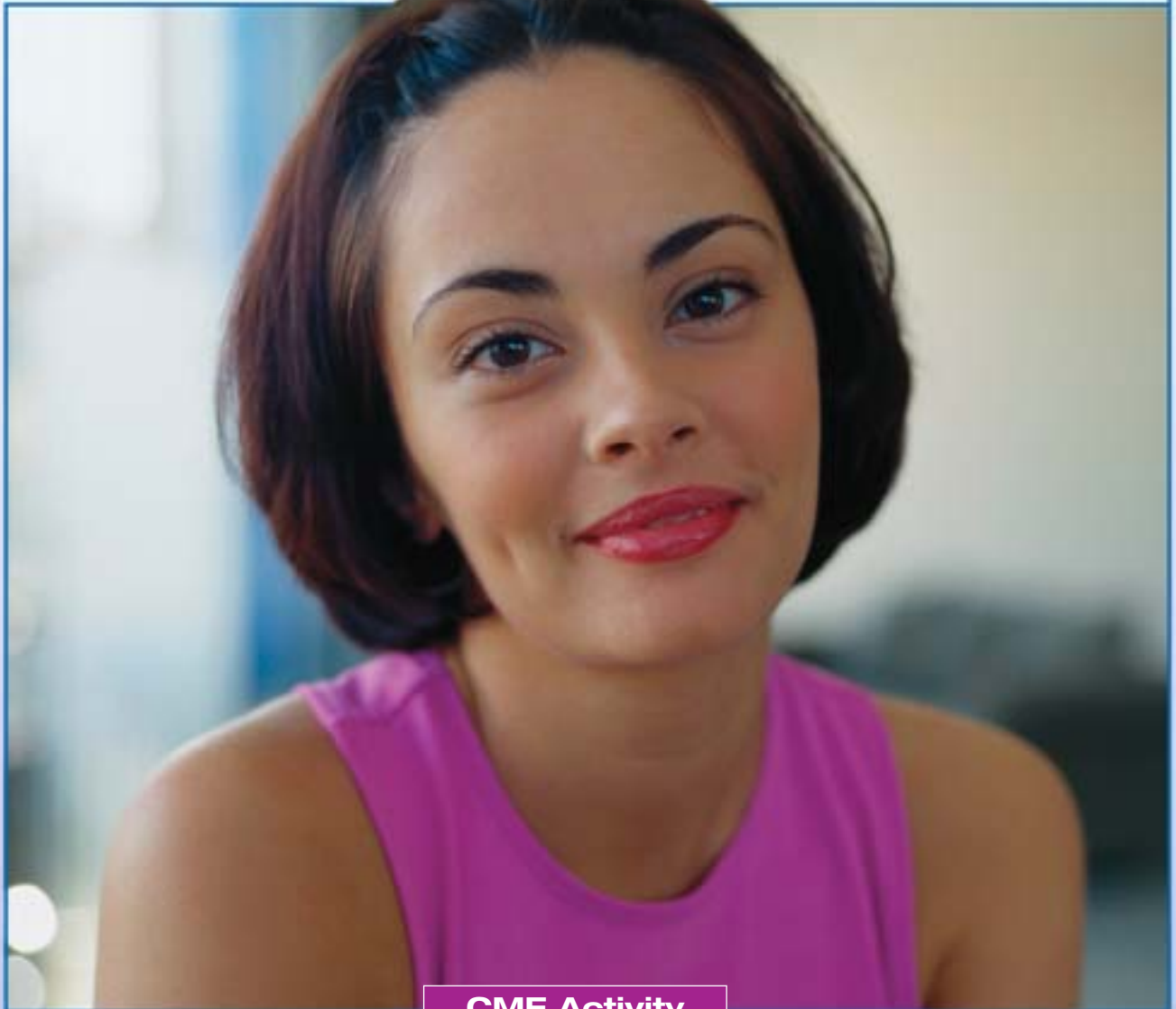


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CME Activity

## PMS/PMDD and Quality of Life: Advances in Management

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**Andrea J. Rapkin, MD**, receives grants and research support from Berlex Laboratories and is a consultant for Barr Laboratories. She serves on the Speakers Bureaus for Eli Lilly, Berlex Laboratories, and Wyeth-Ayerst Pharmaceuticals.

**Vivian M. Dickerson, MD, FACOG**, is on the scientific advisory board for Eli Lilly, Pfizer Pharmaceuticals, Berlex Laboratories, and Ortho-McNeil. She also serves on the Speakers Bureaus for Eli Lilly, Wyeth-Ayerst Pharmaceuticals, Ortho-McNeil, Berlex Laboratories, Parke-Davis Pharmaceuticals, and TAP Pharmaceuticals. She also receives research support from Ortho-Biotech.

## Program Audience

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This program is designated for the obstetrician/gynecologist.

## Educational Objectives

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After reviewing this material, the physician should be able to:

- Describe the symptoms associated with PMS/PMDD.
- List the pharmacologic and nonpharmacologic therapies available for PMS/PMDD.
- Understand the pharmacokinetics of a drospirenone-containing OC.
- Identify patients for whom a drospirenone-containing OC would be most appropriate.

# FOREWORD



**Vivian M. Dickerson,  
MD, FACOG**

**P**remenstrual Syndrome (PMS) is an ambiguous term that has had numerous iterations historically. While the “necessary” criteria are only that the symptoms occur during the luteal phase, strict criteria “sufficient” to make the diagnosis are still lacking. The criteria for diagnosing Premenstrual Dysphoric Disorder (PMDD), on the other hand, are systematically laid out in the index of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*. In reality, however, the diagnostic criteria are interpreted variably in clinical practice. To further complicate the issue, most authorities on the subject currently believe that there is a continuum from premenstrual symptoms through PMS to PMDD.<sup>1,2</sup>

While it is an oversimplification to believe that PMS represents predominantly physical symptoms while PMDD is a more severe form, representing predominantly psychological or emotional symptoms, the everyday reality in the clinician’s office is not nearly so clear-cut.

It is a fact that there are a paucity of standardized clinical criteria for PMS/PMDD. It is for this reason that many women do not seek medical therapy for their symptoms and why many clinicians are uncomfortable diagnosing and treating patients with PMS/PMDD. When the symptoms are addressed at all, or if a diagnosis is entertained, it is at the behest of the patient, who often is more informed than her caregiver. This is not surprising given the dearth of proven therapies and the variation in presentation of the problem(s). The prevalence of either syndrome is unclear and the degree of impairment extremely variable. For example, the reported variation of clinical symptoms consistent with PMS ranges from 40% to 90% depending on the criteria, the population, the instrument used for data collection, and the retrospective or prospective nature of the analysis.<sup>3</sup> Furthermore, no laboratory tests are currently able to make the diagnosis or to suggest the pathophysiology involved. All of this leads to frustration for both the patient and her health-care provider.

In an attempt to bring clarity in diagnosis and a methodical approach to treatment, the goals of this monograph are to:

1. Address pertinent clinical issues for the patient presenting with symptoms related to the menstrual cycle;
2. Assist the clinician in establishing an appropriate diagnosis;
3. Offer treatment options for the patient who has been diagnosed with PMS or PMDD;
4. Emphasize the clinical relevance of premenstrual symptomatology;
5. Identify areas in which further clinical research is needed.

Our panel of three experts elucidates the salient issues in the diagnosis of PMS/PMDD. We further evaluate the impact on women suffering from either symptom complex and present possible modalities for treatment. Finally, we explore “quality of life” issues that relate to menstrual cycle symptoms and present some exciting data on a new therapeutic modality that may address some of these symptoms.

I hope that you will keep our goals in mind as you read this supplement. All of us who care for patients in the clinical setting must take a more proactive role in diagnosis and management of the patient with PMS/PMDD. This will necessitate an understanding of the principles of diagnosis and the alternatives for therapy. It also requires an open mind and an ongoing desire to seek out new research and to try new therapeutic modalities that may be helpful in management. While it may be uncomfortable, in this era of evidence-based medicine, to tread on ground not thoroughly “solidified” by rock-hard data, it is clearly a patient imperative and one that the clinician can no longer ignore.

A handwritten signature in black ink that reads "V M Dickerson MD". The signature is written in a cursive, flowing style.

