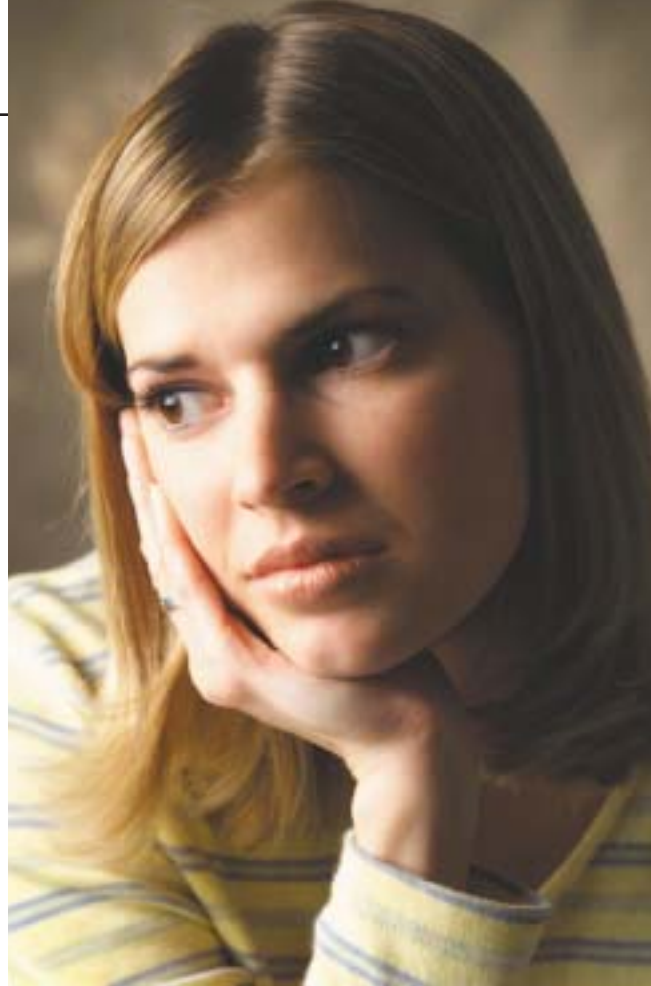




Improving Treatment for Premenstrual Syndrome



By François Lajoie, MD, FSOGC, FACOG,
CSPQ; and Sophie Desindes, MD, LMCC,
FRCPC, CSPQ

Premenstrual syndrome (PMS) consists of a myriad of physical and psychological symptoms, the only common point being the onset of menstruation. While most women experience physical, emotional or behavioral symptoms before menstruating, a minority experience symptoms so severe that their quality of life is significantly affected.

R.T. Frank described this clinical phenomenon first in 1931, when he used the term premenstrual tension.¹ Over the past few decades, countless publications have appeared on the prevalence, etiology and treatment of the disorder. PMS morbidity seems to be increasingly recognized by not only the medical community, but also by the legal profession. Nonetheless, PMS remains one of the greatest challenges in gynecology, given the vast spectrum of symptoms it encompasses, many of which are psychological. The first problem clinicians face is identifying and diagnosing PMS, which is sometimes mistaken for normal psychopathology or normal symptomatology.² The second problem concerns treatment and case management because the pathophysiology of PMS is not clearly understood.

What is PMS?

PMS is defined as the cyclical recurrence of physical, psychological or behavioral symptoms that appear after ovulation and disappear a few days after the end of the menstrual cycle. More than 150 different symptoms attributed to PMS can affect how women function in the workplace, in interpersonal relations and in day-to-day life.³

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PMS differs from premenstrual dysphoric disorder (PMDD) which, as described in the Diagnostic and Statistical Manual (DSM)-IV, has a much narrower definition.⁴ To meet the criteria for PMDD, the individual must have experienced one of four primary symptoms—irritability, dysphoria, tension or affective lability—and at least five of the eleven symptoms listed in Table 1. The DSM-IV also emphasizes the cyclical nature of the symptoms (as is the case with PMS), which peak in the last week of the luteal phase, but are absent in the follicular phase.⁵ Most women do not meet the DSM criteria. They do, however, meet the criteria for PMS outlined in the International statistical classification (ISC) of Disease and Related Health Problems, which include psychological discomfort associated with various nonspecific symptoms, such as bloating, increased breast tenderness, peripheral edema, nonspecific pain, difficulty concentrating, trouble sleeping and changes in appetite.²⁻³⁴

What is the Etiology?

