

Premenstrual Syndrome

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Premenstrual syndrome, a common cyclic disorder of young and middle-aged women, is characterized by emotional and physical symptoms that consistently occur during the luteal phase of the menstrual cycle. Women with more severe affective symptoms are classified as having premenstrual dysphoric disorder. Although the etiology of these disorders remains uncertain, research suggests that altered regulation of neurohormones and neurotransmitters is involved. Premenstrual syndrome and premenstrual dysphoric disorder are diagnoses of exclusion; therefore, alternative explanations for symptoms must be considered before either diagnosis is made. The disorders can manifest with a wide variety of symptoms, including depression, mood lability, abdominal pain, breast tenderness, headache, and fatigue. Women with mild symptoms should be instructed about lifestyle changes, including healthy diet, sodium and caffeine restriction, exercise, and stress reduction. Supportive strategies, such as use of a symptom diary, may be helpful in diagnosing and managing the disorders. In women with moderate symptoms, treatment includes both medication and lifestyle modifications. Dietary supplements, such as calcium and evening primrose oil, may offer modest benefit. Selective serotonin reuptake inhibitors such as fluoxetine and sertraline are the most effective pharmacologic agents. Prostaglandin inhibitors and diuretics may provide some relief of symptoms. Only weak evidence supports the effectiveness of gonadotropin-releasing hormone agonists, androgenic agents, estrogen, progesterone, or other psychotropics, and side effects limit their use. (Am Fam Physician 2003;67:1743-52. Copyright© 2003 American Academy of Family Physicians.)

See page 1649 for definitions of strength-of-evidence levels.

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Premenstrual syndrome (PMS) affects millions of women during their reproductive years. The disorder is characterized by the cyclic recurrence of symptoms during the luteal phase of the menstrual cycle (Table 1).¹⁻³ Symptoms typically begin between the ages of 25 and 35 years. Women who have severe affective symptoms may also meet criteria for premenstrual dysphoric dis-

order (PMDD). In both PMS and PMDD, symptoms diminish rapidly with the onset of menses.

Up to 85 percent of menstruating women report having one or more premenstrual symptoms, and 2 to 10 percent report disabling, incapacitating symptoms.^{4,5} More than 200 symptoms have been associated with PMS, but irritability, tension, and dysphoria are the most prominent and consistently described.⁵

The management of PMS is often frustrating for both patients and physicians. Clinical outcomes can be expected to improve as a result of recent consensus on diagnostic criteria for PMS and PMDD, data from improved clinical trials, and the availability of evidence-based clinical guidelines.

Etiology

The etiology of PMS remains unknown and may be complex and multifactorial. The role of ovarian hormones is unclear, but symptoms often improve when ovulation is suppressed.⁶ Changes in hormone levels may

TABLE 1
Common Symptoms of Premenstrual Syndrome

Behavioral symptoms: fatigue, insomnia, dizziness, changes in sexual interest, food cravings or overeating
Psychologic symptoms: irritability, anger, depressed mood, crying and tearfulness, anxiety, tension, mood swings, lack of concentration, confusion, forgetfulness, restlessness, loneliness, decreased self-esteem, tension
Physical symptoms: headaches, breast tenderness and swelling, back pain, abdominal pain and bloating, weight gain, swelling of extremities, water retention, nausea, muscle and joint pain

Information from references 1, 2, and 3.

TABLE 2

Diagnostic Criteria for Premenstrual Syndrome**National Institute of Mental Health**

A 30% increase in the intensity of symptoms of premenstrual syndrome (measured using a standardized instrument) from cycle days 5 to 10 as compared with the six-day interval before the onset of menses

and

Documentation of these changes in a daily symptom diary for at least two consecutive cycles

University of California at San Diego

At least one of the following affective and somatic symptoms during the five days before menses in each of the three previous cycles:

Affective symptoms: depression, angry outbursts, irritability, anxiety, confusion, social withdrawal

Somatic symptoms: breast tenderness, abdominal bloating, headache, swelling of extremities

Symptoms relieved from days 4 through 13 of the menstrual cycle

Information from references 4 and 7.

influence centrally acting neurotransmitters such as serotonin,¹ but circulating sex hormone levels are typically normal in women with PMS. Some evidence suggests that the disorder is related to enhanced sensitivity to progesterone in women with underlying serotonin deficiency.^{1,4,7} This mechanism may not explain all cases, because some patients do not respond to treatment with selective serotonin reuptake inhibitors (SSRIs).⁸ Deficiencies in prostaglandins, related to an inability to convert linoleic acid to prostaglandin precursors, may be involved in PMS.^{2,9} Genetic factors

