



# Evidence-based tools for premenstrual disorders

A symptoms chart, an algorithm, and a treatment options resource are among the tools you'll find here to diagnose and treat premenstrual symptoms.

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*The authors reported no potential conflict of interest relevant to this article.*

## PRACTICE RECOMMENDATIONS

› Start calcium supplementation in all patients who report significant premenstrual symptoms. **A**

› Add a selective serotonin reuptake inhibitor (SSRI) to calcium supplementation for patients who have more severe premenstrual psychological symptoms. **A**

› Consider hormonal treatment options for patients who require treatment beyond calcium and an SSRI. **B**

› Provide nutrition and exercise information to all patients who report significant premenstrual symptoms. **C**

### Strength of recommendation (SOR)

- A** Good-quality patient-oriented evidence
- B** Inconsistent or limited-quality patient-oriented evidence
- C** Consensus, usual practice, opinion, disease-oriented evidence, case series

## CASE ►

A 30-year-old G2P2 woman presents for a well-woman visit and reports 6 months of premenstrual symptoms including irritability, depression, breast pain, and headaches. She is not taking any medications or hormonal contraceptives. She is sexually active and currently not interested in becoming pregnant. She asks what you can do for her symptoms, as they are affecting her life at home and at work.

## Symptoms and definitions vary

Although more than 150 premenstrual symptoms have been reported, the most common psychological and behavioral ones are mood swings, depression, anxiety, irritability, crying, social withdrawal, forgetfulness, and problems concentrating.<sup>1-3</sup> The most common physical symptoms are fatigue, abdominal bloating, weight gain, breast tenderness, acne, change in appetite or food cravings, edema, headache, and gastrointestinal upset. The etiology of these symptoms is usually multifactorial, with some combination of hormonal, neurotransmitter, lifestyle, environmental, and psychosocial factors playing a role.

■ **Premenstrual disorder.** In reviewing diagnostic criteria for the various premenstrual syndromes and disorders from different organizations (eg, the International Society for Premenstrual Disorders; the American College of Obstetricians and Gynecologists; the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*), there is agreement on the following criteria for premenstrual syndrome (PMS)<sup>4-6</sup>:

- The woman must be ovulating. (Women who no longer menstruate [eg, because of hysterectomy or endometrial ablation] can have premenstrual disorders as long as ovarian function remains intact.)
- The woman experiences a constellation of disabling physical and/or psychological symptoms that appears

**➤ Women who no longer menstruate can have premenstrual disorders as long as ovarian function remains intact.**

in the luteal phase of her menstrual cycle.

- The symptoms improve soon after the onset of menses.
- There is a symptom-free interval before ovulation.
- There is prospective documentation of symptoms for at least 2 consecutive cycles.
- The symptoms are sufficient in severity to affect activities of daily living and/or important relationships.

**■ Premenstrual dysphoric disorder.** PMDD is another common premenstrual disorder. It is distinguished by significant premenstrual psychological symptoms and requires the presence of marked affective lability, marked irritability or anger, markedly depressed mood, and/or marked anxiety (TABLE 1).<sup>7</sup>

**■ Exacerbation of other ailments.** Another premenstrual disorder is the premenstrual exacerbation of underlying chronic medical or psychological problems such as migraines, seizures, asthma, diabetes, irritable bowel syndrome, fibromyalgia, anxiety, or depression.

**Differences in interpretation lead to variations in prevalence**

Differences in the interpretation of significant premenstrual symptoms have led to variations in estimated prevalence. For example, 80% to 95% of women report premenstrual symptoms, but only 30% to 40% meet criteria for PMS and only 3% to 8% meet criteria for PMDD.<sup>8</sup> Many women who report premenstrual symptoms in a retrospective questionnaire do not meet criteria for PMS or PMDD based on prospective symptom charting. The Daily Record of Severity of Problems (DRSP), a prospective tracking tool for premenstrual symptoms, is sensitive and specific for diagnosing PMS and PMDD if administered on the first day of menstruation.<sup>9</sup>

**Ask about symptoms and use a tracking tool**

When you see a woman for a well-woman visit or a gynecologic problem, inquire about physical/emotional symptoms and their se-

verity during the week that precedes menstruation. If a patient reports few symptoms of a mild nature, then no further work-up is needed.