The physiopathology of PMS remains an enigma, despite several decades of research. Various factors have been hypothesized, but none has been clearly proven or can explain all of the symptoms reported. An inadequate understanding of the physiopathology of the syndrome often has generated hypotheses that attribute the cause to affective disorders, personality disorders or stress. Such hypotheses, however, are steadily losing popularity. Stress is attributed as a precipitating factor in only 6% to 10% of the cases studied.⁹

Even before Frank's formal description of the disorder, PMS was considered a hormonal disorder. The presence of ovulatory cycles in women suffering from PMS has given rise to a number of hypothe-

ses involving estrogen and progesterone. These hypotheses, which suggest a progesterone deficiency, hypoestrogenism and an ovarian steroid imbalance, were popular for many years, but no difference has been demonstrated in the corresponding plasma levels in subjects with PMS and those in control groups. Moreover, normal ovarian functions seem to be a prerequisite for developing PMS,² and anovulation—whether spontaneous or induced by gonadotropin releasing hormone (GnRH) agonists—causes remission of PMS symptoms. A recurrence of PMS

Summary

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- Diagnosis of PMS is strictly clinical. It requires a rigorous questionnaire and attentive listening skills on the part of the clinician.
- The therapeutic means initially should be non-pharmacological, however, resorting to medication may prove necessary in some situations. There is no standard treatment for all patients.



Dr. Lajoie is associate professor, department of obstetrics and gynecology, and director of the Gynecology/ Obstetrics Residency Program, Université de Sherbrooke, Quebec. Dr. Lajoie is a gynecologist with special interest in urogynecology and pelvic floor surgery.



Dr. Desindes is staff, department of obstetrics and gynecology, Université de Sherbrooke, Quebec. Dr. Desindes is currently doing a fellowship on menopause in Boston.

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Table 1

Research Criteria for Premenstrual Dysphoric Disorder

A. In most menstrual cycles during the past year, five (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week postmenses, with at least one of the symptoms being either (1), (2), (3), or (4):

- (1) Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts.
- (2) Marked anxiety, tension, feeling of being "keyed up," or "on-edge."
- (3) Marked affective lability (*e.g.*, feeling suddenly sad or tearful or an increased sensitivity to rejection.)
- (4) Persistent and marked anger or irritability or increased interpersonal conflicts.
- (5) Decreased interest in usual activities (*e.g.*, work, school, friends, hobbies).
- (6) Subjective sense of difficulty in concentrating.
- (7) Lethargy, easy fatigability, or marked lack of energy.
- (8) Marked change in appetite, overeating, or specific food cravings.
- (9) Hypersomnia or insomnia.
- (10) A subjective sense of being overwhelmed or out of control.
- (11) Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating," weight gain.

B. The disturbance markedly interferes with work or school or with usual social activities and relationships with others (*e.g.*, avoidance of social activities, decreased productivity and efficiency at work or school)

C. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder (although it may be superimposed on any of these disorders).

D. Criteria A, B and C must be confirmed by prospective daily ratings during at least two consecutive symptomatic cycles. (The diagnosis may be made provisionally prior to this confirmation).

Adapted from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, ed 4th. Washington, DC, American Psychiatric Association, 1994.

can be noted in postmenopausal patients undergoing hormone replacement therapy (HRT) combined with cyclical progesterone. There is a consensus with regard to the absence of peripheral markers of hypothalamic-pituitary-gonadal disorder in PMS.¹⁰

Certain progesterone metabolites (*i.e.*, allopregnanolone and pregnanolone) interact with the central nervous system (CNS) *via* the gamma aminobutyric acid (GABA) neurotransmitter and are qualified as neurosteroids. These substances seem to have an anxiolytic effect and help patients cope with stress. The hypothesis of reduced sensitivity of the CNS to these substances is interesting, yet it remains to be proven.^{11,12}

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Table 2

Most Common PMS Symptoms

Behavioral Symptoms		Physical Symptoms	
Mood lability, anger, sadness	81%	Acne	71%
Hypersensitivity	69%	Changes in appetite	70%
Crying	65%	Gastrointestinal discomfort	48%
Tendency towards isolation	65%	Hot flashes	18%
Memory loss	56%	Dizziness	13%
Trouble concentrating	47%	Palpitations	13%

