John's wort was also shown to be effective in women with PMS. In this study, 19 women with PMS given St. John's wort extract (300 mg/day) for 2 menstrual cycles reported significant improvements in overall symptoms. The greatest reductions in symptoms included depression, confusion, anxiety, and insomnia.<sup>58</sup>

The natural antidepressive actions of St. John's wort seem to be multifactorial. It appears to inhibit serotonin, norepinephrine, and dopamine reuptake by postsynaptic receptors; increase the density of serotonin and dopamine receptors; elevate the affinity for GABA receptors; and inhibit monoamine concentrations in the synaptic cleft (resembling some conventional approaches to management).<sup>59-61</sup>

Although St. John's wort is generally considered a benign, well-tolerated herb, there is accumulating evidence of possible interactions between certain medications. St. John's wort has been shown to induce a specific cytochrome P-450 liver enzyme system (3A4), which may result in altered levels of medications that are metabolized via this pathway. Medications that are influenced by St. John's wort can be found in the literature, and patients taking these medications should therefore avoid using St. John's wort.<sup>62</sup>

**5-Hydroxytryptophan (5-HTP)**—Derived from the seed of the African plant *Griffonia simplicifolia*, 5-HTP is well known for its serotonergic properties and has over 20 years of clinical use in managing mild to moderate depression.<sup>63</sup> Due to its role in serotonin synthesis, it has also been evaluated in patients experiencing insomnia and food cravings.<sup>64-66</sup> Studies conducted during the late 1970s to the present suggest that oral administration of 50 to 300 mg/day of 5-HTP is effective and well tolerated.<sup>63-67</sup>

Levels of brain serotonin are dependent on the available levels of L-tryptophan and 5-HTP. 5-HTP is the intermediate metabolite in tryptophan metabolism, and therefore bypasses the conversion of the essential amino acid L-tryptophan into 5-HTP. Because it does not require a transport molecule in intestinal absorption, 5-HTP is unaffected by the presence of other amino acids; therefore, it can be taken with meals without hindering its effectiveness. 5-HTP also readily passes the blood-brain barrier, unlike

L-tryptophan. As the immediate precursor of serotonin, 5-HTP is considered highly effective in increasing the production of serotonin, a neurotransmitter that has been implicated in the regulation of depression, anxiety, and appetite.<sup>63,67</sup>

### Ayurvedic Medicine

The Indian traditional system of medicine known as Ayurveda requires identifying certain patterns of symptoms, characteristics, and history to determine diagnosis and treatment. Women who regularly experience cyclical disorders often demonstrate similar patterns and thus are commonly treated with the tonifying herbs shatavari (*Asparagus racemosus*) and ashwagandha (*Withania somnifera*).

Shatavari is possibly the most widely used herb in maintaining women's health. Known to have rejuvenating, anti-inflammatory, and diuretic properties, it is indicated in PMS symptoms such as menstrual cramps and excessive menstrual bleeding.<sup>68</sup> Among its many properties, ashwagandha (commonly known as Indian ginseng) is used as a general tonic, nutritive, nerve, sedative, and diuretic.<sup>68</sup> The clinical use of ashwagandha in Ayurveda has been demonstrated in animal research, wherein it has been shown to have anti-stressor and adaptogenic activities, possibly through acting via the GABA<sub>A</sub> receptor system.<sup>69-71</sup>

### Traditional Chinese Medicine (TCM)

Ancient Chinese medicine has a fully developed botanical system for managing gynecological problems including PMS, irregular menses, uterine blood weakness, and fibrocystic breasts.<sup>72,73</sup> Interestingly, one of the most commonly used TCM formulas known as *Xiao Yao San*—employing the roots of bupleurum (*Bupleurum chinense*), peony (*Paeonia lactiflora*), dong quai (*Angelica sinensis*), bai-zhu atractylodes (*Atractylodes macrocephala*), poria sclerotium (*Poria cocos*), ginger rhizome (*Zingiber officinale*), licorice (*Glycyrrhiza uralensis*), and mint leaf (*Mentha haplocalyx*)—focuses on liver function and strengthening the blood.<sup>72</sup> The traditional Chinese strategy behind this formula is to “release constrained liver ch'i,” and correct “blood deficiency.” This parallels what may be the role of enterohepatic circulation in the management of estrogen.

