REVIEW

KATHRYN S. MUZINA, MD
Department of Psychiatry and Psychology, Cleveland Clinic.

LILIAN GONSALVES, MD
Vice chair, Department of Psychiatry and Psychology; and Department of Gynecology and Obstetrics, Cleveland Clinic.

Commonly asked questions about premenstrual dysphoric disorder

ABSTRACT

Although the etiology of premenstrual dysphoric disorder (PMDD), a severe form of premenstrual syndrome, is as yet unconfirmed, it is a biological condition that responds to biological therapies. With education, psychotherapy, and somatic and psychotropic treatment, women with PMDD can attain improved health and quality of life.

KEY POINTS

Most women of reproductive age have some symptoms of premenstrual syndrome (PMS), but only approximately 2.5% to 5% have symptoms severe enough to affect function and qualify for a diagnosis of premenstrual dysphoric disorder (PMDD).

PMDD is diagnosed by ruling out organic causes of symptoms, and then asking patients to record their daily symptoms and basal body temperature during two or three cycles to confirm that symptoms occur in the luteal phase.

Treatment for PMDD depends on severity and type of symptoms; mild cases may respond to education, lifestyle modifications, and somatic treatments alone.

Severe cases of PMDD may require hormonal and psychotropic drugs such as oral contraceptives and selective serotonin reuptake inhibitors, and may also require a psychiatric consult. Surgical ovariectomy is a last resort.

PREMENSTRUAL SYNDROME (PMS) is among the more common and puzzling problems that primary care physicians and gynecologists encounter. Too often, physicians dismiss premenstrual complaints as functional or psychosomatic, thereby invalidating the patient's symptoms and depriving her of treatment that can be quite helpful and relatively easy to prescribe and manage.

Most women experience PMS to some degree, and to most it is a nuisance at worst. However, some women have a severe variety of PMS called premenstrual dysphoric disorder (PMDD) that can disrupt their life. This article reviews common questions about the definition of PMDD and its prevalence, risk factors, differential diagnosis, diagnostic evaluation, etiologic theories, and current treatment strategies.

WHAT IS PMDD? HOW IS IT DIFFERENT FROM PMS?

PMS is a group of physical, cognitive, and emotional symptoms that occurs in the late luteal phase of the menstrual cycle. It was described in ancient times as a virgin's disease, because in those times any woman who was married was generally pregnant and therefore not cycling. And from ancient times it was recognized that in a subset of women, PMS is severe enough to interfere with social and occupational functioning. Pliny the Elder, born in AD 23, wrote in his *Historia Naturalis* that:

"On the approach of a woman in this state, milk will turn sour, seeds which are touched by her become sterile, grafts writhe away…her very look, even, will dim the brightness of mirrors, blunt the edge of steel, and take the polish from ivory."

Previously known as late luteal phase dysphoric disorder, this severe variety of PMS is described in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*[1] under its new name, in an appendix of diagnoses warranting further study.

Symptoms of PMDD include:

- Depressed mood
- Anxiety
- Affective lability
- Anger or irritability
- Decreased interest in usual activities
- Difficulty concentrating
- Decreased energy
- Appetite changes
- Hypersomnia or insomnia
- A sense of being overwhelmed
- Other physical symptoms such as breast swelling or tenderness, headaches, joint or muscle pain, a sensation of bloating, and weight gain.

Diagnostic criteria for PMDD. These symptoms must:

- Be present in most of the menstrual cycles in the past year, and five or more symptoms must be present during the last week of the luteal phase.
- Begin to remit several days after the onset of menses, and be absent during the week after menses ceases.
- Markedly interfere with school, work, social activities, or relationships.
- Not be an exacerbation of the symptoms of another disorder such as major depressive disorder.
- Be confirmed by prospective daily ratings through a minimum of two consecutive symptomatic menstrual cycles.

In contrast, the term PMS is generally used to describe milder physical symptoms such as breast changes, headaches, bloating, and minor changes in mood that do not interfere with daily functioning.