TABLE 3

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 after menses, with at least one of the symptoms being 1, 2, 3, or 4:

1. Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
2. Marked anxiety, tension, or feelings of being "keyed up" or "on edge"
3. Marked affective lability (e.g., feeling suddenly sad or tearful or 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," or weight gain

NOTE: In menstruating females, the luteal phase corresponds with the period between ovulation and the onset of menses, and the follicular phase begins with menses. In nonmenstruating females (e.g., those who have had a hysterectomy), determining the timing of the luteal and follicular phases may require measurement of circulating reproductive hormones.

- 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 before this confirmation.)

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TABLE 4

Differential Diagnosis of Premenstrual Syndrome

Affective disorder (e.g., depression, anxiety, dysthymia, panic)	Endometriosis
Anemia	Hypothyroidism
Anorexia or bulimia	Oral contraceptive pill use
Chronic medical conditions (e.g., diabetes mellitus)	Perimenopause
Dysmenorrhea	Personality disorder
	Substance abuse disorders

Information from references 3 and 4.

also seem to play a role, as the concordance rate is two times higher in monozygotic twins than in dizygotic twins.¹⁰

Diagnosis

The American College of Obstetrics and Gynecology (ACOG) recommends the PMS diagnostic criteria developed by the University of California at San Diego and the National Institute of Mental Health (Table 2).^{4,7} In women with severe dysphoric symptoms and significant dysfunction, research criteria can be used to establish the diagnosis of PMDD (Table 3).¹¹ All diagnostic criteria emphasize the periodicity and severity of symptoms.

PMS and PMDD can only be diagnosed after a variety of physical and psychiatric disorders have been excluded (Table 4).^{3,4} PMS also must be distinguished from simple premenstrual symptoms (e.g., bloating, breast tenderness) that do not interfere with daily functioning and are characteristic of normal ovulatory cycles⁷ (Figure 1). The three key elements of the diagnosis are symptoms consistent with PMS, consistent occurrence of symptoms only during the luteal phase of the menstrual cycle, and negative impact of symptoms on function and lifestyle.⁴

When PMS or PMDD is suspected, patients should be instructed to keep a premenstrual daily symptom diary for several consecutive months so that cycle-to-cycle variability can be examined (Figure 2). Based on this diary, many women may be found to have nonluteal symptom patterns.⁷ Standardized daily symptom calendars, such as the Calendar of Premenstrual Experiences and the Prospective Record of the Impact and Severity of Menstruation, provide reliable and convenient records.^{4,7}

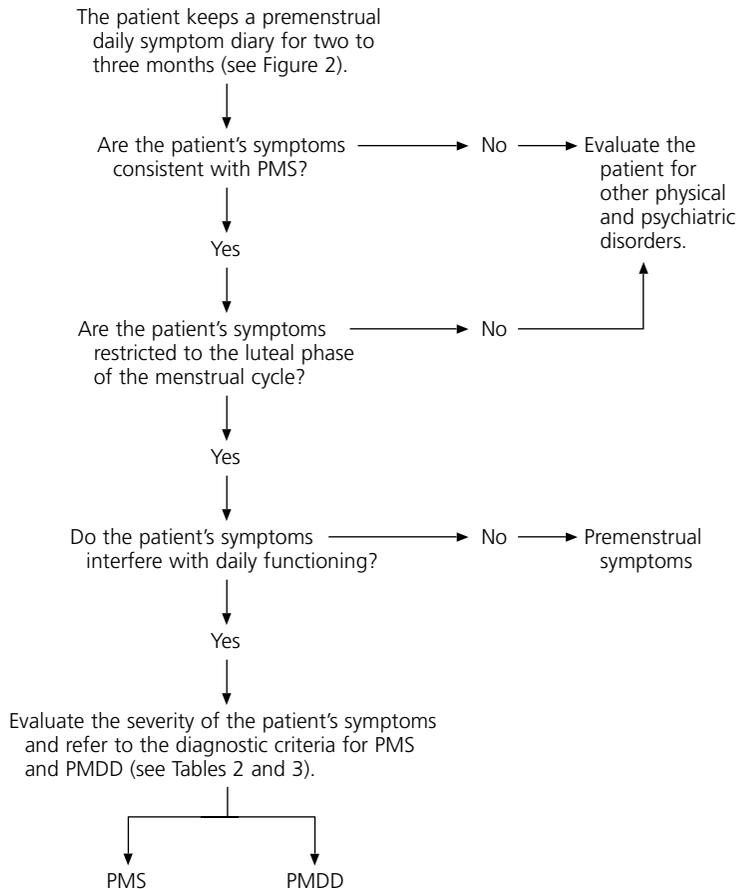
Diagnosis of Premenstrual Symptoms, PMS, and PMDD

FIGURE 1. Algorithm for use in differentiating premenstrual symptoms, premenstrual syndrome (PMS), and premenstrual dysphoric disorder (PMDD).