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# PMS and PMDD: The diagnostic spectrum

By Vivian M. Dickerson, MD, FACOG

*Because many women with PMS or PMDD do not seek or receive treatment, clinicians must take the lead in making the diagnosis and recommending therapy where appropriate. Understanding the diagnostic spectrum and criteria is key.*

**P**remenstrual syndrome (PMS) is characterized by a constellation of cyclic and recurrent symptoms that occur during the luteal phase of the menstrual cycle. Despite broad recognition of this entity on the part of medical professionals, it continues to defy concrete characterization and the exact etiology remains unclear. Premenstrual dysphoric disorder (PMDD), a related condition, has been concretely defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*, but has only recently emerged as a well-recognized clinical entity.<sup>1</sup> The two conditions may overlap significantly, but the latter emphasizes problems of mood and the symptoms are generally more severe. In both PMS and PMDD, the symptoms are virtually nonexistent in the follicular phase of the menstrual cycle, begin at varying points after ovulation, peak in the late luteal phase, and resolve with the onset of menses or shortly thereafter.

## Historical perspective

Premenstrual signs and symptoms have been a part of menstrual taboos in many ancient and modern cultures. In many settings the menstrual period and associated symptoms are viewed as “possession,” witchcraft, or “the curse.” Women are often segregated or untouchable during this time of the month. Numerous behavioral injunctions are also imposed, such as avoidance of sexual activity, exercise, cooking, cold air, or certain types of foods. The clear message was that the perimenstrual and menstrual events are to be feared and avoided, and are definitely not normal. Hippocrates addressed premenstrual syndrome and called it the “sickness of virgins.” He also ascribed a number of cognitive and behavioral symptoms, including delusions and mania, to “retained menstrual blood.” Later iterations of these

fears include the modern mythology that women are inherently more labile than men, that they are perhaps unsuitable for certain jobs due to premenstrual instability, or that the whole thing is all in their heads and that they are merely neurotic. It is small wonder that scientific understanding and investigation of PMS/PMDD have been limited until very recently.

In 1931, Robert T. Frank published an article designating a combination of physical and affective changes that occurred premenstrually as “Premenstrual Tension”.<sup>2</sup> Dr. Frank attributed his findings to low renal excretion of estrogen and suggested treating with x-ray to “tone” the ovaries. Greene and Dalton first used the term “premenstrual syndrome” in 1953.<sup>3</sup> The term was quickly abbreviated to PMS, and it became widely recognized among practitioners and health-care providers. The subsequent evolving disagreement over diagnostic criteria and effective therapeutic modalities hampered understanding of the syndrome over the next 40 years.

On the other hand, in 1987 the DSM-III published established broad criteria for “Late Luteal Phase Dysphoric Disorder” (LLPDD) and suggested that further research in this area was warranted.<sup>4</sup> In 1994, the DSM-IV created a tight definition for PMDD, which was considered as a “depressive disorder not otherwise specified.”<sup>1</sup> The past decade has seen a plethora of studies addressing therapy and diagnosis. While significant progress has been made in these areas, to date the pathophysiology of PMS and PMDD has not been elucidated. Currently it is accepted that PMS/PMDD and premenstrual symptoms represent a continuum of diagnosis (Figure 1).

## Definitions

**Premenstrual symptoms.** Most regularly cycling women experience some degree of symptomatology prior to the onset of the menstrual period. These symptoms are also known as molimina and may

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Dr. Dickerson is Associate Professor and Director, Division of General Obstetrics and Gynecology, University of California, Irvine.

include a variety of mild, often physical symptoms. In fact, there are over 100 physical, behavioral, and emotional symptoms that may mark the end of the luteal phase of the cycle (Table 1). The important element that distinguishes premenstrual symptoms from PMS and PMDD is the fact that these symptoms do not interfere with daily functioning either at home or at work and are considered to be a normal sign of ovulatory cycles.

**Premenstrual syndrome.** This term is used to describe a poorly defined syndrome. There may be only one symptom or a combination of physical, affective, and behavioral symptoms. It is unclear if functional impairment is necessary and if prospective recording is required. Many researchers have found this description inadequate in differentiating PMS from premenstrual symptoms.<sup>5</sup> A more appropriate definition might address the place of PMS in a continuum by identifying PMS as cyclic symptoms severe enough to interfere with some aspects of life and occurring up to 2 weeks prior to the menstrual period.<sup>6</sup> Indeed, even the prevalence of PMS cannot be accurately ascertained due to the lack of consistent research criteria: It is thought that between 11% and 32% of reproductive-age women suffer from PMS.

**Premenstrual dysphoric disorder.** The diagnosis of PMDD requires prospective documentation of symptoms for at least two consecutive cycles, functional impairment in activities of daily living, presence during most cycles, and at least 5 of 11 symptoms including at least one mood symptom. Impairment may be severe. Indeed, Yonkers and colleagues found that interference with functioning is not statistically significantly different between patients with PMDD and those with diagnosed depression.<sup>7</sup> This diagnosis pertains to approximately 4% of menstruating women.

**Premenstrual exacerbation.** Also known as menstrual exacerbation, this is a descriptive term addressing the fact that some medical disorders may become

more active or worse during the premenstrual phase of the cycle. The most common of these disorders are depression, migraines, irritable bowel syndrome, seizure disorders, asthma, chronic fatigue syndrome, and allergies.<sup>8</sup>

### Diagnostic criteria

**Premenstrual syndrome.** PMS is a symptom or constellation of symptoms that do not fit the DSM-IV criteria for PMDD. The *Tenth Revision of the International Classification of Diseases (ICD-10)* requires the presence of only one cyclic symptom without prospective charting or functional impairment.

FIGURE 1

### Symptom severity

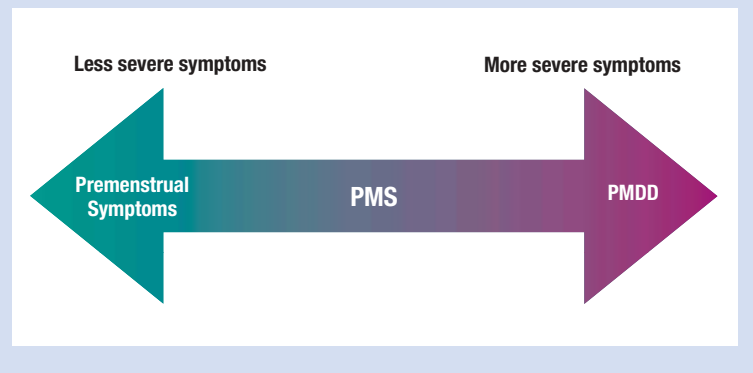


TABLE 1

### Premenstrual symptoms

Physical	Behavioral	Emotional
Headache, migraines	Food cravings	Irritability
Backache	↓ interest in usual activities	Sadness, depression
Abdominal cramps	Wanting to be alone	Tearfulness
Bloating, weight gain	Poor concentration	Anxiety, nervousness, panic
Breast tenderness	Clumsiness	Unpleasant, unwanted thoughts
Hot flashes	Difficulty making decisions	Oversensitivity
General malaise and fatigue	Slow, muddled thinking	Feeling overwhelmed
Diarrhea, constipation	Poor judgment	Anger, rage, hostility
Palpitations	↑ Appetite	Confusion
Nausea, lack of appetite		Forgetfulness
Skin changes, acne		Low self-esteem
Swelling of ankles, hands, feet		Paranoia
Muscle spasms		Insomnia
		Moodiness
		Sleep disturbances

TABLE 2

**ACOG diagnostic criteria for PMS****Affective symptoms**

Depression  
 Anger  
 Irritability  
 Anxiety  
 Confusion  
 Social withdrawal

**Somatic symptoms**

Breast tenderness  
 Abdominal bloating  
 Headache  
 Swelling of extremities

PMS can be diagnosed if the patient reports at least one of these symptoms during the 5 days before menses in three consecutive cycles

TABLE 3

**DSM-IV diagnostic criteria for PMDD**

5 of the following symptoms must occur during the week before menses and remit a few days after onset of menses	<b>At least one must be</b>	<ul style="list-style-type: none"> <li>• Irritability</li> <li>• Affective lability (sudden mood swings)</li> </ul>	<ul style="list-style-type: none"> <li>• Depressed mood or hopelessness</li> <li>• Tension or anxiety</li> </ul>
	<b>Along with any combination of</b>	<ul style="list-style-type: none"> <li>• Decreased interest in activities</li> <li>• Difficulty concentrating</li> <li>• Lack of energy</li> <li>• Change in appetite, e.g., food cravings</li> </ul>	<ul style="list-style-type: none"> <li>• Change in sleep</li> <li>• Feeling out of control or overwhelmed</li> <li>• Other physical symptoms, e.g., breast tenderness, bloating</li> </ul>
	Symptoms markedly interfere with work, school, usual activities or relationships Symptoms must not be merely an exacerbation of another disorder All criteria should be confirmed for at least 2 consecutive menstrual cycles		
<b>Candidate for PMDD Treatment</b>			