Modern science supports the use of *Xiao Yao San* in managing gynecological issues. Preliminary research conducted in China suggests *Xiao Yao San* may regulate the endocrine system, possibly through suppression of prolactin secretion and restoration of follicle-stimulating hormone activity and follicle function.<sup>74</sup> Furthermore, the hepatoprotective activities of ingredients in *Xiao Yao San* have been shown in animal research.<sup>75-79</sup> The coupling of these activities may begin to further establish the mechanisms of *Xiao Yao San*, which is also commonly used by Western practitioners in the treatment of PMS.

### DIETARY AND LIFESTYLE INFLUENCES

**Diet**—Dietary factors appear to have an important influence on PMS. Studies have shown that vegetarian women have lower serum estrogen levels when compared to omnivorous women.<sup>80</sup> Studies also have demonstrated that vegetarians consume less total fat and more fiber than omnivores, which suggests that dietary fiber and decreased fat intakes may be significant contributors to lower serum estrogen levels in women. Other researchers have found an association between a lowfat vegetarian diet and an increase in sex-hormone binding globulin concentration, a reduction in body weight, and a decrease in premenstrual symptoms such as water retention and behavioral changes.<sup>81</sup> In these studies, it appears that PMS symptom reduction may be mediated by dietary influences on estrogen activity.

Research has also shown that intake of carbohydrates, a common food craving in women with PMS, increases serum tryptophan in relation to other amino acids, which is associated with increased brain tryptophan levels and serotonin synthesis.<sup>82</sup> To test the hypothesis that carbohydrate intake may attenuate premenstrual psychological symptoms associated with serotonin deficiency, researchers conducted a study in women with PMS. Subjects who consumed a specially formulated, carbohydrate-rich beverage during the luteal phase of their menstrual cycle, when premenstrual symptoms had significantly worsened, reported significant decreases in depression, anger, confusion, and carbohydrate craving. In addition, subjects also demonstrated significant improvements in memory word recognition scores.<sup>83</sup>

A diet that centers around maintaining healthy hormonal and neurotransmitter balance may play an important part in an intervention program for PMS. Consuming small meals throughout the day providing balanced ratios of fiber-rich complex carbohydrates, proteins, and small amounts of healthy fats is recommended. Complex carbohydrates rich in fiber include vegetables, fruits, whole grains, and legumes. Health-promoting fats include fish, flax, pumpkin, walnuts, sesame, sunflower, and almonds. The avoidance of polyunsaturated vegetable oils, refined sugar, refined carbohydrates, alcohol, and caffeine-containing foods and beverages may also help in controlling PMS symptoms. It is further recommended to limit intake of dairy products and animal fats. Women suffering from edema should also avoid salt to reduce fluid retention. Contrary to popular belief, increased water consumption flushes the body out and actually reduces fluid retention.<sup>3,4</sup>

**Body Composition**—Altered body composition, due to increased fat deposition and/or decreased muscle mass leading to an unhealthy fat-to-lean body mass, has been associated with PMS symptomatology. The results of one study showed that women with a Body Mass Index (BMI) greater than 27.0 (indicating altered body composition) were 1.9 times more likely to experience PMS than women with lower BMIs. Due to the

fact that circulating androgens are metabolized into active estrogens, it has been suggested that an altered body composition influences the amount of estrogen, and thereby, the balance of estrogen to progesterone.<sup>84</sup> (For detailed information on the role of body composition in women's health, please refer to the Applied Nutritional Science Report entitled *Body Composition and Optimal Health* by Robert H. Lerman, MD.)

**Stress**—The role of chronic stress in PMS has also been evaluated.<sup>84</sup> Interviews designed to assess menstrual distress completed by 874 women between the ages 18 and 44 years suggested that women with stressful lifestyles are more likely to suffer from PMS.<sup>84</sup> A possible mechanism for this outcome may be that during a stress response, the body secretes a range of hormones—such as aldosterone and the catecholamines epinephrine and norepinephrine—that interact with the sex hormones.<sup>85,86</sup>

An important part of stress reduction is regular aerobic exercise, which helps to improve circulatory health and regulate neurotransmitter levels that are important to a positive mood. Regular exercise has been reliably associated with reduced incidence of menstrual pain, water retention, negative affect, and behavior change.<sup>87,88</sup> (For more information on nutritional support for individuals under increased stress, please refer to the Applied Nutritional Science Report entitled *Nutritional Management of Stress-Induced Dysfunction* by Richard L. Shames, MD.)