TABLE 1

Differential diagnosis of premenstrual dysphoric disorder

Anemia
Endometriosis
Menopause
Pelvic inflammatory disease
Premenstrual magnification of a primary psychiatric condition
Primary or secondary dysmenorrhea
Seizure disorder
Thyroid disease
Uterine fibroids

HOW COMMON IS PMDD?

An estimated 75% of women with regular menstrual cycles note some symptoms of premenstrual dysphoria, and these women are usually seen by primary care physicians or gynecologists.[2]

PMDD, in contrast, is significantly less common, affecting perhaps 2.5% to 5% of women of reproductive age.[3] Women with PMDD generally do not respond to the usual treatments for PMS, and thus are frequently referred to psychiatrists or tertiary care centers. Of these women, approximately 60% have "true" PMDD, another 8% are thought to have magnification of symptoms of another major psychiatric disorder or physical condition during the luteal phase of their cycle, and the remainder either have only mild symptoms or meet criteria for another major psychiatric diagnosis at the time of the evaluation, thereby not qualifying as having PMDD.[4]

PMDD interferes with function; PMS does not

PREDISPOSING FACTORS FOR PMDD

Reproductive age. Because PMDD is a phenomenon of the menstrual cycle, it affects only women of reproductive age. Freeman et al,[5] in a study of 332 women ages 20 to 44, found symptoms to be most severe in women in their late 20s through mid-30s.

Depression. Numerous studies have linked the premenstrual syndrome to depression. Approximately 80% of women with PMDD have depression at some time in their lives. Further, 65% of women with major

depressive disorder experience premenstrual exacerbation of their symptoms.[6] In one study, Harrison et al[7] found a higher lifetime prevalence of depression, suicide attempts, panic disorder, and substance abuse in women seeking treatment for PMDD than in a control group. However, the difference disappeared after women with a primary psychiatric diagnosis were excluded.

Additional risk factors include a family history of mood disorders and a personal history of postpartum depression.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of PMDD is extensive (TABLE 1); therefore it is important to rule out organic causes of symptoms. The following case report illustrates the type of case where PMDD might be suspected, but in which a detailed investigation unearthed another organic cause.

PMS and PMDD are linked to depression

CASE REPORT

A 39-year-old woman with PMS

A 39-year-old woman was referred to the PMS clinic at the Cleveland Clinic Foundation. For the past 6 months, she had experienced diminished concentration, decreased energy, nausea, dizziness, and occasional fainting during the 2 days before the onset of her period. These symptoms were documented on daily symptom-rating forms.

Approximately 1 month previously, the patient fainted while driving; her car hit a tree, and she fractured her right arm. The workup at a community hospital included an electroencephalogram, echocardiogram, and computed tomographic (CT) scan of her head, all of which were normal. She had no history of medical or psychiatric disorders or chemical dependency. Her family history was negative for psychiatric and neurologic illnesses. The only medication she used was vitamin B_6. Her mental status was within normal limits.

Because her symptoms were not typical of PMDD, the patient was referred for further neurologic and cardiac evaluation. Serum levels of thyroid-stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3), follicle-stimulating hormone, luteinizing hormone, and electrolytes were normal. Holter monitoring showed short runs of ventricular tachycardia, which were presumed to be the cause of her syncope and for which propranolol 20 mg four times a day was started. However, the symptoms continued.

Twenty-two days after her initial evaluation, the patient's husband witnessed her having a 20-second seizure while she slept. She was admitted to the hospital, where she described a strange odor that had preceded the seizure. Further telemetric monitoring failed to demonstrate an arrhythmia with which her symptoms might be correlated. A magnetic resonance imaging scan of her head was normal. She was eventually diagnosed by her neurologist with a complex partial seizure disorder. Catamenial epilepsy is a grouping of seizures around the perimenstrual or periovulatory phases of the menstrual cycle. Carbamazepine therapy was started, and at last report the patient remains symptom-free.