APA. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington DC: American Psychiatric Assoc; 1994

Symptoms that are included in the ICD-10 are mild psychological discomfort, bloating/weight gain, breast tenderness, swelling of hands or feet, aches and pains, poor concentration, sleep disturbance, or change in appetite. The American College of Obstetricians and Gynecologists (ACOG) adapted criteria from Mortola and colleagues further refining diagnosis by suggesting that one or more symptoms be present at least 5 days before menses in each of three prior menstrual cycles.<sup>9</sup> Symptoms may be either somatic or affective as outlined in Table 2. Symptoms must be present in the absence of any pharmacologic therapy, hormone ingestion, or drug or alcohol use. Identifiable dysfunction is required as is prospective recording during at least two menstrual cycles. The inclusion of dysfunction in the diagnostic criteria has a basis in the literature. In 2000, Robinson and Swindle surveyed a random sample of women ages 18 to 49 experiencing regular menstrual cycles. They found significant interference with work/school, household activities, relationships with family, and social life.<sup>10</sup> While the impairment seen with PMDD was more severe across all categories, 10% to 35% of women with PMS

responded positively to each category (Figure 2).

**Premenstrual dysphoric disorder.** The specific DSM-IV criteria are presented in Table 3. There are several important aspects to this diagnostic tool. First, patients presenting with only physical symptoms, no matter how severe, do not qualify. Indeed, no single symptom is adequate to diagnose PMDD. Because of the emphasis on a symptom complex and, more importantly, an affective symptom complex, research has tended to focus on this aspect of PMDD. Research in this area has been facilitated by the precise delineation of symptoms as well as the requirement for prospective calendaring.

### Diagnostic tools

It is clear that the diagnosis of PMS/PMDD is difficult. In addition to the variability of criteria, there is the issue of differential diagnoses. A number of physical and psychiatric disorders may be mistaken for PMS/PMDD (Table 4). One must of course also exclude premenstrual exacerbation of under-

lying disorders as previously described. In order to aid the clinician and to make the diagnosis accurately, a number of validated tools have been created, which are to be used as an adjuvant to a careful history and physical examination. Among these are the Calendar of Premenstrual Experiences (COPE), the Daily Rating Form (DRF), the Menstrual Distress Questionnaire (MDQ), and the Premenstrual Symptom Diary (PMSD). Patients must fill out one of these “calendars” for 2 or preferably 3 months consecutively. The fact that symptoms are prominent only during the late luteal phase is clear from even cursory examination. Premenstrual exacerbation would show the presence of symptoms all month long, although they might be more prominent during the luteal phase. Noncyclic disorders would demonstrate a random pattern. If there is still doubt as to the diagnosis, other instruments such as the Beck’s Depression Scale may assist in ruling out an underlying disorder.

The pros and cons of prospective recording, particularly in the case of PMS where it has not been strictly required, are numerous. Reasons for using prospective recording include obtaining an

accurate diagnosis, avoiding missing more severe diagnoses, creating an opportunity for patient involvement, encouraging patient compliance, and assessing prescription effectiveness. Reasons for not recording prospectively include the fact that it is time-consuming for the patient and perhaps the clinician, that it might convey lack of empathy, and that it would delay interventions. It is apparent that consistent use of such recordings would create more appropriate information for scientific research.

### Pathophysiology

While a definitive etiology of PMS/PMDD has not been determined, there is much that has been learned since the time when it was attributed to retained menstrual blood, sodium retention, or low renal excretion of estrogen. Due to the cyclic nature of the symptoms, it was natural to presume that there was somehow a difference in circulating sex steroids. Multiple studies on this subject have refuted this hypothesis.<sup>11</sup> Many other hormones, including adrenocorticotropic hormone, cortisol, and beta-endorphin, have been found to be unchanged. The early progesterone hypothesis may have, in part, led to a recent discovery that allopregnanolone metabolism may be involved in PMS symptomatology.<sup>12</sup>

Allopregnanolone is a progesterone metabolite that interacts with the gamma-aminobutyric acid (GABA) pathway in the brain. As seen in a 1997 study, a deficiency of allopregnanolone could increase anxiety in PMS patients via this pathway.<sup>13</sup>

Any role of genetic and sociocultural factors remains unclear. While PMS appears to exist across cultures and across time, the symptom clusters vary between cultures.<sup>14</sup> Twin studies have suggested that there is an inherited component to the existence and severity of premenstrual symptomatology.<sup>15</sup>

The role of the neuroendocrine system in PMS/PMDD has focused on the serotonergic system. However, numerous neurotransmitters exert their influence on the menstrual/reproductive cycle via the hypothalamus. These include norepinephrine, corticotropin, endorphins and opiates, dopamine, and GABA.<sup>13,16,17</sup> The overall conclusions

TABLE 4

### Differential diagnoses

#### Physical disorders

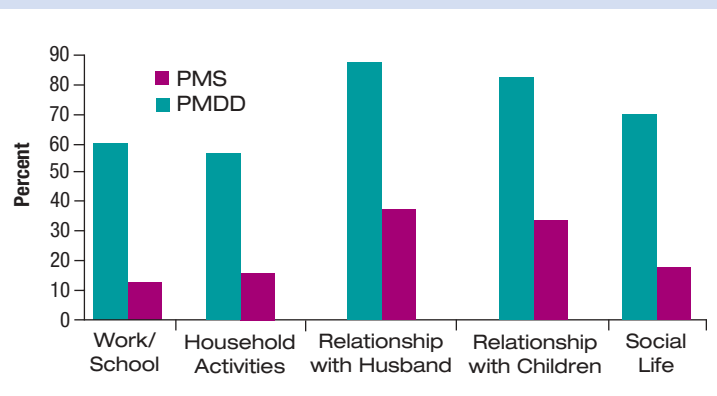
Anemia  
Autoimmune disorders  
Thyroid disease  
Eating disorders  
Diabetes  
Seizure disorders  
Endometriosis  
Chronic fatigue syndrome  
Collagen vascular diseases  
Perimenopause  
Hypokalemia

#### Psychiatric disorders

Major depression  
Dysthymia  
Generalized anxiety  
Panic disorders  
Bipolar illness  
Personality disorders  
Somatoform disorders  
Substance abuse

FIGURE 2

### Interference due to premenstrual symptoms



Robinson RL and Swindle RW. *J Womens Health Gen Based Med*. 2000;9:757-768.

from the myriad of studies on these neurotransmitters are that the nervous systems of patients with PMS metabolize steroids differently and/or that the sensitivity of the central nervous system may be altered and therefore react differently when exposed to sex steroids.

### To treat or not to treat?

It is apparent based on the demographic data presented that many women do not seek or receive treatment for PMS/PMDD. Hylan and colleagues elucidated some of the reasons that women fail to seek treatment.<sup>18</sup> In their study, only 26% of women sought treatment. The others felt that their symptoms were not severe enough (60%), just part of being a woman (7%), not treatable (12%), or treatable by nonmedical means (12%). Of the patients who

sought treatment, 45% had severe symptoms. Another group of authors reported that only 15.7% of eligible women have ever been or are currently being treated for PMS.<sup>10</sup> Fifty-three percent of the patients in their study first reported their symptoms during an appointment made for another purpose. Seventy-one percent of the patients were seen by their

gynecologist for that appointment and 72.5% received a prescription medication for their symptoms. The issues raised in this article regarding reporting, documentation, diagnosis, and treatment indicate the need for additional research on the part of scientists and rigorous attention on the part of clinicians.