If patients report significant premenstrual symptoms, recommend the use of a tool to track the symptoms. Older tools such as the DRSP and the Premenstrual Symptoms Screening Tool (PSST), newer symptom diaries that can be used for both PMS and PMDD, and questionnaires that have been used in research situations can be time consuming and difficult for patients to complete.<sup>10-12</sup> Instead, physicians can easily construct their own charting tool, as we did for patients to use when tracking their most bothersome symptoms (FIGURE 1). Tracking helps to confirm the diagnosis and helps you and the patient focus on treatment goals.

Keep in mind other diagnoses (eg, anemia, thyroid disorders, perimenopause, anxiety, depression, eating disorders, substance abuse) that can cause or exacerbate the psychological/physical symptoms the patient is reporting. If you suspect any of these other diagnoses, laboratory evaluation (eg, complete blood count, thyroid-stimulating hormone level or other hormonal testing, urine drug screen, etc) may be warranted to rule out other etiologies for the reported symptoms.

**Develop a Tx plan that considers symptoms, family-planning needs**

Focus treatment on the patient's predominant symptoms whether they are physical, psychological, or mixed (FIGURE 2). The patient's preferences regarding family planning are another important consideration. Women who are using a fertility awareness-based method of family planning may not desire a contraceptive hormonal treatment for their premenstrual disorder. Also, patients may have cultural and/or religious beliefs that need to be respected.

Although the definitions for PMS and PMDD require at least 2 cycles of prospective documentation of symptoms, dietary and lifestyle changes can begin immediately. Regular follow-up to document improvement of symptoms is important; using the

TABLE 1

**DSM-5 criteria for premenstrual dysphoric disorder**

**A.** In the majority of menstrual cycles, at least 5 symptoms must be present in the final week before menses, start to improve within a few days after the onset of menses, and become minimal or absent in the week after menses.

**B.** One (or more) of the following symptoms must be present:

1. Marked affective lability (eg, mood swing, feeling suddenly sad or tearful, increased sensitivity to rejection)
2. Marked irritability/anger or increased interpersonal conflicts
3. Marked depressed mood, feelings of hopelessness, or self-deprecating thoughts
4. Marked anxiety, tension, and/or feelings of being keyed up or on edge

**C.** One (or more) of the following symptoms must additionally be present, to reach a total of 5 symptoms when combined with symptoms from Criterion B above:

1. Decreased interest in usual activities (eg, work, school, friends, hobbies)
2. Subjective difficulty concentrating
3. Lethargy, easy fatigability, or marked lack of energy
4. Marked change in appetite, overeating, or specific food cravings
5. Hypersomnia or insomnia
6. A sense of being overwhelmed or out of control
7. Physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of bloating, or weight gain

Note: The symptoms in Criteria A–C must have been met for most menstrual cycles that occurred in the preceding year.

Adapted from: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. 2013.<sup>7</sup>

patient's symptoms charting tool can help with this.

**Focus on diet and lifestyle right away**

Experts in the field of PMS/PMDD suggest that simple dietary changes may be a reasonable first step to help improve symptoms. Researchers have found that diets high in fiber, vegetables, and whole grains are inversely related to PMS.<sup>13</sup> Older studies have suggested an increased prevalence and severity of PMS with increased caffeine intake; however, a newer study found no such association.<sup>14</sup>

A case-control study nested within the Nurses' Health Study II cohort showed that a high intake of both dietary calcium and vitamin D prevented the development of PMS in women ages 27 to 44.<sup>15</sup> B vitamins, such as thiamine and riboflavin, from food sources have been associated with a lower risk of PMS.<sup>16</sup>

A variety of older clinical studies showed benefit from aerobic exercise on PMS symptoms,<sup>17-19</sup> but a newer cross-sectional study of young adult women found no association between physical activity and the prevalence

of PMS.<sup>20</sup> Acupuncture has demonstrated efficacy for the treatment of the physical symptoms of PMS and PMDD, but more rigorous studies are needed.<sup>21,22</sup> Cognitive behavioral therapy has been studied as a treatment, but data to support this approach are limited so it cannot be recommended at this time.<sup>23</sup>

**Make the most of supplements—especially calcium**

■ **Calcium** is the nutritional supplement with the most evidence to support its use to relieve symptoms of PMS and PMDD (TABLE 2<sup>21,22,24-45</sup>). Research indicates that disturbances in calcium regulation and calcium deficiency may be responsible for various premenstrual symptoms. One study showed that, compared with placebo, women who took 1200 mg/d calcium carbonate for 3 menstrual cycles had a 48% decrease in both somatic and affective symptoms.<sup>24</sup> Another trial demonstrated improvement in PMS symptoms of early tiredness, appetite changes, and depression with calcium therapy.<sup>25</sup>