NAME: _____ MONTH/YEAR _____

Scale for symptoms: 1-Not present 2-Minimal 3-Mild 4-Moderate 5-Severe 6-Extreme

DATE:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
BASAL BODY TEMPERATURE (ALSO CHECK EACH DAY OF MENSTRUAL PERIOD)																															
ACNE OR PIMPLES																															
ANGRY/IRRITABLE																															
CRAMPS																															
CRYING/FEELING LIKE CRYING																															
DEPRESSED																															
DISTURBING THOUGHTS																															
EMPTY FEELING																															
ENERGY DECREASED																															
ENERGY INCREASED																															
FOOD CRAVINGS																															
SUGAR																															
SALT																															
HALLUCINATIONS																															
HEADACHES																															
HELPLESSNESS																															
HOPELESSNESS																															
NERVOUS																															
NEED TO BE ALONE																															
NOISE SENSITIVITY																															
OUT OF CONTROL																															
SEXUAL INTEREST INCREASED																															
SEXUAL INTEREST DECREASED																															
SLEEP DISTURBANCE																															
SUICIDAL																															
TENSION																															
UNREAL FEELING																															
VIOLENT FEELING																															

FIGURE 1. Symptom card used by patients at the Cleveland Clinic. A space for comments for each day is provided on the back.

CLINICAL EVALUATION

Rule out organic syndromes

The initial steps in evaluating a patient for PMDD are aimed at ruling out organic syndromes presenting as PMDD, such as thyroid disorders, perimenopause, and menopause.

The history should include the medical, gynecologic, and psychiatric areas, with careful attention to responses to pregnancy (ie, postpartum depression) and any psychiatric disorders. Patients should also be asked about current drug and alcohol use.

The physical examination should include a pelvic examination.

Laboratory studies should include thyroid function tests, a complete blood count, and estrogen and progesterone levels.

Record and rate the symptoms

Next, patients are asked to:

- Rate their symptoms every day for two or three menstrual cycles, and record them on a "symptom card" (FIGURE 1).
- Take and record their basal body temperatures on the symptom card before getting out of bed every morning; the basal body temperature typically reaches a nadir at ovulation and then rises approximately 1°F.
- Take a psychological test such as the Minnesota Multiphasic Personality Inventory or the Beck Depression Inventory, a week prior to menses and repeated a week after menses; this can lend objective evidence to support the patient's subjective reporting of symptoms.

The diagnosis is made after examining the symptom cards to confirm that the symptoms occur in the luteal phase based on basal body temperature, ruling out medical or gynecological disease, and ruling out primary psychiatric diagnoses.

WHAT ARE POSSIBLE CAUSES OF PMDD?

Many women with PMDD who enter menopause prematurely as the result of surgi-

TABLE 2

Therapy for premenstrual dysphoric disorder

First-step treatments
- Education and lifestyle modifications
  - Diet modifications
  - Exercise
  - Vitamins and minerals
- Somatic treatments
  - Acetaminophen
  - Bromocriptine
  - Diuretics
  - Nonsteroidal anti-inflammatory drugs

Second-step therapies
- Hormonal therapies
  - Oral contraceptives (mild symptoms)
  - Gonadotropin-releasing hormone analogs or danazol (severe or refractory symptoms)
- Psychotropic drugs
  - Alprazolam
  - Buspirone
  - Selective serotonin reuptake inhibitors
  - Tricyclic antidepressants

Third-step treatment
- Psychotherapy

cal ovariectomy or medical therapy subsequently experience a dramatic reduction in their symptoms. This implies that some part of the menstrual cycle goes awry in PMDD, but which one? Theories abound, but none have been conclusively verified.

Progesterone deficiency, a theory proposed by Dalton[8] and once popular, has not been confirmed in prospective studies.[9,10]

Ovarian steroid imbalance. The importance of ovarian steroids in the pathophysiology of PMDD was first demonstrated by Muse et al,[11] who gave a gonadotropin releasing hormone (GnRH) agonist to women with PMDD, after which ovarian stimulation ceased and premenstrual symptoms resolved. Recently, Schmidt et al[12] studied the different behavioral effects of gonadal steroids in 20 women with PMS and 15 women without PMS. They concluded that in women with PMS, the occurence of symptoms represented an abnormal response to normal hormonal changes.