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# Treatment of women with PMDD and PMS

By Andrea J. Rapkin, MD

*A variety of treatment strategies can benefit women suffering from PMDD and PMS, but clinicians must be certain of the diagnosis before initiating pharmacologic therapy. Several interim approaches, however, may benefit the patient during the 2-month symptom charting period required to confirm the diagnosis.*

When a patient presents with complaints suggesting premenstrual dysphoric disorder (PMDD) or severe premenstrual syndrome (PMS), the first visit should focus on a complete history and

physical examination, to help exclude other somatic and psychiatric diagnoses.<sup>1,2</sup> If a physical disorder is suspected, a complete medical work-up is indicated, and PMDD should not be confirmed or treated until any related abnormality has been managed. PMDD may be confused with a number of other disorders because of its wide range of symp-

Dr. Rapkin is Professor of Obstetrics and Gynecology and Director of the Pelvic Pain Clinic, University of California, Los Angeles.

toms and also because certain medical conditions may be exacerbated during the luteal phase of the menstrual cycle.<sup>3</sup> Once those possibilities have been ruled out, a diagnosis of PMDD or PMS requires confirmation of luteal-phase timing and cyclicity of symptomatology by prospective daily recording for at least two menstrual cycles.

### Tracking symptoms

Nightly recording of the patient's subjective recounting of symptoms is essential to establish the cyclical nature of the complaints. Patients should be instructed how to chart their symptoms throughout at least two successive menstrual cycles (Figure 1). The diaries can help differentiate between PMDD and other psychological and medical conditions.

When the woman returns with her charts, dividing them into three phases—premenstrual, menstrual, and postmenstrual—can help show the temporal relationship between symptoms and menses. The most important differentiating feature in the patient with PMDD is a clear, symptom-free interval during the follicular phase, from the end of the menstrual cycle until ovulation. Severe PMS and PMDD are by definition disabling syndromes that interfere with work, social relationships, or both; they are not merely an annoyance to the patient. Mild premenstrual symptoms, so-called moliminal symptoms, are not consistent with a diagnosis of PMDD.

The initial office visit should also include a brief overview of the etiology of and diagnostic and therapeutic approaches to the disorder. A patient is less likely to leave the clinician's office feeling frustrated and dissatisfied if she understands the rationale behind the diagnostic modalities (i.e., prospective recording). The importance of the diary is supported by evidence that the correlation between retrospective recall of symptoms and prospective diary recording is only approximately 50%. Furthermore, some of the disorders that may masquerade as severe PMS/PMDD are treated differently.<sup>4,5</sup> In fact, certain disorders, such as bipolar mood disorder, are exacerbated by the selective serotonin reuptake inhibitors (SSRIs) that are often used to treat PMDD. Some medications used to treat PMDD are contraindicated in pregnancy and many pregnancies are unplanned. Therefore, it is reasonable during prospective screening to begin with nonpharmacologic measures.

TABLE 1

### Therapeutic measures after initial evaluation

Patient education
Lifestyle changes – stress reduction, social support, dietary changes, exercise
*Calcium carbonate
Relaxation training
Cognitive behavioral or biofeedback therapy
*L-tryptophan premenstrually
Nonsteroidal anti-inflammatory drugs
Vitamin B <sub>6</sub>
*Magnesium

\*Randomized controlled trial suggesting efficacy for PMS/PMDD.

### Interim therapies

Given that women presenting with complaints of PMDD will leave the office after the initial visit without a definitive diagnosis, it is crucial both for the therapeutic relationship and for patient compliance to provide treatment recommendations that can be followed during the 2 months of prospective diary recording (Table 1). The pharmacologic approaches discussed in this review have demonstrated vigorous study design in which subjects were selected on the basis of prospective charting of symptoms and exclusion of underlying affective disorder and were randomized in a double-blind fashion to treatment or placebo. Only a few of the nonpharmacologic measures—lifestyle changes or over-the-counter (OTC) products—have been subjected to placebo-controlled trials for relief of PMDD. Still, they can contribute to general health, are not associated with harmful side effects, and give the patient a sense that she is taking positive action beyond charting her symptoms.

Nonpharmacologic or OTC treatments include lifestyle changes, dietary additives or modifications, aerobic exercise, stress reduction or relaxation techniques, psychological interventions, and nonsteroidal anti-inflammatory agents. Lifestyle modifications include avoidance of stressful situations, education of family members about PMDD symptoms to generate social support, and nutritional recommendations, such as avoiding caffeine (which may be anxiety-provoking) and decreasing consumption of alcohol (which may be a depressant).<sup>6,7</sup> Other dietary changes, such as incorporating a carbohydrate drink that promotes the transport of the amino acid tryptophan across the blood-brain barrier, may be useful for PMS.<sup>8,9</sup>

FIGURE 1

Sample menstrual symptom chart

Symptoms	Date (circle days of your period)																															
	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	
Depression																																
Anxiety, tension																																
Mood swings																																
Irritable, angry																																
Decreased interest in usual activities																																
Trouble concentrating																																
Lack of energy, tire easily																																
Overeating, food cravings																																
Insomnia or sleeping too much																																
Feeling overwhelmed or out of control																																
Physical symptoms (breast pain or swelling, headache, bloating, etc.)																																
Other _____																																

A number of validated tools are available for recording menstrual symptoms, including the Calendar of Premenstrual Experiences (COPE), Daily Rating Form (DRF), Menstrual Distress Questionnaire (MDQ), or Premenstrual Symptom Diary (PMSD). A simple chart, listing the days of the cycle across the top and a list of symptoms along the side, can be customized according to the patient's primary complaints. Patients should circle the days of menses, and nightly rank the occurrence of each symptom on a scale of 0 (no occurrence) to 3 (severe).

For a larger version of this chart that can be downloaded for patient use, visit [www.contemporaryobgyn.net](http://www.contemporaryobgyn.net), look for the "online cme/ce" button, and then "PMS/PMDD and Quality of Life: Advances in Management."

Calcium 1,200 mg per day in divided doses, vitamin E 400 units per day, magnesium, and vitamin B<sub>6</sub> not more than 50 mg per day may be useful to treat the symptoms of PMS/PMDD and/or provide other health benefits.<sup>10-14</sup> At least one placebo-controlled trial of L-tryptophan 6 g per day during the premenstrual symptomatic phase showed efficacy.<sup>15</sup> L-tryptophan has not been linked with the eosinophilia-myalgia syndrome in recent years. This syndrome was determined to be related to a contaminant of the tryptophan from one manufacturer, not due to tryptophan supplementation.

Aerobic exercise may diminish the symptoms of PMS/PMDD.<sup>16, 17</sup> Nonsteroidal anti-inflammatory drugs (NSAIDs) may be helpful for such physical symptoms of PMS/PMDD as breast pain or headache. Both mefenamic acid and naproxen sodium have been found helpful in randomized trials of PMS.<sup>18, 19</sup>

The clinician can also suggest that patients use cognitive/behavioral stress reduction skills, whether utilizing relaxation tapes or books, or seeking the help of a professional psychologist for biofeedback on cognitive/behavioral or relaxation training. Although there are some studies supporting the efficacy of

cognitive/behavioral therapy, biofeedback, or relaxation therapy as well as bright light therapy, these modalities are not without cost and therefore could be reserved until after diagnosis of PMDD.<sup>20-25</sup>

**Pharmacologic treatment**

Once the diary has been reviewed, and the diagnosis of PMDD confirmed, if the initial recommendations were not successful, further treatment can ensue. Considerations when prescribing for PMDD include efficacy across PMDD symptom clusters (e.g., mood, physical, and social functioning), rapid onset of action, and the long-term safety and tolerability profile.

Serotonergic psychotropics (Table 2), the treatment of choice, have been studied in rigorously controlled trials and have been found to be uniformly effective across different PMDD symptom clusters.<sup>26</sup> Approximately 60% of women with PMDD respond to an initial trial of SSRI administration. Numerous studies support the efficacy of fluoxetine 20 to 60 mg per day in the morning,<sup>27-32</sup> sertraline 50 to 150 mg per day in the morning,<sup>33-35</sup> paroxetine 10 to 30 mg per day,<sup>36-38</sup> citalopram 20 to 40 mg

per day,<sup>39</sup> clomipramine 25 to 75 mg per day,<sup>40</sup> and venlafaxine 50 to 200 mg per day, in divided doses twice daily.<sup>41</sup> The serotonergic antidepressants are effective by the first treatment cycle and, at least for fluoxetine, efficacy has been demonstrated to be sustained for at least six cycles of treatment.<sup>30, 42</sup> There is improvement not only in mood but also in physical symptoms, such as bloating, breast tenderness, and appetite, although headache is not significantly improved. Headaches may require NSAIDs or acetaminophen. Psychosocial functioning is also improved.<sup>35</sup> If a serotonergic antidepressant is initially ineffective, one should try different drugs within this category, since the side-effect profiles and treatment responses differ among the drugs and from patient to patient.