Various other hypotheses have been put forth over the years, but none has been clearly substantiated. They involve nutritional factors, such as vitamin B₆, calcium and magnesium deficiencies, as well as subclinical hypoglycemia. A prostaglandin imbalance also has been suspected, but is unproven, along with various other theories suggesting excessive secretion or activity of aldosterone, cortisol or prolactin, a lack of endogenous endorphins, and abnormal secretion of thyrotropin-releasing hormone (TRH) and melatonin.³ A predisposing genetic factor probably exists, given the equal prevalence of PMS in identical twins.⁸

It is well established that neurotransmitters are linked to psychiatric disorders. Certain neurotransmitters probably are involved in the physiopathology of PMS, as well. Various studies demonstrate the presence of an alteration in the functioning of the serotonergic system in patients suffering from premenstrual symptoms. PMS sufferers likely have a certain neurobiological vulnerability that makes them more susceptible to events in the luteal phase because of the ovarian steroids that come into play.^{3,13}

Certain clinical data suggest anomalies in the GABA and noradrenergic systems. These anomalies are present in the pathogenesis of anxiety problems and mood disorders.^{11,14}

The physiopathology of PMS seems multifactorial, primarily involving ovarian steroids, neurosteroids and neurotransmitters (*i.e.*, serotonin).

What is the Diagnosis?

Diagnosis of PMS is strictly clinical. It requires a rigorous questionnaire and attentive listening skills on the part of the clinician. More than 150 symptoms are attributed to PMS, but one group of symptoms—both physical and psychological—tends to occur more frequently (Table 2).¹⁵

The most important criterion in evaluating PMS is the cyclical nature of the symptoms. The occurrence and severity of symptoms in the luteal phase, as well as their psychosocial consequences, merit particular attention.

As many as 75% of women who consult a physician for PMS have an underlying medical or psychiatric disorder (Table 3),¹⁶ and certain pathologies may be exacerbated during the premenstrual

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phase. It is important, therefore, to rule out other physical, psychiatric and drug-related pathologies that may explain the symptomatology. A detailed review of a patient's medical and psychiatric history, as well as a physical examination, are strongly recommended.

There is no specific diagnostic test for PMS; however, testing serum TSH and hemoglobin levels can be useful for making a differential diagnosis. The psychiatric pathologies most often encountered in such patients are mood swings, anxiety, eating disorders, personality disorders and drug dependency. From medical and gynecological standpoints, the pathologies to be ruled out are anemia, hypothyroidism, hypoglycemia, auto-immune disorders, pregnancy, postpartum status, perimenopause, endometriosis, menstrual irregularity and polycystic ovary syndrome (PCOS).³

Having the patient keep a daily prospective journal of symptoms for at least two to three menstrual cycles is the best way to confirm the diagnosis, and it provides a means of assessing the severity of the syndrome. There are standardized instruments available for quantifying and qualifying the symptoms.³ The "Prospective Record of the Impact and Severity of Menstruation" (PRISM) calendar¹⁷ and the "Calendar of Premenstrual Experience" (COPE)¹⁸ are both excellent tools. They enable patients to note their symptoms, day-to-day events, and any medications used on each day in their cycle. Using the PRISM calendar, a score can be calculated and used to determine whether a patient's symptoms constitute PMS or not. The total score is calculated from days three to nine of the cycle (*i.e.*, follicular phase) and during the last seven days (*i.e.*, luteal phase). If the total score in the luteal phase is double that in the follicular phase, a positive diagnosis of PMS can be made. Alternatively, a score over 42 in the luteal phase, but under 40 in the follicular phase, would also constitute a positive diagnosis. If the total score in the follicular phase is over 40, however, PMS can be ruled out.¹⁷

How is PMS Treated?

The multiple physiopathological hypotheses explain the numerous therapeutic possibilities described in the literature. They cover a broad spectrum of potential therapies, ranging from patient education, vitamin supplements and antidepressants to hysterectomy with bilateral salpingo-oophorectomy. Several randomized controlled studies have been carried out over the past few years with an adequate methodology, and have provided indispensable leads to appropriate treatment options. In light of the overwhelming placebo effect (30% to 50% in most studies), only the comparative trials have any real merit. Treatment objectives should be to improve symptoms significantly and social and professional functioning, as well as optimize the overall health of women.¹⁹ The therapeutic means should initially be non-pharmacological, however, resorting to medication may prove necessary in some situations. There

Table 3

Other Pathologies

Pathology	Frequency
• Symptoms throughout the cycle	20.5%
• Affective or personality disorders	11.0%
• Use of oral contraceptives	10.6%
• Menopausal symptoms	10.2%
• Diabetes or hypothyroidism	8.4%
• Eating disorders	5.3%
• Drug or alcohol use	3.8%

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is no standard treatment for all patients. Therapies should be selected according to the symptoms and their severity, taking into account the possible side effects. A judicious combination of various therapeutic measures is often required.