## CONCLUSION

The multifactorial and complex nature of PMS has led to a variety of management approaches. A natural intervention program for PMS should begin with correcting possible nutrient deficiencies that can exacerbate symptoms. Select, time-tested herbal remedies that have also obtained scientific merit can support underlying mechanisms associated with the menstrual cycle—such as hormonal balance, neurotransmitter activity, kidney function, and liver health—and therefore may provide clinically relevant benefits in women with PMS.

**Table 2. Selected Herbs for the Management of PMS**

Common Name (Botanical Name)	Country of Origin	Traditional Use	Some Active Constituents
Chaste Tree Berry ( <i>Vitex agnus castus</i> )	Mediterranean	Control and regulation of female reproductive system	Monoterpene: agnuside, eucubane, aucubin; flavonoid: vitexin
St. John's Wort Bud and Flowering Top ( <i>Hypericum perforatum</i> )	United States, Europe	Antidepressant, anti-anxiety, antiviral	Hypericin, hyperforin
Griffonia Seed ( <i>Griffonia simplicifolia</i> )	Africa	Antidepressant, anti-anxiety, regulates appetite and sleep	5-HTP
Shatavari Root ( <i>Asparagus racemosus</i> )	India	Nutritive, tonic, anti-inflammatory, antispasmodic, diuretic	Saponins
Ashwagandha Root ( <i>Withania somnifera</i> )	India	Tonic, nutritive, nervine, sedative, diuretic	Withanolides
Licorice Root ( <i>Glycyrrhiza uralensis</i> )	China, North America, Europe	Demulcent, expectorant, anti-inflammatory, spasmolytic	Triterpene saponin: glycyrrhizin; flavonoids: liquiritin, quercetin
Bupleurum Root ( <i>Bupleurum chinense</i> )	China	Sedative, anodyne, adaptogen	Saikosaponins A, B1-B4, C-F
Dong Quai Root ( <i>Angelica sinensis</i> )	China	Antianemic, regulates menses, smooth muscle relaxant	Vitamin B <sub>12</sub> , ferulic acid, ligustilide, folic acid, choline, iron
Peony Root ( <i>Paeonia lactiflora</i> )	China	Antimicrobial, astringent, anti-inflammatory	Monoterpene glycosides: paeoniflorin, benzoylpaeoniflorin; sterols
Ginger Rhizome ( <i>Zingiber officinale</i> )	China, Pacific Rim, India	Stimulant, carminative, digestant, anti-inflammatory	Terpenoid: zingiberene; gingerols

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# Natural Interventions for Premenstrual Syndrome: A Summary

BY JOSEPH L. MAYO, MD, FACOG

Premenstrual syndrome (PMS) is a common disorder in women of reproductive age that is characterized by recurring physical and psychological symptoms. The symptoms generally begin in the week or two weeks before menstruation and resolve shortly after menstruation begins. A diagnosis of PMS requires that symptoms are severe enough to negatively impact a woman's ability to function at home, in the workplace, or in personal relationships.

As many as 85% of menstruating women experience one or more symptoms of PMS, and approximately 5% to 10% have symptoms severe enough to be debilitating.<sup>1</sup> More than 300 symptoms have been associated with PMS; these include irritability, tension, fluid retention, and a general unwell feeling.<sup>2-5</sup>

## THE CAUSE OF PMS

The exact cause of PMS is not fully understood and may be related to a number of factors. The current theories on the underlying causes focus mostly on levels of sex hormones (e.g., estrogen, progesterone) and neurotransmitters (i.e., brain chemicals that control mood), as well as regulation of fluid balance by the kidneys and hormone balance by the liver.<sup>2</sup>

## NUTRITIONAL STRATEGIES FOR INTERVENTION

The multifactorial nature of PMS has resulted in a variety of natural interventions, from addressing possible nutrient deficiencies to focusing on hormone or neurotransmitter support with select herbal approaches.<sup>2</sup> Successful management of PMS should begin with correcting possible nutrient deficiencies that can exacerbate symptoms. Select, time-tested herbal approaches that have also been scientifically studied can be used to address a variety of PMS symptoms.