The serotonergic antidepressants have been found to be more effective than drugs with purely noradrenergic activity such as bupropion, tricyclics, and maprotiline.<sup>36, 43</sup> There is also evidence that luteal-phase dosing alone is as effective as daily dosing for fluoxetine, sertraline, citalopram, and clomipramine.<sup>40, 44-48</sup> It is also reasonable to utilize more than one modality, for example, a SSRI plus an anxiolytic or relaxation, cognitive/behavioral, or biofeedback interventions for residual anxiety.

Side effects of SSRIs can include nervousness, restlessness, agitation, insomnia, fatigue, dizziness, headache, difficulty concentrating, impaired memory, nausea, diarrhea, excessive perspiration, dry mouth, and weight gain. Side effects are often related to dose.<sup>30, 38, 49</sup>

Additionally sexual dysfunction (decreased libido, anorgasmia) may occur in women receiving SSRIs. However, PMDD may also be associated with changes in sexual function during the luteal phase. It is important to distinguish between baseline and drug-related events. Lowering the dose may be helpful, as may switching medications or using antidotes, such as dopaminergic agents (bupropion, 75 to 100 mg per day), postsynaptic 5-HT antagonists, (nefazodone, 100 to 150 mg per day), cholinergic agonists (bethanechol, 10 to 40 mg as needed), herbals (gingko biloba, 60 to 120 mg bid), postsynaptic 5-HT<sub>1</sub> agonists (buspirone, 15 to 60 mg per day) or presynaptic alpha-antagonists (yohimbine, 5.4 mg 2 to 4 hours prior to sexual activity).<sup>50, 51</sup> SSRI efficacy is not

TABLE 2

**Selected PMDD treatments**

**Serotonergic psychotropics**

Fluoxetine	20-60 mg/day (am) or luteal phase
Sertraline	50-150 mg/day (am) or luteal phase
Citalopram	20-40 mg/day (am) or luteal phase
Paroxetine	10-30 mg/day (am)
Venlafaxine	50-200 mg/day taken in divided doses twice daily
Clomipramine	25-75 mg/day or luteal phase

**Anxiolytics**

Alprazolam	0.25 to 0.5 mg bid to tid luteal phase
Buspirone	7.5 to 15 mg bid luteal phase

**Hormonal**

Estradiol transdermal	200 µg with progestin withdrawal
Danazol	200 - 400 mg/day
GnRH analog + add-back HRT	
Oral contraceptives	
Oophorectomy	
Spironolactone	25-50 mg/day luteal phase

affected by concomitant oral contraceptive (OC) use, nor have SSRIs been shown to contribute to OC failure.

Although there is less supportive evidence for the efficacy of other antidepressants, such as nefazodone (100 to 300 mg twice a day)<sup>52</sup> and fluvoxamine (100 to 300 mg per day, divided twice a day),<sup>53</sup> these medications can be utilized if other agents are not found to be effective or are not well tolerated.

Conflicting studies exist in the literature supporting the efficacy of luteal-phase alprazolam 0.25 to 0.5 mg two to three times a day<sup>54-56</sup> and buspirone 7.5 to 15 mg twice a day<sup>57</sup> for irritability and anxiety. Side effects of anxiolytics include drowsiness, fatigue, dependence, and tolerance for benzodiazepines. Dosing must be tapered before discontinuation to minimize withdrawal symptoms.

Hormonal therapy administered to achieve anovulation has also been used successfully to treat PMS/PMDD. High-dose transdermal estradiol patches, 200 µg with oral progestin for at least 7 days per month, have been found to be effective.<sup>58, 59</sup> The long-term side effects of the high dose of estrogen with the relatively short course of progestin withdrawal have not been evaluated, however, and could include a significant incidence of endometrial hyperplasia. Standard OCs have not been well studied for the treatment of PMS or PMDD. Early reports sug-

gested improvement of PMS, but these studies were not well controlled.<sup>60,61</sup>

The oral contraceptive pill containing drospirenone, a spironolactone analogue, demonstrated a trend toward significant improvement in both physical and psychological symptoms of PMDD.<sup>62</sup> In an open-label multicenter study to evaluate the efficacy, safety, and cycle control of the drospirenone-containing OC, menstrual symptoms were assessed in 326 women at baseline and at cycle 6, using a modified Menstrual Distress Questionnaire. The occurrence of menstrual-related symptoms was documented for three phases of the menstrual cycle: premenstrual (the 4-day period before menstruation), menstrual (the first through the last day of menstruation), and postmenstrual (the remainder of the menstrual cycle). Statistically significant decreases from baseline to cycle 6 were observed in all menstrual phases for negative affect and water retention. In the premenstrual and menstrual phases, severity of appetite increase was also significantly lower in cycle 6 compared with baseline.<sup>63</sup>

Hormonal medications, including danazol and GnRH agonists, have shown evidence of efficacy for the treatment of severe PMS/PMDD, but possibly worse side effect profiles. Danazol is an androgen derivative that suppresses ovulation in dose-dependent fashion. Only those who fail to ovulate on doses of 200 to 400 mg per day would be expected to achieve benefit from low-dose danazol.<sup>64-66</sup>

Dose-dependent side effects of danazol include acne, bloating, and depression. If conception occurs, possible virilization of the female fetus is a concern.

Use of a GnRH agonist with hormonal add-back has support in the literature.<sup>67-70</sup> Side effects include vaginal dryness, decreased bone density, hot flashes, myalgias,<sup>71,72</sup> and depression, particularly in individuals with underlying affective disorder or with severe depression as a prominent PMDD symptom.<sup>73,74</sup> Oophorectomy with hysterectomy and estrogen replacement is obviously an effective but highly invasive option.<sup>75</sup>

For water retention that persists in spite of the above pharmacologic approaches, there is some evidence for spironolactone 25 to 50 mg per day in the treatment of PMS.<sup>76,77</sup>

Treatment response can be followed by history (recall of symptoms). The daily diary need not be completed throughout therapy, although it may provide insight if the patient is not responding to treatment.

Duration of therapy has not been clearly defined. For women attempting conception, serotonergic agents can be discontinued, or maintained until the first missed period. Hormonal agents obviously should be discontinued while attempting conception. Although the etiology of PMDD is not completely understood, effective options currently exist for most, if not all, women with PMDD.

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# Drospirenone and ethinyl estradiol: The opportunities of a new OC

By Mitchell D. Creinin, MD

*The first new progestin to be marketed in the US in decades, drospirenone may produce less weight gain in women who experience the problem with other OCs. Further studies are necessary, however, to determine if the progestin's unique properties translate into higher continuation rates, lower pregnancy rates, or significant noncontraceptive benefits.*

Of the highly effective methods of contraception, oral contraceptives (OCs) are the most common, used by more than 60 million women worldwide.<sup>1</sup> For decades, OCs have been the method of reversible contraception most commonly used by women in the US. Currently, more than 10 million American women between the ages of 15 and 44 years use OCs.<sup>2</sup> Eighty percent of US women will use OCs at some point in their lifetime.<sup>3</sup>

In addition to effective pregnancy prevention, combination hormonal contraceptives have long been known to provide multiple health benefits, including reduced menorrhagia, prevention of

menstrual-related anemia, and decreased risk of ovarian and endometrial cancer. As we develop new contraceptive hormones, we have the potential to expand the range of benefits. A new OC formulation containing drospirenone and ethinyl estradiol (EE) may provide added opportunities for patients. This article will discuss the unique properties of such a formulation and review important information about potential benefits related to weight change and menstrual cycle symptoms.

## Drospirenone and ethinyl estradiol

In May 2001, the FDA approved a new OC formulation containing drospirenone 3 mg and EE 30 µg. Whereas all OCs previously available in the US contained a progestin derived from testosterone (estranses [norethindrone, norethindrone acetate, ethynodiol diacetate] and gonanes [norgestrel,

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**Dr. Creinin** is Associate Professor and Director of Family Planning and Family Planning Research, Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine, and Associate Professor, Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA.

levonorgestrel, norgestimate, desogestrel]), the progestin in this new product is a derivative of 17 $\alpha$ -spiro-lactone. As such, it is an analogue of the aldosterone antagonist spironolactone (Figure 1) and exhibits mild antimineralocorticoid properties, similar to natural progesterone.<sup>4-7</sup> The 3-mg dose of drospirenone is comparable in antimineralocorticoid effect to spironolactone 25 mg. Additionally, drospirenone exhibits direct antiandrogenic activity, a characteristic lacking in all available progestins in the US and found in cyproterone acetate, available in Europe (Figure 2). The testosterone-derived estranes and gonanes lack both the antimineralocorticoid and antiandrogenic actions of drospirenone.