Management

Treatment goals for PMS are to ameliorate or eliminate symptoms, reduce their impact on activities and interpersonal relationships, and minimize adverse effects of treatment. Although numerous treatment strategies are available, few have been adequately evaluated in randomized, controlled trials. Furthermore, research findings can be difficult to apply because of the variability of inclusion criteria and outcome measures in clinical trials, the lack of studies directly comparing treatment modalities, and the high response rate to placebo (25 to 50 percent).^{2,3}

Initially, all patients with PMS should be offered nonpharmacologic therapy.⁴ Medication should be offered to patients with persistent symptoms of PMS and those who meet

criteria for PMDD. Surgical treatment, principally hysterectomy plus bilateral oophorectomy, is controversial because it is irreversible and associated with significant risks. Surgery may be considered in severely affected patients who fail to respond to other therapies and also have significant gynecologic problems for which surgery would be appropriate.^{1,4}

NONPHARMACOLOGIC THERAPY

Nonpharmacologic interventions for PMS include patient education, supportive therapy, and behavioral changes.^{1,3} Women who have been educated about the biologic basis and prevalence of PMS report an increased sense of control and relief of symptoms.⁴

Although not rigorously evaluated, supportive therapy may be responsible for the high placebo-response rates in clinical trials. Small comparative trials^{1,4,12} show some benefit for formal psychologic interventions such as relaxation therapy and cognitive behavioral therapy. Behavioral measures include keeping a symptom diary, getting adequate rest and exercise, and making dietary changes.

The daily symptom diary may help patients identify optimal times for implementing behavioral and other changes to manage symptom exacerbations. Women report that maintaining a symptom diary helps them manage PMS or PMDD.^{3,7}

Sleep disturbances, ranging from insomnia to excessive sleep, are common in women with PMS. A structured sleep schedule with consistent sleep and wake times is recommended, especially during the luteal phase.³

Dietary restrictions and exercise may also be useful in patients with PMS.^{3,7} Sodium restriction has been proposed to minimize bloating, fluid retention, and breast swelling and tenderness. Caffeine restriction is recommended because of the association between caffeine and premenstrual irritability and insomnia. In epidemiologic and short-term prospective studies,^{1,4,13,14} women with PMS who practiced aerobic exercise reported fewer symptoms than control subjects.

In one randomized, placebo-controlled crossover trial,¹⁵ chiropractic therapy was associated with a decrease in PMS symptoms. However, this effect was only noted in patients randomized to initially receive chiropractic treatment.

DIETARY SUPPLEMENTATION

Dietary supplements that have been evaluated in women with PMS include vitamins (A, E, and B₆), calcium, magnesium, multivitamin/mineral supplements, and evening primrose oil. Because most studies have been small or poorly designed, efficacy needs to be confirmed in large, well-designed clinical trials before evidence-based recommendations can be made.

In nine randomized, controlled clinical trials of vitamin B₆ as a single supplement or in a multivitamin, improvement of symptoms was reported, but the poor quality of the trials limits their usefulness.¹⁶ [Evidence level B, systematic review of lower quality randomized controlled trials (RCTs)] Vitamin B₆ should not be routinely recommended for women with PMS.^{1,4,16}

Studies of vitamin A do not support its use, but vitamin E supplementation is a recognized treatment for mastalgia.^{3,4} In one randomized, controlled trial, the administration of 400 IU per day of vitamin E during the luteal phase was found to improve affective and somatic symptoms in women with PMS.⁴ The ACOG⁴ recognizes vitamin E as a potential treatment for PMS, because of minimal harm and its potentially beneficial antioxidant effect.