■ **Pyridoxine (vitamin B6)** has potential



**Focus treatment on the patient's predominant symptoms, whether they are physical, psychological, or mixed.**

**FIGURE 1**  
**Premenstrual symptoms chart**

MONTH: \_\_\_\_\_

Indicate daily severity of symptoms:  
 0 = None/not applicable  
 1 = Mild; does not interfere with activities  
 2 = Moderate; interferes with activities but is not disabling  
 3 = Severe; disabling

Record menstrual flow using the following:																							
(Day 1 = first day of menstrual cycle)																							
Day of cycle	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Menstrual flow (H, M, L)																							
(H = heavy; M = medium; L = light)																							

Your symptoms that matter most. (List symptoms below and then rate the severity of each for each day of the cycle.)


benefit in treating PMS due to its ability to increase levels of serotonin, norepinephrine, histamine, dopamine, and taurine.<sup>26</sup> An older systematic review showed benefit for symptoms associated with PMS, but the authors concluded that larger randomized controlled trials (RCTs) were needed before definitive recommendations could be made.<sup>27</sup>

■ **Chasteberry.** A number of studies have evaluated the effect of vitex agnus castus (VAC), commonly referred to as chasteberry, on PMS and PMDD symptoms. The exact mechanism of VAC is unknown, but in vitro studies show binding of VAC extracts to dopamine-2 receptors and opioid receptors, and an affinity for estrogen receptors.<sup>28</sup>

A recent meta-analysis concluded that VAC extracts are not superior to selective serotonin reuptake inhibitors (SSRIs) or oral contraceptives (OCs) for PMS/PMDD.<sup>28</sup> The authors suggested a possible benefit of VAC compared with placebo or other nutritional supplements; however, the studies supporting its use are limited by small sample size and potential bias.

■ **Magnesium.** Many small studies have evaluated the role of other herbal and nutritional supplements for the treatment of PMS/PMDD. A systematic review of studies on the effect of magnesium supplementation on

anxiety and stress showed that magnesium may have a potential role in the treatment of the premenstrual symptom of anxiety.<sup>29</sup> Other studies have demonstrated a potential role in the treatment of premenstrual migraine.<sup>30,31</sup>

■ **Vitamin E** has demonstrated benefit in the treatment of cyclic mastalgia; however, evidence for using vitamin E for mood and depressive symptoms associated with PMS and PMDD is inconsistent.<sup>32-34</sup> Other studies involving vitamin D, St. John's wort, black cohosh, evening primrose oil, saffron, and ginkgo biloba either showed these agents to be nonefficacious in relieving PMS/PMDD symptoms or to require more data before they can be recommended for use.<sup>34,46</sup>

**Patient doesn't respond? Start an SSRI**

Pharmacotherapy with antidepressants is typically reserved for those who do not respond to nonpharmacologic therapies and are experiencing more moderate to severe symptoms of PMS or PMDD. Reduced levels of serotonin and serotonergic activity in the brain may be linked to symptoms of PMS and PMDD.<sup>47</sup> Studies have shown SSRIs to be effective in reducing many psychological symptoms (eg, depression, anxiety, lethargy, irritability) and some physical symptoms (eg, headache, breast tenderness, muscle or joint

	24	25	26	27	28	29	30	31	32	33	34	35			

pain) associated with PMS and PMDD.

A Cochrane review of 31 RCTs compared various SSRIs to placebo. When taken either continuously or intermittently (administration during luteal phase), SSRIs were similarly effective in relieving symptoms when compared with placebo.<sup>35</sup> Psychological symptoms are more likely to improve with both low and moderate doses of SSRIs, while physical symptoms may only improve with moderate or higher doses. A direct comparison of the various SSRIs for the treatment of PMS or PMDD is lacking; therefore, the selection of SSRI may be based on patient characteristics and preference.