Drospirenone 3 mg/EE 30  $\mu$ g is comparable to other OCs at preventing pregnancy, with a Pearl index in clinical trials of <0.5.<sup>5,8,9</sup> Likewise, cycle control is similar to that reported with other OC formulations. In a noncomparative US study including 333 women, the greatest incidence of intermenstrual bleeding (spotting or bleeding) occurred in cycle 1 (25%).<sup>5</sup> By cycle 3, only 15% of women experienced any intermenstrual bleeding, and this rate continued to decrease to around 8% by cycle 13. Approximately 75% of those women who experienced any intermenstrual bleeding had only spotting. Amenorrhea (lack of a withdrawal bleed) rates per cycle ranged from 1% to 5% over the 13 cycles. In a comparative study of more than 2,000 European women, the incidence of intermenstrual bleeding was similar between women using drospirenone 3 mg/EE 30  $\mu$ g and those using desogestrel 150  $\mu$ g/EE 30  $\mu$ g.<sup>5</sup> Approximately two thirds of women in each group experienced intermenstrual bleeding during the first cycle, a rate higher than in the US study. This rate of intermenstrual bleeding decreased rapidly to <10% by cycle 2 for both formulations. Bleeding patterns did not differ significantly at any point during the 13-cycle duration of the study.

FIGURE 1

**Drospirenone, a spironolactone analogue**

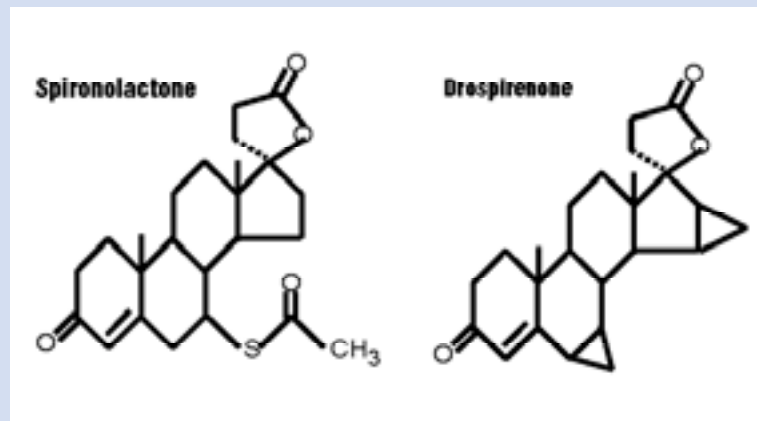


FIGURE 2

**Pharmacologic profile of contraceptive progestins**

	Progestogenic activity	Androgenic activity	Antiandrogenic activity	Antimineralocorticoid activity
Progesterone	+	-	(+)	+
Drospirenone	+	-	+	+
Cyproterone acetate	+	-	+	-
Desogestrel*	+	(+)	-	-
Gestodene	+	(+)	-	(+)
Levonorgestrel	+	(+)	-	-
Norgestimate**	+	(+)	-	-

\* active metabolite (3-ketodesogestrel)

\*\* main metabolite (17-deacetyl norgestimate)

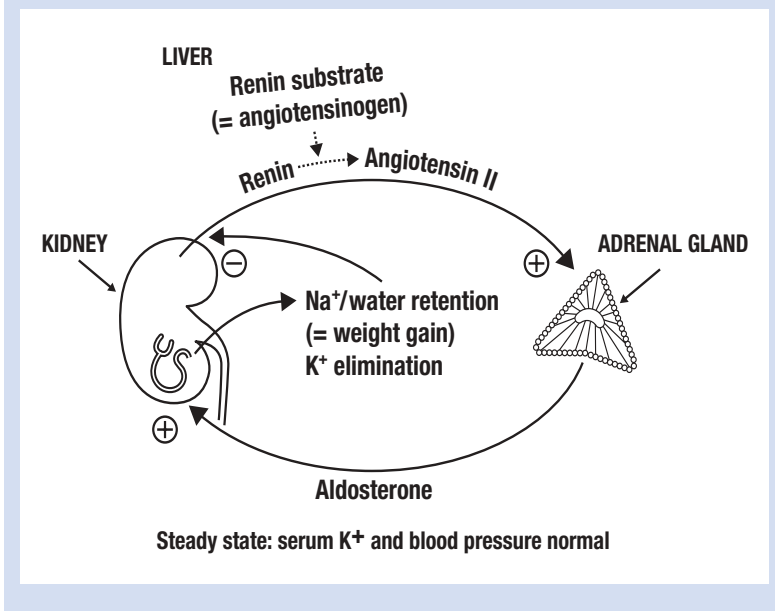
+, effect; (+), negligible at therapeutic dosages; -, no effect

**Unique properties of drospirenone**

**Antimineralocorticoid activity.** The renin-angiotensin-aldosterone (RAA) system is responsible, through the actions of aldosterone on the kidney, for maintaining a steady-state intravascular fluid and electrolyte balance (Figure 3). During the normal menstrual cycle, progesterone acts as an aldosterone antagonist, resulting in slight sodium wasting and fluid loss in the latter half of the menstrual cycle. In women using combination OCs, the RAA system is significantly impacted by the action of EE at the level of the liver to induce angiotensinogen production. The resultant increase in levels of angiotensin and, subsequently, aldosterone, acts

FIGURE 3

Renin-angiotensin-aldosterone system



on the kidney to induce sodium and water retention. Despite these known effects, women using low-dose OCs are not more likely to gain weight than are women using a placebo in prospective, randomized trials.<sup>10,11</sup>

Drospirenone, like progesterone, has antiminer-  
alocorticoid activity. Compared to placebo, women  
treated with drospirenone demonstrate an increase  
in urinary sodium excretion.<sup>6</sup> Potassium levels  
remained in the normal range in all subjects.

Clinically, these antiminer-  
alocorticoid effects would be detectable in blood pressure over time. A  
randomized trial compared the effects of lev-  
onorgestrel 150 µg/EE 30 µg to products containing  
drospirenone 3 mg combined with either 15, 20, or  
30 µg of EE.<sup>7</sup> Subjects were randomized to the study  
medication, which they used for 6 months, and then  
were followed for an additional month off treat-  
ment. Whereas the levonorgestrel-containing prod-  
uct demonstrated a slight increase in mean systolic  
and diastolic blood pressures, all of the drospirenone-containing products demonstrated a slight decrease. Overall, none of the changes in mean blood pressure measurements with any of the products was clinically significant.

Similarly, the antiminer-  
alocorticoid effects of drospirenone would be expected to result in signif-  
icantly different effects on weight change as com-  
pared to contraceptives containing testosterone-

derived progestins. In a 26-cycle, ran-  
domized, open-label European trial  
comparing drospirenone 3 mg/EE  
30 µg to desogestrel 150 µg/EE 30 µg,  
women using the latter product  
demonstrated a weight change con-  
sistent with an expected normal  
change over time in reproductive-age  
women (mean increase of 0.2 kg at 1  
year and 1 kg at 2 years).<sup>5</sup> However,  
women using drospirenone 3 mg/EE  
30 µg had a mean decrease of approx-  
imately 0.5 kg at 1 year, after which  
a gradual increase began, paralleling  
the increase in the desogestrel  
150 µg/EE 30 µg group. By 2 years of  
drospirenone 3 mg/EE 30 µg use, the  
population average had decreased  
by approximately 0.2 kg as compared  
to baseline. Additionally, significantly  
more women using the drospirenone  
3 mg/EE 30 µg lost more than 2 kg  
and fewer women gained more than  
2 kg over the 24-month study period