An abnormal thyroid-stimulating hormone response to thyrotropin-releasing hormone was demonstrated in one study[13]; however, most other studies did not support this finding.

Dysregulation in central neurotransmission, due to ovarian steroid flux, is a more recent theory. Estrogen, progesterone, and their metabolites are known to alter function in the noradrenergic and gamma-aminobutyric acid (GABA) systems.[14]

Serotonin dysfunction. Still more recently, interest has turned to the effects of estrogen and progesterone on the serotoninergic system. Rapkin[15] found diminished levels of serotonin in whole blood and platelets during the late luteal phase in women with PMDD. Furthermore, patients with PMDD have responded dramatically to the selective serotonin reuptake inhibitor, fluoxetine.[16–18]

FIRST-STEP TREATMENTS

Many treatments for PMDD have been devised over the years, all aimed at the possible causes discussed above. These have included exercise, vitamin supplementation, dietary changes, various hormones, diuretics, psychotropic medications, nonsteroidal anti-inflammatory drugs (NSAIDs), medical and surgical oophorectomy, light therapy, and sleep deprivation. However, most of these have proved ineffective in prospective studies.

TABLE 2 outlines the current treatments for PMDD and the milder syndrome, PMS. The first step is to review the individual patient's symptoms and then select treatment that addresses her specific complaints. The first line of treatment consists of education, lifestyle changes, and somatic therapies. These steps provide adequate relief for PMS, and at least some relief from less severe forms of PMDD.

Education and lifestyle changes

Patients should be told that PMDD is a legitimate syndrome, and that anticipating it and responding appropriately can decrease its severity considerably. The patient's spouse, children, and significant friends may also need to hear this message and be more supportive. Support groups for women with PMDD also provide education and psychological support,

and participants in such groups may enjoy greater symptom relief than nontreated controls, as noted by Pearlstein et al.[19]

Dietary modifications may modulate some symptoms. A dietitian can assess whether dietary factors may be contributing to the symptoms. General recommendations:

- Reduce consumption of caffeine and its equivalents (theophylline, theobromine, and other methylxanthines) during the late luteal phase; these have been linked to more severe premenstrual symptoms, including irritability and insomnia.[20]
- Reduce salt intake to minimize temporary water weight gain.
- Increase intake of complex carbohydrates.
- Decrease consumption of refined sugars.
- Eat frequent small meals to avoid hypoglycemia.

Exercise may improve mood, perhaps by increasing circulating endorphin levels.[21] Several studies[22–24] found exercise beneficial in nonclinical settings. Increasing the frequency of exercise was found to reduce symptoms related to fluid retention.[22] A program of regular aerobic exercise produced greater symptom relief than did strength training.[23] One recent prospective study showed both low-intensity and moderate-intensity aerobic training to be beneficial over three menstrual cycles.[24] These studies were not controlled and therefore lacked scientific rigor. However, at the very least, regular aerobic exercise will contribute to improved general health and will likely provide some relief from PMDD.

Vitamin and mineral supplements. Pyridoxine (vitamin B_6), a cofactor in the production of several neurotransmitters thought to be related to PMDD, is a popular treatment discussed in the lay press. Low doses (50 mg daily) may reduce depression, irritability, and fatigue.[25] However, very large doses may produce neurotoxicity, marked by muscle weakness, numbness, paresthesias, and clumsiness. Calcium (80 mg daily) and magnesium (360 mg daily) have been examined in clinical trials, and have both been found helpful in reducing premenstrual symptoms.[26,27]

Treatment of somatic symptoms

Some treatments are aimed at specific somatic symptoms such as bloating, weight gain, swelling, headaches, breast tenderness, and joint or muscle pain.