Supplements of calcium carbonate in a dosage of 1,200 mg per day for three menstrual cycles resulted in symptom improvement in 48 percent of women with PMS, compared with 30 percent of placebo-treated women.¹⁷ [Evidence level A, RCT] Magnesium in a dosage of 200 to 400 mg per day has shown minimal benefit in alleviating bloating.^{1,4,18} The ACOG⁴ recommends calcium supplementation but not magnesium supplementation.

Evening primrose oil, a prostaglandin precursor, has been studied in women with PMS, based on the theory of inadequate levels of prostaglandin E₁. A systematic review of placebo-controlled trials of evening primrose oil suggested lack of benefit in PMS, although mild relief was demonstrated in women with breast tenderness.⁹ [Evidence level B, systematic review of lower quality RCTs]

PHARMACOLOGIC THERAPY

Nonpharmacologic measures should be monitored at least every three months. If symptoms are not adequately relieved, the addition of pharmacologic treatment should be considered (Table 5).^{19,20} Medications are given to treat specific symptoms or alter the menstrual cycle. Treatment should be individualized to target the most troublesome symptoms in each patient.

Nonprescription Preparations. Several nonprescription products (e.g., Midol, Premysyn) contain mild diuretics, analgesics, prostaglandin inhibitors, and antihistamines.³ Women should be cautioned about using combination products, which may provide inadequate doses of some ingredients and excessive doses of others. If nonprescription preparations are used, single-ingredient products (i.e., vitamins or analgesics) are preferred.

Psychotropic Agents. Because serotonin has been implicated in the pathogenesis of PMS and PMDD, various SSRIs have been tested in these disorders.^{1,4} The U.S. Food and Drug Administration (FDA) has labeled fluoxetine (Sarafem and sertraline [Zoloft]) for the treatment of PMDD.¹⁹ The ACOG recommends SSRIs as initial drug therapy in women with severe PMS and PMDD.⁴ [Evidence level C, expert/consensus guidelines]

Common side effects of SSRIs include insomnia, drowsiness, fatigue, nausea, nervousness, headache, mild tremor, and sexual dysfunction.^{1,4,21} Use of the lowest effective dosage can minimize side effects. Morning dosing can minimize insomnia.

In general, 20 mg of fluoxetine or 50 mg of

sertraline taken in the morning is best tolerated and sufficient to improve symptoms.^{22,23} Benefit has also been demonstrated for the continuous administration of citalopram (Celexa).²⁴

SSRI therapy during the luteal phase has been shown to be efficacious in several randomized, double-blind, placebo-controlled trials.²⁴⁻²⁷ In one study, intermittent citalopram therapy was found to be more effective than continuous therapy. A recent systematic review²¹ found that SSRIs were effective in alleviating physical and behavioral symptoms, with similar efficacy for continuous and intermittent therapies.²⁴ [Evidence level A, systemic review or RCT]

Fluoxetine is currently labeled for use as continuous therapy in a dosage of 20 mg per day.¹⁹ Sertraline, in a dosage of 50 mg per day, is labeled for continuous therapy or for use during the luteal phase. Administration only during the luteal phase decreases drug cost, minimizes drug exposure and side effects, and may be more acceptable to some women.⁴ For intermittent therapy, fluoxetine or sertraline can be given during the 14 days before the menstrual period, or treatment can be initiated just before the expected onset of symptoms.

Treatment using anxiolytic agents such as alprazolam (Xanax) is not recommended because of addictive potential, tolerance, and significant side effects.^{3,4,28} Although some beneficial effects have been demonstrated for other psychotropic agents, including bupropion (Wellbutrin), tricyclic antidepressants, buspirone (BuSpar), and lithium, as well as the beta blockers atenolol (Tenormin) and propranolol (Inderal), treatment with these drugs is not recommended because potential harms outweigh any benefit.¹ Bromocriptine (Parlodel) has been shown to relieve breast tenderness and menstrual migraine in women with PMS, but side effects also limit its usefulness.^{1,29}

Diuretics. Spironolactone (Aldactone), an aldosterone antagonist structurally similar to steroid hormones, is the only diuretic that has been shown to effectively relieve PMS symptoms such as breast tenderness and fluid

TABLE 5

Prescription Medications Commonly Used in the Treatment of Premenstrual Syndrome (PMS)