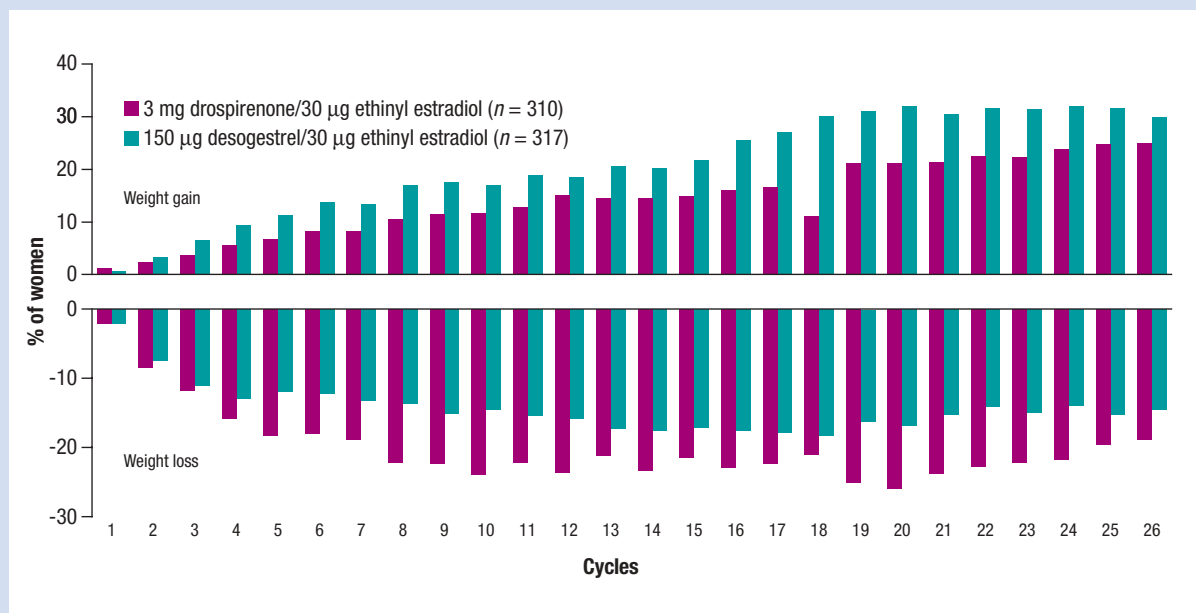
(Figure 4). Although these changes in weight may  
seem clinically significant, the overall discontinua-  
tion rates in the drospirenone 3 mg/EE 30 µg and  
desogestrel 150 µg/EE 30 µg groups were identical  
(21% and 19%, respectively). Thus, the true clinical  
impact of these changes is unknown.

**Antiandrogenic activity.** The androgenic pathway is  
widely affected by all OCs, through effects on total  
testosterone production, sex-hormone-binding  
globulin levels, and inhibition of the intracellular  
conversion of free testosterone to dihydrotestos-  
terone by 5α-reductase. To date, no preparation  
has been demonstrated to be superior to any other  
in clinical practice. None of the currently available  
agents in the US, though, contains a progestin that  
also has direct antiandrogenic effects, like  
drospirenone.

The only other combined contraceptive product  
on the market worldwide with antiandrogenic activ-  
ity is cyproterone acetate 1 mg/EE 30 µg. Clinical-  
ly, randomized comparative trials of drospirenone  
3 mg/EE 30 µg and cyproterone acetate 1 mg/EE 30  
µg demonstrate equal effects on acne and sebum  
production.<sup>12</sup> Both demonstrated statistically sig-  
nificant improvement in the number of lesions  
from baseline by the third month of use. No com-  
parative or noncomparative trials have been per-  
formed to evaluate clinical effects on hirsutism.

FIGURE 4

Percentage of women with a weight loss or weight gain of >2 kg



Reprinted with permission from Foidart, et al.<sup>5</sup>

Further comparative studies will be needed to understand if the direct antiandrogenic effect results in any additional clinical benefit.

### Menstrual cycle symptoms

One of the documented complaints of OC users is mood changes. Although not as common as estrogen-related effects, complaints related to irritability and mood swings are among the most common side effects women name as reasons for OC discontinuation.<sup>13</sup> Oddly, in placebo-controlled trials, complaints related to mood occur in equal frequency between hormone and placebo users.<sup>10,11</sup> These studies fail to identify, though, when in the menstrual cycle these problems arise.

Premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) are associated with mood and somatic changes (commonly, bloating or water retention) that occur in a cyclic fashion related to the menstrual cycle. As such, an OC that both inhibits ovulation and possesses antiminer-  
alocorticoid activity, like drospirenone and ethinyl estradiol, may uniquely provide advantages for the treatment of PMS or PMDD.

**PMS/PMDD.** PMS is defined by the temporal relationship of specific psychological and physiological

symptoms to the menses. PMDD represents a form of PMS in which psychological symptoms are emphasized and physical symptoms need not be present. While the emotional symptoms of PMS and PMDD are similar, they are significantly more serious with PMDD. It is not uncommon for women with PMS to experience sadness or mild depression. Women with PMDD, however, experience significant depression and hopelessness; in extreme cases, they may feel like killing themselves or others.

Women with PMDD exhibit symptoms comparable in severity to those of major depression, with marked impairment in the ability to function normally in the week prior to menses. Other important symptoms can include marked anxiety, affective lability, and decreased interest in activities. These symptoms must be experienced regularly during the last week of the luteal phase in most menstrual cycles during the previous year.

**Drospirenone 3 mg/EE 30 µg and PMDD.** A recent double-blind, multicenter, placebo-controlled study enrolled 82 women who met DSM-IV criteria for PMDD.<sup>14</sup> The women were nonsmokers between 18 and 40 years of age. During the preceding month they had menstrual cycles between 25 and 34 days in length, documented as ovulatory by progesterone

TABLE 1

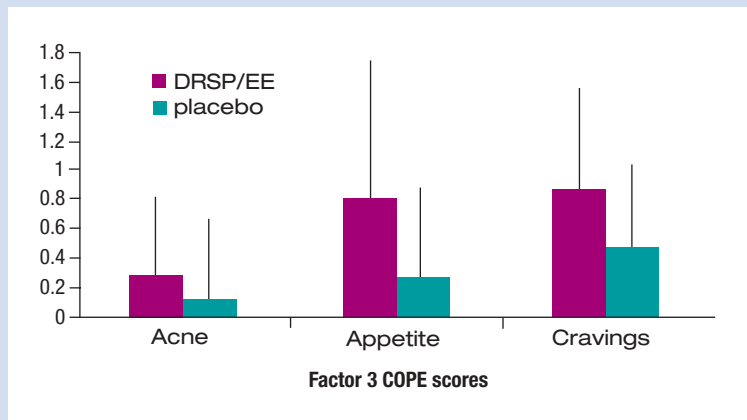
### Calendar of Premenstrual Experiences (COPE) factor structure

Factor 1 Mood factors	Factor 2 Physical factors	Factor 3 Androgenic factors	Factor 4 Estrogenic factors
Mood swings	Fatigue	Acne	Breast tenderness
Angry outbursts	Dizziness	Food cravings	Swelling
Irritability	Confusion	Increased appetite	Bloating
Sensitive	Forgetfulness		
Crying easily	Hot flashes		
Anxiety	Palpitations		
Wish to be alone	Headache		
Depression	Nausea		

Adapted from: Mortola JF, Girton L, Beck L, et al.<sup>15</sup>

FIGURE 5

### Improvement in COPE factor 3 (androgenic factors) scores in women using DRSP 3 mg/EE 30 µg vs. placebo



Reprinted with permission from Freeman EW, et al.<sup>14</sup>

levels. They used a barrier method of contraception. They were excluded if they had any significant medical or psychiatric disorders in the preceding 2 years, were receiving counseling or treatment for PMS, or had used any hormonal therapies in the preceding 3 months. Women who met the study criteria were observed for 2 cycles with daily prospective recording of PMDD symptoms through the Calendar of Premenstrual Experiences (COPE) form (Table 1).<sup>15</sup>

The 82 women who maintained eligibility after the 2-month observation and who, based on the

COPE form, truly met the DSM-IV criteria for PMDD were enrolled. They were randomized to 3 months of treatment with drospirenone 3 mg/EE 30 µg (n=42) or placebo (n=40). Based on the COPE score, the primary outcome was the change from baseline in luteal phase mood scores (Factor 1). Secondary outcomes included the changes in the other factor scores, the total change in luteal phase COPE score, and changes in mood based on the Beck Depression Inventory (BDI) and the Profile of Mood States (POMS).