The benefits of SSRIs are noted much earlier in the treatment of PMS/PMDD than they are observed in their use for depression or anxiety.<sup>36</sup> This suggests that the mechanism by which SSRIs relieve PMS/PMDD symptoms is different than that for depression or anxiety. Intermittent dosing capitalizes upon the rapid effect seen with these medications and the cyclical nature of these disorders. In most studies, the benefit of intermittent dosing is similar to continuous dosing; however, one meta-analysis did note that continuous dosing had a larger effect.<sup>37</sup>

The doses of SSRIs used in most PMS/PMDD trials were lower than those typically

used for the treatment of depression and anxiety. The withdrawal effect that can be seen with abrupt cessation of SSRIs has not been reported in the intermittent-dosing studies for PMS/PMDD.<sup>38</sup> While this might imply a more tolerable safety profile, the most common adverse effects reported in trials were still as expected: sleep disturbances, headache, nausea, and sexual dysfunction. It is important to note that SSRIs should be used with caution during pregnancy, and paroxetine should be avoided in women considering pregnancy in the near future.

**Other antidepressant classes** have been studied to a lesser extent than SSRIs. Continuously dosed venlafaxine, a serotonin and norepinephrine reuptake inhibitor, demonstrated efficacy in PMS/PMDD treatment when compared with placebo within the first cycle of therapy.<sup>39</sup> The response seen was comparable to that associated with SSRI treatments in other trials.

Buspirone, an anxiolytic with serotonin receptor activity that is different from that of the SSRIs, demonstrated efficacy in reducing the symptom of irritability.<sup>48</sup> Buspirone may have a role to play in those presenting with irritability as a primary symptom or in those who are unable to tolerate the adverse effects of SSRIs. Tricyclic antidepressants, bupropion, and alprazolam have either limited data regarding efficacy or are associated with adverse effects that limit their use.<sup>38</sup>

### Hormonal treatments may be worth considering

One commonly prescribed hormonal therapy for PMS and PMDD is continuous OCs. A 2012 Cochrane review of OCs containing drospirenone evaluated 5 trials and a total of 1920 women.<sup>40</sup> Two placebo-controlled trials of women with severe premenstrual symptoms (PMDD) showed improvement after 3 months of taking daily drospirenone 3 mg with ethinyl estradiol 20 mcg, compared with placebo.

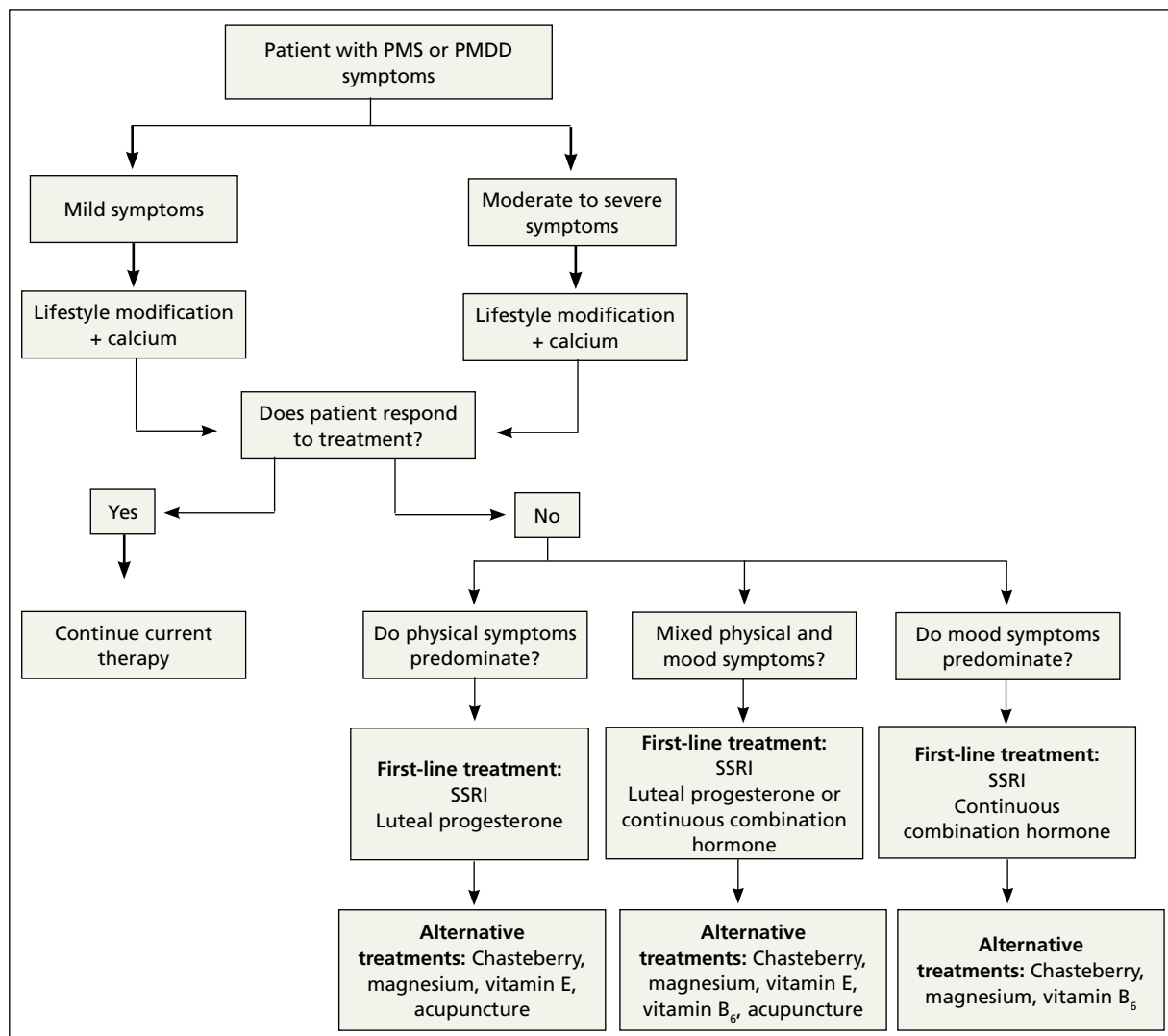
While experiencing greater benefit, these groups also experienced significantly more adverse effects including nausea, intermenstrual bleeding, and breast pain. The respective odds ratios for the 3 adverse effects were 3.15 (95% confidence interval [CI], 1.90-5.22), 4.92 (95% CI, 3.03-7.96), and 2.67 (95% CI, 1.50-