<i>Drug class and representative agents</i>	<i>Dosage*</i>	<i>Average cost (generic)†</i>	<i>Recommendations for use</i>	<i>Side effects</i>
SSRIs				
Fluoxetine (Sarafem)‡	10 to 20 mg per day	\$ 91	First-choice agents for the treatment of PMDD; at present, only fluoxetine is labeled for this indication.	Insomnia, drowsiness, fatigue, nausea, nervousness, headache, mild tremor, sexual dysfunction
Sertraline (Zoloft)	50 to 150 mg per day	76	Clearly effective in alleviating behavioral and physical symptoms of PMS and PMDD	
Paroxetine (Paxil)	10 to 30 mg per day	78		
Fluvoxamine (Luvox)	25 to 50 mg per day	88 (69-79)	For intermittent therapy, administer during luteal phase (14 days before menses).	
Citalopram (Celexa)	20 to 40 mg per day	67		
Diuretics				
Spironolactone (Aldactone)	25 to 100 mg per day during luteal phase	16 (6)	Clearly effective in alleviating breast tenderness and bloating	Antiestrogenic effects, hyperkalemia
NSAIDs				
Naproxen sodium (Anaprox)	275 to 550 mg twice daily	60 (37-50)	Effective in alleviating various physical symptoms of PMS but not breast tenderness Any NSAID should be effective.	Nausea, gastric ulceration, renal dysfunction Use with caution in women with preexisting gastrointestinal or renal disease.
Androgens				
Danazol (Danocrine)	100 to 400 mg twice daily	149 (120)	Somewhat effective in alleviating mastalgia when taken during luteal phase Continuous therapy is not recommended because of side effect profile and cost.	Weight gain, decreased breast size, deepening of voice Monitor lipid profile and liver function.
GnRH agonists				
Leuprolide (Lupron)	3.75 mg IM every month or 11.25 mg IM every three months	535	Somewhat effective in alleviating physical and behavioral symptoms of PMS Side effect profile and cost limit use, especially as long-term therapy (more than 6 months). "Add-back" therapy with estrogen and/or progesterone is necessary if GnRH agonists are used as long-term therapy (more than 6 months).	Hypoestrogenic side effects, including atrophic vaginitis, hot flashes, cardiovascular effects, and osteoporosis
Goserelin (Zoladex)	3.6 mg SC every month or 10.8 mg SC every three months	470		
Nafarelin (Synarel)	200 to 400 mcg intranasally twice daily	523 for 8-mL nasal spray bottle		
Histrelin (Supprelin)	10 mcg per kg per day SC	471		

SSRIs = selective serotonin reuptake inhibitors; PMDD = premenstrual dysphoric disorder; NSAID = nonsteroidal anti-inflammatory drug; GnRH = gonadotropin-releasing hormone; IM = intramuscularly; SC = subcutaneously.

*—Taken orally unless otherwise indicated.

†—Estimated cost to the pharmacist for 30 days of treatment (continuous therapy) at the lowest given dosage (unless otherwise indicated), based on average wholesale prices (rounded to the nearest dollar) in Red book. Montvale, N.J.: Medical Economics Data, 2001. Cost to the patient will be greater, depending on prescription filling fee. Monthly cost for intermittent therapy (i.e., only during the luteal phase) is one half the monthly cost for continuous therapy.

‡—Fluoxetine (more common brand name: Prozac) is marketed under the brand name Sarafem for the treatment of PMDD.

Information from references 19 and 20.

retention.^{1,4,30} In most studies, spironolactone was administered only during the luteal phase.³⁰ Thiazide diuretics have not been found to be beneficial in the treatment of patients with PMS.^{1,4}

Prostaglandin Inhibitors. Nonsteroidal anti-inflammatory drugs (NSAIDs) are traditional therapy for primary dysmenorrhea and menorrhagia. Use of these agents, especially mefenamic acid (Ponstel) and naproxen sodium (Anaprox; also, nonprescription Aleve), is based on the theory that PMS symptoms are related to prostaglandin excess.³

Most NSAIDs should be effective, but mefenamic acid and naproxen sodium have been the most studied. Mefenamic acid therapy given during the luteal phase is effective in relieving symptoms, but gastrointestinal toxicity prohibits its use. Naproxen sodium improves physical symptoms and headache in women with PMS. Overall, NSAIDs may alleviate a wide range of symptoms, but they do not appear to improve mastalgia. All NSAIDs must be used with caution in patients with underlying gastrointestinal or renal disorders.

Agents Used to Alter the Menstrual Cycle. Danazol (Danocrine), gonadotropin-releasing hormone (GnRH) agonists, estrogen, and progesterone have been studied in the treat-

ment of PMS and PMDD. Although efficacy has been demonstrated for some of these agents, their use is limited by significant adverse effects and treatment costs.