Fluid retention can be addressed by a low-salt diet and calcium and magnesium supplements. Diuretics can be prescribed if these conservative measures fail. Spironolactone is preferred over the thiazides, as it is less likely to produce dependence on diuretics or rebound cyclic edema.[28]

Headaches, joint and muscle pain, and breast tenderness can be treated with NSAIDs or acetaminophen. Breast tenderness can also be reduced by wearing a supportive bra. More severe breast tenderness can be treated with bromocriptine, beginning at 2.5 mg daily and increased according to severity of symptoms and as tolerated; the common side effects are nausea and constipation.[28]

SECOND-STEP THERAPIES

If the measures described above do not provide adequate relief, the next step is to modify the menstrual cycle and to give a psychotropic medication. A good option would be to begin with an oral contraceptive and then, if it provides no benefit after 2 months, switch to a selective serotonin reuptake inhibitor (SSRI).

Patients should consume less caffeine during the late luteal phase

Hormonal therapies

As previously noted, early attempts to treat PMDD with progesterone were not particularly beneficial. There are currently four hormonal alternatives available.

Oral contraceptives have been found useful in treating PMDD, particularly the symptom of painful menses; however, they have also been reported to worsen dysphoric symptoms in some patients.[29] Oral contraceptives that are estrogen dominant rather than androgen dominant are recommended.

Estradiol has been used successfully in PMDD; however, coadministration of progestins is required to prevent endometrial hyperplasia.[30]

GnRH agonists and danazol can be used to eliminate the menstrual cycle, and both have led to significant reductions in PMDD

symptoms.[11,31] Commonly used GnRH agonists include leuprolide, goserelin, and nafarelin. Hot flashes, mood swings, and bone loss are some of the common side effects. These drugs should not be prescribed alone for longer than 6 months because of the risk of osteoporosis.

Surgical ovariectomy also eliminates the menstrual cycle—permanently. Although it eradicates PMDD, it may lead to decreased libido and accelerated osteoporosis (comparable to that which can occur after natural menopause), and many other unwanted effects ascribed to low estrogen states. It is a last resort in women with severe symptoms for whom conservative therapies have failed.

Anxiolytic medications

A multitude of studies have demonstrated the benefits of treating PMDD with anxiolytic and antidepressant medications.

Alprazolam (0.25 mg four times a day) has been demonstrated effective in double-blind studies.[32–34] The most common side effect is sedation. One advantage of alprazolam is that patients need to take it only during the symptomatic phase of the cycle, not continuously. This dosing schedule may reduce the risk of addiction to this highly potent benzodiazepine.

Exercise may improve mood by increasing endorphin levels

Buspirone was noted to produce improvements in symptoms at a dose of 5 to 10 mg three times a day during the luteal phase.[35]

Antidepressant medications

Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), has been demonstrated effective in several prospective studies, including double-blind, placebo controlled trials,[15–17] producing significant reductions in affective and behavioral symptoms. The usual dose is 20 mg daily. Side effects include headaches, nausea, changes in appetite, and sexual dysfunction.

Sertraline, a second SSRI, produced similar results at doses of 50 to 150 mg daily in a recent controlled trial.[36] The side effect profile of sertraline is similar to that of fluoxetine. Our clinical experience reveals that all the SSRIs (fluoxetine, fluvoxamine, paroxetine, and sertraline) are equally effective in treating PMDD and that they are more similar than different in their side effect profiles.

Tricyclic antidepressants such as nortriptyline and clomipramine are also effective.[37,38] Their side effects are predominantly anticholinergic, ie, dry mouth and sedation.

Venlafaxine and nefazodone, two novel antidepressants, remain in preliminary trials.

Unlike alprazolam and buspirone, the antidepressants are most effective if taken continuously.

Psychotherapy

Should symptoms persist, patients should receive a psychiatric referral, especially if they have a personal or family history of mood disorder or if substance abuse is suspected. Psychiatrists are uniquely qualified to treat severe or treatment-resistant cases, given the close ties between PMDD and depression, and the training that psychiatrists receive in psychotherapy. But regardless of clinical specialty, clinicians need to be aware of psychological issues specific to women, and the increased risk of depression in women in general.

PMDD and the changing roles of women in society

Women today function in a myriad of complex roles. They may be wives and mothers in traditional nuclear families or single parents. Blended families (merged by divorce and remarriage) and stepparenting are common. Many women also care for aging parents.