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FIGURE 2

## Treatment algorithm for premenstrual disorders and symptoms



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

4.78). The review concluded that drospirenone 3 mg with ethinyl estradiol 20 mcg may help in the treatment of severe premenstrual symptoms (PMDD) but that it is unknown whether this treatment is appropriate for patients with less severe premenstrual symptoms.

■ **Another multicenter RCT** evaluated women with PMDD who received levonorgestrel 90 mcg with ethinyl estradiol 20 mcg or placebo daily for 112 days.<sup>41</sup> Symptoms were recorded utilizing the DRSP. Significantly more women taking the daily combi-

nation hormone (52%) than placebo (40%) had a positive response ( $\geq 50\%$  improvement in the DRSP 7-day late luteal phase score and Clinical Impression of Severity score of  $\geq 1$  improvement, evaluated at the last “on-therapy” cycle [ $P = .025$ ]). Twenty-three of 186 patients in the treatment arm dropped out because of adverse effects.

■ **Noncontraceptive estrogen-containing preparations.** Hormone therapy preparations containing lower doses of estrogen than seen in OC preparations have also been studied

TABLE 2

## Nutritional supplements, antidepressants, and hormonal treatments for PMS and PMDD symptoms

Drug	Dose	Adverse effects	Symptoms targeted	SOR
<b>NUTRITIONAL AND HERBAL SUPPLEMENTS</b>				
Calcium <sup>24,25</sup>	1200 mg/d	Constipation Nausea Renal stones (doses > 2500 mg/d)	Mood symptoms, breast tenderness, bloating/swelling, pain, headache, food cravings	A
Vitamin B <sub>6</sub> <sup>26,27</sup>	50-100 mg/d	Neurotoxicity (doses > 200 mg/d) Neuropathy	Psychological	C
VAC or Chasteberry <sup>28</sup>	Extract: 20-40 mg/d <sup>a</sup> Capsules: 200-400 mg/d <sup>a</sup>	Nausea/vomiting Headache Bloating	Breast tenderness, headache, irritability, anger, mood swings	C
Vitamin E <sup>32-34</sup>	150-400 IU/d	No significant adverse effects	Psychological and physical, mastalgia	C
Magnesium <sup>29-31</sup>	200-400 mg/d during luteal phase of cycle	Diarrhea	Anxiety, somatic pain, premenstrual migraine	C
<b>OTHER</b>				
Acupuncture <sup>21,22</sup>		None	Physical symptoms	C
<b>ANTIDEPRESSANTS (can be given continuously throughout cycle or just during luteal phase)<sup>35-39</sup></b>				
Citalopram	10-30 mg/d	Anxiety	Psychological	B
Escitalopram	10-20 mg/d	Nausea Sleep disturbance	Psychological	B
Fluoxetine <sup>b</sup>	10-20 mg/d	Headache Sexual dysfunction	Psychological and physical	A
Paroxetine CR <sup>b,c</sup>	12.5-25 mg/d		Psychological and physical	A
Sertraline <sup>b</sup>	50-150 mg/d		Psychological and physical	A
Venlafaxine	50-200 mg/d	Anxiety Nausea Insomnia Dizziness Headache Sexual dysfunction	Psychological and physical	B