**Multivitamin/Mineral**—Scientific studies suggest a role of nutritional deficiencies in PMS symptoms, suggesting that reversing any possible nutrient deficiencies should be the first step in PMS management.<sup>27-29</sup> This is of particular importance due to the fact that women with PMS have been reported to consume more refined sugar, refined carbohydrates, and dairy products that may lack adequate quantities of vitamins and minerals.<sup>28,30</sup>

**Vitamin B<sub>6</sub>**—Vitamin B<sub>6</sub> (pyridoxine) has been studied as a possible intervention for PMS for over two decades. A deficiency of vitamin B<sub>6</sub> has been associated with decreased levels of neurotransmitters that control depression and anxiety, suggesting that adequate vitamin B<sub>6</sub> status may have a positive effect on mood.<sup>30-32</sup> This may explain how supplementation of vitamin B<sub>6</sub> has been shown to favorably impact symptoms such as depression, irritability, and fatigue during the premenstrual period.<sup>28,33,35-37</sup>

**Magnesium and Calcium**—Women with PMS have been shown to have significantly lower magnesium levels than women without PMS symptoms, and magnesium supplementation has been shown to reduce premenstrual complaints.<sup>28,38-40</sup> Similarly, calcium deficiency has also been associated with PMS, whereas supplemental calcium has been associated with significant improvements in symptoms that are representative of PMS, including negative mood, water retention, food cravings, and pain.<sup>29,43,44</sup>

## HERBAL APPROACHES TO MANAGEMENT

A variety of herbal approaches have successfully been used to help manage PMS symptoms, many with a history of use dating back centuries. These natural interventions include herbs that support hormone and neurotransmitter balance, fluid balance, and liver health.

**Chasteberry**—Native to the Mediterranean, chasteberry (*Vitex agnus castus*) has been used for centuries in the management of gynecological complaints. Evidence of its effectiveness has led to its approval by the German Commission E health authorities as an intervention for premenstrual symptoms and menstrual cycle irregularities.<sup>45</sup> Today, chasteberry is among the most popular herbs used to help relieve a broad spectrum of PMS symptoms, including breast tenderness, weight gain, abdominal cramps, depression, and mood swings.

**St. John's Wort**—St. John's wort (*Hypericum perforatum*) has been popularly used for decades in the management of mild depression, and clinical trials have demonstrated its effectiveness.<sup>51-57</sup> A pilot study provided some evidence that supplementation with St. John's wort may also improve PMS symptoms, such as depression, confusion, anxiety, and insomnia.<sup>58</sup>

**5-HTP (5-Hydroxytryptophan)**—Derived from the seed of the African plant *Griffonia simplicifolia*, 5-HTP has over 20 years of clinical use in managing mild depression, and studies suggest it is well tolerated.<sup>63-67</sup> Researchers theorize that 5-HTP enhances levels of serotonin—a neurotransmitter involved in the regulation of depression, anxiety, and appetite.<sup>63,67</sup>

**Ayurvedic Medicine**—In the Indian traditional system of medicine, known as Ayurveda, women who regularly experience menstrual disorders are commonly treated with the tonifying herbs shatavari (*Asparagus racemosus*) and ashwagandha (*Withania somnifera*). Historically, shatavari is promoted as having rejuvenative, anti-inflammatory, and diuretic properties, and is indicated in PMS symptoms such as menstrual cramps, bloating, and excessive menstrual bleeding.<sup>68</sup> Among its many properties, ashwagandha is used as a general tonic, sedative, and diuretic.<sup>68</sup>

**Traditional Chinese Medicine (TCM)**—Ancient Chinese medicine has a fully developed botanical system for managing gynecological problems, including PMS, irregular menses, and fibrocystic breasts.<sup>72,73</sup> One of the most commonly used TCM formulas, known as *Xiāo Yào Sān*—incorporating the roots of bupleurum (*Bupleurum chinense*), peony (*Paeonia lactiflora*), dong quai (*Angelica sinensis*), bai-zhu atractylodes (*Atractylodes macrocephala*), poria sclerotium (*Poria cocos*), ginger rhizome (*Zingiber officinale*), licorice (*Glycyrrhiza uralensis*), and mint leaf (*Mentha haplocalyx*)—focuses on liver function and strengthening the blood.<sup>72</sup> Modern science also supports the use of *Xiāo Yào Sān* in managing gynecological issues, possibly through its influence on liver health and hormone activity.<sup>74-79</sup>

## CONCLUSION

The multifactorial nature of PMS has led to a variety of management approaches. A natural intervention program for PMS should begin with correcting possible nutrient deficiencies that can exacerbate symptoms. Select, time-tested herbal remedies that have also been scientifically studied can support underlying mechanisms associated with the menstrual cycle—such as hormone and neurotransmitter balance, kidney function, and liver health—and therefore may provide clinically relevant benefits in women with PMS.