At the same time, increasing numbers of mothers work outside the home in ever-more-demanding jobs. Women run companies, universities, states, day care centers, and police precincts, and also manage their homes day-to-day. These conflicting roles can produce considerable stress, which, left unrecognized, can lead to depression—and depression has close ties to PMDD. Therefore, the primary care clinician should be alert and sensitive to the stresses a woman may be under, and take these into account in their treatment.

A diagnosis of PMDD can also have legal ramifications. Women accused of murder and child abuse have used PMDD as a defense.[39] Conversely, husbands have attempted to use the diagnosis of PMDD as a means of declaring a woman an unfit parent.

REFERENCES

1. **American Psychiatric Association.** Diagnostic and Statistical Manual of Mental Disorders. Fourth edition. Washington, DC: American Psychiatric Association; 1994:715–718.
2. **Johnson SR.** The epidemiology and social impact of premenstrual symptoms. Clin Obstet Gynecol 1987; 30:367–376.
3. **Mortola JF.** Issues in the diagnosis and research of premenstrual syndrome. Clin Obstet Gynecol 1992; 35:587–598.
4. **Steiner M.** Premenstrual dysphoric disorder. An update. Gen Hosp Psychiatry 1996; 18:244–250.
5. **Freeman EW, Rickels K, Schweizer E, Ting T.** Relationships between age and symptom severity among women seeking medical treatment for premenstrual symptoms. Psychol Med 1995; 25:309–315.
6. **Endicott J, Halbreich U.** Clinical significance of premenstrual dysphoric changes. J Clin Psychiatry 1988; 49:486–489.
7. **Harrison WM, Endicott J, Nee J, Glick H, Rabkin JG.** Characteristics of women seeking treatment for premenstrual syndrome. Psychosomatics 1989; 30:405–411.
8. **Dalton K.** The premenstrual syndrome and progesterone therapy. 2nd edition. Chicago: Chicago Yearbook; 1984.
9. **Rapkin A, Chang LH, Reading AE.** Premenstrual syndrome: A double-blind placebo controlled study of treatment with progesterone vaginal suppositories. J Obstet Gynecol 1987; 7:217–220.
10. **Freeman E, Rickels K, Sondheimer SJ, Polansky M.** Ineffectiveness of progesterone suppository treatment for premenstrual syndrome. JAMA 1990; 254:349–353.
11. **Muse KN, Cetel NS, Futterman LA.** The premenstrual syndrome: effects of medical ovariectomy. N Engl J Med 1984; 44:317–318.
12. **Schmidt PJ, Nieman LK, Danaceau MA, et al.** Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. N Engl J Med 1998; 338:209–16.
13. **Rubinow DR, Hoban MC, Grover GN, Galloway DS, Roy-Byrne PP, Andersen R, Merriam GR.** Changes in plasma hormones across the menstrual cycle in patients with menstrually-related mood disorder and in control subjects. Am J Obstet Gynecol 1996; 158:5–11.
14. **McEwen BS.** Basic research perspective: ovarian hormone influence on brain neurochemical functions. In: Gise LH, Kase NG, Berkowitz RL, editors. The Premenstrual Syndromes. New York: Churchill Livingstone, 1988:21–33.
15. **Rapkin A.** The role of serotonin in premenstrual syndrome. Clin Obstet Gynecol 1992; 35:629–636.
16. **Stone AB, Pearlstein TB, Brown WA.** Fluoxetine in the treatment of late luteal phase dysphoric disorder. J Clin Psychiatry 1991; 52:290–293.
17. **Wood SH, Mortola JF, Chan YF, Moossazadeh F, Yen SS.** Treatment of premenstrual syndrome with fluoxetine: a double-blind, placebo-controlled, crossover study. Obstet Gynecol 1992; 80(3, part 1):339–344.
18. **Steiner M, Steinberg S, Stewart D, Carter D, Berger C, Reid R, et al.** Fluoxetine in the treatment of premenstrual dysphoria. N Engl J Med 1995; 332:1529–1534.