Danazol is an androgenic agent that inhibits gonadotropin release, thereby improving mastalgia.³¹ Continuous danazol therapy may also relieve other PMS symptoms.^{1,31} However, continuous therapy is limited by side effects such as masculinization (e.g., decreased breast size, deepening of the voice, weight gain), as well as adverse effects on liver function tests and serum lipid profiles.

GnRH agonists are synthetic analogs of naturally occurring GnRH and suppress ovulation by inhibiting the release of pituitary gonadotropins. GnRH agonists have been shown to be more effective than placebo in treating behavioral and physical symptoms of PMS.^{1,4,6,32,33} Side effects and cost may limit GnRH agonist therapy to patients with severe PMS.

The hypoestrogenic effects of GnRH agonists can lead to atrophic vaginitis, urinary tract symptoms, and a decrease in skin collagen content. Use of these agents for longer than six months can significantly increase the risk of osteoporosis. If treatment for more than six months is necessary, "add-back" therapy with estrogen and/or progesterone should be considered to minimize long-term adverse effects.^{1,4} Unfortunately, add-back therapy is often associated with a recurrence of PMS symptoms.⁴ Some improvement in premenstrual depression and irritability has been demonstrated for lower dosages of GnRH agonists.³²

Tibolone (Xyvion) is an investigational synthetic steroid with weak estrogenic, progestogenic, and androgenic activity. Although this agent has primarily been studied in the treatment of menopause and osteoporosis, it has been shown to provide significant improvement in premenstrual symptoms compared with placebo and a multivitamin.³⁴ FDA labeling of tibolone for the treatment of menopause and osteoporosis is expected in 2002.¹⁹

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Limited evidence suggests that estrogen therapy is efficacious in alleviating PMS symptoms.^{1,3} The administration of estrogen late in the luteal phase (to minimize premenstrual decline in the hormone) relieves premenstrual migraine.^{1,7} For overall symptom management, estrogen must be given continuously to suppress ovarian activity. Because unopposed estrogen can promote endometrial hyperplasia and carcinoma, cyclic progesterone must be added. The progesterone may induce PMS symptoms, thereby limiting the efficacy of estrogen.¹

Although oral contraceptive pills (OCPs) are widely prescribed for the management of PMS, they have not been shown to be consistently effective.¹ Any benefits are probably due to the estrogenic component; therefore, monophasic pills may be most appropriate. OCPs may improve physical symptoms such as bloating, headaches, abdominal pain, and breast tenderness, but they can also exacerbate these symptoms. Anecdotal reports indicate that women with PMS who take OCPs tend to have fewer physical symptoms than those who do not take them. However, the pills do not appear to have a positive effect on mood symptoms.⁴

Historically, progesterone delivered by vaginal or rectal suppository has been widely prescribed for women with PMS. Synthetic progesterone-like drugs, such as medroxyprogesterone acetate (Provera), have also been studied. Paradoxically, some evidence indicates that progesterone may be responsible for some of the physical and emotional symptoms of PMS.^{1,35} The administration of progesterone is commonly associated with abdominal bloating and pain, nausea, breast discomfort, and menstrual irregularities.² A systematic review³⁶ of 14 randomized controlled trials found no improvement in overall symptoms among women taking progesterone.

Use of progesterone during the luteal phase remains one of the most controversial treatments for PMS. Because efficacy compared with placebo has not been demonstrated,

TABLE 6

Summary of Management Guidelines

All women with PMS or PMDD

Nonpharmacologic treatment: education, supportive therapy, rest, exercise, dietary modifications

Symptom diary to identify times to implement treatment and to monitor improvement of symptoms

Treatment of specific physical symptoms

Bloating: spironolactone (Aldactone)

Headaches: nonprescription analgesic such as acetaminophen, ibuprofen, or naproxen sodium (Anaprox; also, nonprescription Aleve)

Fatigue and insomnia: instruction on good sleep hygiene and caffeine restriction

Breast tenderness: vitamin E, evening primrose oil, luteal-phase spironolactone, or danazol (Danocrine)

Treatment of psychological symptoms

For symptoms of PMDD, continuous or intermittent therapy with an SSRI

Treatment failure

Hormonal therapy to manipulate menstrual cycle

PMS = premenstrual syndrome; PMDD = premenstrual dysphoric disorder; SSRI = selective serotonin reuptake inhibitor.

progesterone is not recommended for the management of PMS.³

Management guidelines are summarized in *Table 6*.

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