There were no differences in the demographics of the study population. Although attrition over the 3 months was slightly higher in the drospirenone 3 mg/EE 30 µg group, the rates were not statistically significant (50% vs. 30%). Women were more likely to report side effects with drospirenone 3 mg/EE 30 µg as compared to placebo but because of the small number in each group, these differences were not significant.

Based on the COPE scoring system, there was no statistically significant difference between drospirenone 3 mg/EE 30 µg and placebo treatment for the total score and for factors 1, 2, and 4. A statistically significant difference was present for factor 3 (increased appetite, food cravings, acne) (Figure 5). Although there was a better response to treatment with drospirenone 3 mg/EE 30 µg for all four COPE factors, the BDI, and the POMS, a sample size of at least 300 women would be necessary to evaluate if these trends in improvement were truly significant.

Other studies have attempted to use other scoring mechanisms to assess quality of life with OCs. A large US multicenter study with the primary focus of evaluating the contraceptive efficacy, safety, and cycle control of drospirenone 3 mg/EE 30 µg also evaluated subjective measures of menstrually related symptoms for three phases of the menstrual cycle using a questionnaire that inquired about menstrual-related symptoms.<sup>9</sup> These three phases were premenstrual (4 days before menstruation), menstrual (the first

through the last day of menstruation), and the rest of the cycle. The health assessment included a subset of 22 items from Form C of the Menstrual Distress Questionnaire plus three additional items: increased appetite, feelings of well-being, and undesirable hair change.<sup>16</sup> Assessments were performed at baseline and after cycle 6. Small but statistically significant decreases from baseline were noted for water retention and negative affect in all three menstrual phases. Increased appetite was also significantly lower but only in the premenstrual phase. No other significant changes in menstrually related symptoms were noted. The results were similar between new OC users and women who had switched from another OC to the drospirenone-containing product.<sup>17</sup>

These studies have not yet demonstrated any widespread overall benefit of drospirenone 3 mg/EE 30 µg for PMDD or PMS. There may be some isolated benefits related to individual menstrual-related symptoms. At present, the lack of a randomized comparison to other formulations hinders the clinical utility of these results.

## Conclusion

Drospirenone is the first truly new progestin to be introduced to the US market in decades. Unlike

the estrane and gonane progestins currently used in OC preparations in the US, drospirenone is not a derivative of testosterone. The actions of drospirenone are more similar to natural progesterone than the estranes and gonanes. Like progesterone, drospirenone is able to counteract the “weight-increasing” tendency of estrogens, which is due to aldosterone-induced sodium and water retention (through activation of the renin-angiotensin-aldosterone system). Importantly, this sodium-wasting effect has not been shown to result in any significant increase in serum potassium levels. Additionally, unlike the estrane and gonane progestins, drospirenone has direct antiandrogenic activity.

For individual women who experience weight gain with available formulations, an OC containing drospirenone and EE may result in less weight gain. Otherwise, at the current time, the unique qualities of an OC containing drospirenone and EE have not been proven to be of any clinical significance as compared to other OC formulations. Further studies are necessary to determine if any of these unique properties result in higher continuation rates, lower pregnancy rates, or significant noncontraceptive benefits as compared to other OCs.

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# POST-TEST

## PMS/PMDD and Quality of Life: Advances in Management

Please select the single best answer and record your response on the answer sheet page (page 21).

- TRUE OR FALSE:** The progestin drospirenone is a derivative of testosterone.
- TRUE OR FALSE:** Most OCs in the US exhibit both antiminerlocorticoid and androgenic actions.
- TRUE OR FALSE:** Progesterone acts as an aldosterone antagonist, resulting in sodium wasting and fluid loss in the latter half of the menstrual cycle.
- Drospirenone may be effective for women with:
  - Premenstrual syndrome
  - Premenstrual dysphoric disorder
  - Endometriosis
  - All of the above
- TRUE OR FALSE:** The “weight-increasing” tendency of estrogen is due to aldosterone-induced sodium and water-retention via activation of the renin-angiotensin-aldosterone system.
- Noncontraceptive benefits of oral contraceptives include:
  - Prevention of menstrual-related anemia
  - Decreased risk of ovarian cancer
  - Decreased risk of endometrial cancer
  - All of the above
- The differential diagnosis of premenstrual dysphoric disorder (PMDD) includes:
  - Hypothyroidism
  - Diabetes
  - Perimenopause
  - All of the above
- TRUE OR FALSE:** The diagnosis of PMDD relies on a patient’s subjective recounting of symptoms.
- TRUE OR FALSE:** The most important differentiating feature in the patient with PMDD is a clear symptom-free interval during the follicular phase.
- TRUE OR FALSE:** Approximately 60% of women with PMDD respond to an initial trial of SSRI administration.
- Side effects of SSRIs can include:
  - Restlessness
  - Insomnia
  - Difficulty concentrating
  - All of the above
- TRUE OR FALSE:** SSRI efficacy is affected by concomitant OC use.
- TRUE OR FALSE:** ACOG has published diagnostic criteria for PMS.
- TRUE OR FALSE:** In both PMS and PMDD, the symptoms are virtually nonexistent in the follicular phase of the menstrual cycle.
- TRUE OR FALSE:** PMS has been defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).
- TRUE OR FALSE:** Between 11% and 32% of reproductive-age women suffer from PMS.
- TRUE OR FALSE:** The diagnosis of PMDD requires functional impairment in activities of daily living.
- TRUE OR FALSE:** The nervous systems of women with PMS metabolize steroids differently and/or have altered sensitivity and therefore react differently when exposed to sex steroids.
- TRUE OR FALSE:** The majority of women seek or receive treatment for PMS/PMDD.
- TRUE OR FALSE:** Clinical investigators believe that PMS and PMDD represent different severities of the same disorder.
- TRUE OR FALSE:** PMS includes three types of symptoms: physical, behavioral, and emotional.
- TRUE OR FALSE:** PMS can include somatic or affective symptoms.
- TRUE OR FALSE:** The DSM-IV diagnostic criteria for PMDD require at least two symptoms from a given list, which must occur during the week before menses and remit a few days after onset of menses.
- TRUE OR FALSE:** Generally women with PMDD report greater interference with daily activities due to premenstrual symptoms than women with PMS.

Questions were written by David B. Seifer, MD, Professor of Obstetrics and Gynecology, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ.



# ANSWER SHEET

PMS/PMDD and Quality of Life: Advances in Management

## Instructions

In order to complete this program successfully, you must:

- Complete the post-test.
- Complete the activity evaluation form located on reverse side.
- Enclose a check for \$10 made payable to American Health Consultants.
- Mail your completed answer sheet and check to:

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**In order to ensure scoring, the answer sheet must be received by 8/01/03.**

- |     |      |       |   |   |     |      |       |
|-----|------|-------|---|---|-----|------|-------|
| 1.  | True | False |   |   | 13. | True | False |
| 2.  | True | False |   |   | 14. | True | False |
| 3.  | True | False |   |   | 15. | True | False |
| 4.  | A    | B     | C | D | 16. | True | False |
| 5.  | True | False |   |   | 17. | True | False |
| 6.  | A    | B     | C | D | 18. | True | False |
| 7.  | A    | B     | C | D | 19. | True | False |
| 8.  | True | False |   |   | 20. | True | False |
| 9.  | True | False |   |   | 21. | True | False |
| 10. | True | False |   |   | 22. | True | False |
| 11. | A    | B     | C | D | 23. | True | False |
| 12. | True | False |   |   | 24. | True | False |

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# ACTIVITY EVALUATION FORM

PMS/PMDD and Quality of Life: Advances in Management

**1. Did the material presented in this program meet the educational objectives stated on page 2?**

- Met the stated objectives.
- Did not meet the stated objectives.

**2. Please rate the contents of this issue using the following scale:**

5=Excellent; 4=Very good; 3=Good; 2=Fair; 1=Poor (Circle one response for each question.)

	<i>Poor</i>			<i>Excellent</i>	
Timely, up to date?	1	2	3	4	5
Practical?	1	2	3	4	5
Relevant to your practice?	1	2	3	4	5

**3. Are there any other topics you would like to have seen addressed in this program?**

- Yes (Please specify): \_\_\_\_\_
- No

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**5. Development and production of this supplement were made possible with educational funding from a commercial sponsor. Did you detect any commercial bias in this supplement?**

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- Completed the post-test and the activity evaluation form?
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