For mild to moderate PMS, most authors recommend that initial treatment be non-pharmacological, with the possibility of an adjunct of vitamin and mineral supplements. For severe symptoms, however, initial treatment should consist not only of non-pharmacological measures, but also appropriate medication. No medication has yet been approved by the US Food and Drug Administration (FDA) as a specific treatment for PMS or PMDD.²⁰

What is the Non-pharmacological approach?

Patient education plays a central role in the treatment of PMS. It is essential to be empathetic and open to discussion, and to clearly explain PMS. A change in diet is often suggested, though this approach is still being studied. It would seem, however, that reducing caffeine, chocolate, alcohol and salt intake, especially in the luteal phase, alleviates symptoms. Certain authors recommend a high-protein diet that is low in refined sugars during the second phase of the menstrual cycle. Complex carbohydrates may increase serotonin activity. Smoking cessation also should be encouraged.

It is clearly established that physical activity, particularly aerobic exercise, increases the serum endorphin level, which seems to improve a patient's mood. A number of minor studies have demonstrated a significant reduction in mood related PMS symptoms in patients who exercise regularly.²¹

Stress levels also seem to have an impact on PMS. Various measures intended to reduce or help manage stress have been studied. Research results suggest that exercise as an adjunct therapy can yield certain benefits. Cognitive and behavioral relaxation and stress-management therapies are also worth considering for certain patients.¹⁹

What is the pharmacological approach?

Vitamin and mineral supplements. Some clinical studies have shown that calcium and magnesium can reduce certain symptoms (both emotional and physical) to some degree.

A recent randomized multicentre study demonstrated a 48% reduction of symptoms in women who take a calcium supplement, as opposed to only 30% for the control group. Given its effectiveness, relative innocuity, and accessibility, a calcium supplement should be suggested for all patients at a dosage of between 1,200 mg and 1,600 mg elementary calcium per day during the luteal phase. The dosage should be lower for women whose diets are rich in dairy products, so as not to exceed the maximum intake of 2,500 mg per day.²² Magnesium supplements in the luteal phase also seem beneficial, though further studies still are required.

The pathophysiological hypothesis of micronutrient deficiencies has led to the development of a high-dose multivitamin. This vitamin supplement, which contains vitamins A and D₃, folic acid, choline and magnesium, seems to reduce PMS symptoms with a dosage of six to 12 tablets per

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day in the luteal phase. The mechanism of action of this vitamin/mineral combination is unclear. The beneficial effect could be due primarily to the magnesium.²¹

Pyridoxine (vitamin B₆) is the micronutrient most often used in the treatment of PMS. The doses used in the multiple studies that have been carried out range from 50 mg to 600 mg per day, largely exceeding the estimated daily requirement of 2 mg per day. It has been clearly established that the chronic ingestion of more than 100 mg to 200 mg per day of pyridoxine can result in peripheral neuropathy. Systematic reviews of the various studies reveal no clear evidence for recommending the use of vitamin B₆ in the treatment of PMS.^{23,24}

Evening primrose oil, which contains a high concentration of gamma-linoleic acid (an essential component in synthesis of prostaglandins), has long been used, especially in England. Its efficacy, however, seems dubious. Vitamin E also seems to be somewhat effective.²¹

Hormone treatments. From 1950 to 1980, the most popular physiopathological theory was that PMS was due to progesterone deficiency. Micronized progesterone, therefore, was used in the luteal phase, first administered vaginally and then orally. Recent studies, however, have not successfully demonstrated the superiority of this treatment over a placebo.

The effect of oral contraceptives (OCs) on PMS symptoms is highly variable and controversial. Certain patients report a slight improvement of physical symptoms, whereas others mention a worsening of their symptoms. Moreover, women suffering from PMS seem to have significantly more side effects from OCs than the general population. OCs may be used, but the results are often very disappointing.