CONTINUED

for PMS management. A 2017 Cochrane review of noncontraceptive estrogen-containing preparations found very low-quality evidence to support the effectiveness of continuous estrogen (transdermal patches or subcutaneous implants) plus progesterone.<sup>49</sup>

■ **Progesterone.** The cyclic use of pro-

gesterone in the luteal phase has been reviewed as a hormonal treatment for PMS. A 2012 Cochrane review of the efficacy of progesterone for PMS was inconclusive; however, route of administration, dose, and duration differed across studies.<sup>42</sup>

Another systematic review of 10 trials



TABLE 2

## Nutritional supplements, antidepressants, and hormonal treatments for PMS and PMDD symptoms (*cont'd*)

Drug	Dose	Adverse effects	Symptoms targeted	SOR
<b>HORMONAL</b>				
Continuous oral contraceptive	3 mg drospirenone/20 mcg ethinyl estradiol daily <sup>40</sup>	Intermenstrual bleeding Nausea Breast pain	Psychological	B
	90 mcg levonorgestrel/20 mcg ethinyl estradiol daily <sup>41</sup>	Intermenstrual bleeding Nausea Headache Mood swings	Psychological and physical	B
Progesterone <sup>42-45</sup>	200-300 mg/d oral <sup>d</sup> 300 mg/d vaginal <sup>d</sup>	Drowsiness	Psychological and physical	C

FDA, Food and Drug Administration; PMDD, premenstrual dysphoric disorder; PMS, premenstrual syndrome; SOR, strength of recommendation; VAC, vitex agnus castus.

<sup>a</sup>Studied and effective in both continuous and luteal phase dosing.

<sup>b</sup>FDA indication for PMDD.

<sup>c</sup>Should be avoided in pregnancy.

<sup>d</sup>Nightly for 10 days, beginning on Day 3 after ovulation.

involving 531 women concluded that progesterone was no better than placebo in the treatment of PMS.<sup>43</sup> However, it should be noted that each trial evaluated a different dose of progesterone, and all but 1 of the trials administered progesterone by using the calendar method to predict the beginning of the luteal phase. The only trial to use an objective confirmation of ovulation prior to beginning progesterone therapy did demonstrate significant improvement in premenstrual symptoms.

This 1985 study by Dennerstein et al<sup>44</sup> prescribed progesterone for 10 days of each menstrual cycle starting 3 days after ovulation. In each cycle, ovulation was confirmed by determinations of urinary 24-hour pregnanediol and total estrogen concentrations. Progesterone was then prescribed during the objectively identified luteal phase, resulting in significant improvement in symptoms.

Another study evaluated the post-ovulatory progesterone profiles of 77 women with symptoms of PMS and found lower levels of progesterone and a sharper rate of decline in the women with PMS vs the control group.<sup>45</sup> Subsequent progesterone treatment during

the objectively identified luteal phase significantly improved PMS symptoms. These studies would seem to suggest that progesterone replacement when administered during an objectively identified luteal phase may offer some benefit in the treatment of PMS, but larger RCTs are needed to confirm this.

### CASE ►

You provide the patient with diet and lifestyle education as well as a recommendation for calcium supplementation. The patient agrees to prospectively chart her most significant premenstrual symptoms. You review additional treatment options including SSRI medications and hormonal approaches. She is using a fertility awareness–based method of family planning that allows her to confidently identify her luteal phase. She agrees to take sertraline 50 mg/d during the luteal phase of her cycle. At her follow-up office visit 3 months later, she reports improvement in her premenstrual symptoms. Her charting of symptoms confirms this. **JFP**


### CORRESPONDENCE

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 The benefits of SSRIs are noted much earlier in the treatment of PMS/PMDD than they are observed in their use for depression or anxiety.