19. **Pearlstein TB, Rivera-Tovar A, Frank E, Thoft J, Jacobs E, Mieczkowski T.** Nonmedical management of late luteal phase dysphoric disorder. J Psychotherapy Pract Res 1990; 1:49–55.
20. **Rossignol AM, Zhang JY, Chen YZ, et al.** Tea and premenstrual syndrome in the People's Republic of China. Am J Public Health 1989; 79:67–69.
21. **Prior JC, Vigna Y.** Conditioning exercise and premenstrual symptoms. J Reprod Med 1987; 32:423–428.
22. **Prior JC, Vigna Y, Sciarretta D, et al.** Conditioning exercise decreases premenstrual symptoms: a prospective, controlled 6-month trial. Fertil Steril 1987; 47:402–408.
23. **Steege JF, Blumenthal JA.** The effects of aerobic exercise on premenstrual symptoms in middle-aged women: a preliminary study. J Psychosom Res 1993; 37:127–133.
24. **Bibi KW.** The effects of aerobic exercise on premenstrual syndrome symptoms. Dissertation Abstracts International. 1995; 56:6678.
25. **Doll H, Brown S, Thurston A, Vessey M.** Pyridoxine (vitamin B6) and the premenstrual syndrome: a randomized crossover trial. J Royal Coll Gen Pract 1989; 9:364–368.
26. **Facchinetti F, Borella P, Sances G, Fiorini L, Nappi RE, Genazzani AR.** Oral magnesium successfully relieves premenstrual mood changes. Obstet Gynecol 1991; 78:177–181.
27. **Thys-Jacobs S, Ceccarelli S, Bierman A, Weisman H, Cohen MA, Alvir J.** Calcium supplementation in premenstrual syndrome. J Gen Intern Med 1989; 4:183–189.
28. **Johnson S.** Clinician's approach to the diagnosis and management of premenstrual syndrome. Clin Obstet Gynecol 1992; 35:637–657.
29. **Bancroft J, Rennie D.** The impact of oral contraceptives on the experience of perimenstrual mood clumsiness, food craving and other symptoms. J Psychosom Res 1993; 37:195–202.
30. **Mangos AL, Brincat M, Stud JWW.** Treatment of the premenstrual syndrome by subcutaneous oestradiol implants and cyclical oral norethisterone: a placebo controlled study. Br Med J 1986; 292:1629–1633.
31. **Watts JF, Butt WR, Edwards RL.** A clinical trial using danazol for the treatment of premenstrual tension. Br J Obstet Gynaecol 1987; 94:30–34.
32. **Freeman EW, Rickels K, Sonheimer SJ, Polansky M.** A double-blind trial of oral progesterone, alprazolam, and placebo in treatment of severe premenstrual syndrome. JAMA 1995; 274:51–57.
33. **Harrison WM, Endicott J, Nee J.** Treatment of premenstrual dysphoria with alprazolam: a controlled study. Arch Gen Psychiatry 1990; 47:270–275.
34. **Smith S, Rinehart JS, Ruddock VE, Schiff I.** Treatment of premenstrual syndrome with alprazolam: results of a double-blind, placebo-controlled, randomized crossover clinical trial. Obstet Gynecol 1987; 70:37–43.
35. **Rickels K, Freeman E, Sondheimer S.** Buspirone in treatment of premenstrual syndrome (letter). Lancet 1989;4:777.
36. **Yonkers K, Halbreich U, Freeman E, et al.** Symptomatic improvement of premenstrual dysphoric disorder with sertraline treatment. JAMA 1977; 278:983–988.
37. **Harrison WM, Endicott J, Nee J.** Treatment of premenstrual depression with nortriptyline: a pilot study. J Clin Psychiatry 1989; 50:136–139.
38. **Sundblad C, Modigh K, Andersch B, et al.** Clomipramine effectively reduces premenstrual irritability and dysphoria: a placebo-controlled trial. Acta Psychiatr Scand 1992; 85:39–47.
39. **Law note.** Premenstrual syndrome: a criminal defense. Notre Dame Law Review 1983; 58:253.

ADDRESS: *Lilian Gonsalves, MD, Department of Psychiatry and Psychology, P57, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.*

Oral contraceptives have been found useful in treating PMDD