Medroxyprogesterone acetate (MPS) at a daily dosage of 15 mg to 30 mg suppresses ovulation and seems to reduce premenstrual symptoms significantly. A higher dosage of 30 mg per day is more effective in suppressing ovulation and causes less spotting. MPS administered intramuscularly seems promising. Estradiol, administered transdermally or in the form of an implant significantly reduces symptoms. The dosage used, however, (*i.e.*, 0.1 mg to 0.2 mg day) creates a significant risk of endometrial hyperplasia, which necessitates an adjunct of progestogen. This, in turn, seems to diminish the efficacy of the treatment.

Studies on the use of danazol at doses ranging from 200 mg to 600 mg per day have demonstrated an impressive reduction in PMS symptoms, however, major side effects cause serious problems of compliance. The usefulness of this regimen is, therefore, very limited. Furthermore, the suppressive effect of danazol on high-density lipoproteins (HDLs) creates an unacceptable risk of cardiovascular problems, thus ruling out its chronic use.

GnRH agonists induce a hypoestrogenic state analogous to menopause and are the most effective agents in the treatment of PMS. This premature hypoestrogenic state can result, nevertheless, in vasculomotor side effects and a premature loss of bone density. The use of HRT with estrogen and a cyclical progestogen, therefore, is essential. The astronomical cost of this treatment is a major obstacle. For patients who do not respond to this treatment, a bilateral oophorectomy would be a pertinent consideration. A therapeutic trial with a GnRH agonist also could prove useful in confirming the diagnosis of PMS and should be carried out on all patients requiring surgical treatment.^{21,25}

Non-hormone therapy. Selective serotonin reuptake inhibitors (SSRIs) are the most effective psychotropes for treating PMS. A number of recent studies using adequate methodology have reported a

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significant reduction of PMS symptoms with the use of an SSRI. The agent most extensively studied and used is fluoxetine, with an efficacy rate of 42% to 65%, depending on the study. A recent multicenter study reported a significant improvement in symptoms as compared with a placebo. A dosage of 20 mg to 60 mg per day was used with a similar efficacy rate, however, a more significant problem of compliance arose with higher doses.²⁶ It is recommended that treatment be initiated at lower doses (*e.g.*, 5 mg to 10 mg per day) and that the dosage be increased gradually every two to three months. A therapeutic response is obtained with 20 mg in most patients. When used in treating PMS, fluoxetine is effective almost immediately, contrary to how it acts in the treatment of affective disorders. Patients often complain less of symptoms in the first month of use. Currently, daily use of fluoxetine throughout the menstrual cycle is recommended, however, some minor studies indicate similar efficacy rates with intermittent use.^{27,28} The use of SSRIs only in the luteal phase would be an excellent means of reducing side effects and, thus, increasing compliance. Side effects depend on the dosage and seem to lessen with time, with the exception of a decrease in libido, which occurs only with chronic use. The therapeutic effects remain stable, however, even after several months of use. PMS symptoms recur as soon as the medication is discontinued. Long-term use, therefore, is necessary, although it is often difficult for patients to accept.^{28,29}

A recent multicentre study comparing sertraline (another member of the SSRI family) at doses of 50 mg to 150 mg per day (average dose of 80 mg) with a placebo, reported a 65% improvement in symptoms, as compared to 34% with the placebo alone.³⁰

Paroxetine at doses of 10 mg to 30 mg is another promising agent, but is still under study. Certain other serotonergic agents, such as clomipramine (25 mg to 75 mg per day), nefazodone and venlafaxine currently are being studied, and the preliminary results bode well.^{21,31,32}

Alprazolam, an anxiolytic drug with antidepressive properties, seems to cause a moderate reduction in premenstrual symptoms at doses of 0.25 mg three times a day (*tid*) during the luteal phase. Buspirone has also been studied, but the results are inconclusive. The use of anxiolytics should be limited in light of their doubtful efficacy and considerable side effects, particularly their sedative effect and the potential for alprazolam dependency.²¹

Diuretics, nonsteroid anti-inflammatories (NSAIDs) (mefenamic acid or naproxen) and bromocriptine affect a specific symptom or group of symptoms rather than the syndrome in general and can prove useful in well-circumscribed situations. Spironolactone, an aldosterone inhibitor, is the only diuretic that can benefit women suffering from PMS. It seems particularly effective in alleviating symptoms of bloating and peripheral edema.

Conclusion

Despite a physiopathology that still seems nebulous, effective case management of patients suffering from PMS is now possible, but it depends on an accurate diagnosis. An individualized treatment plan, which initially favors non-pharmacological measures, should then be suggested. In severe cases or for patients who do not respond to primary measures, an SSRI would seem to be the most effective second-line treatment. [CME](#)

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