A CLINICIAN'S GUIDE TO THE PREMENSTRUAL SYNDROME

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Premenstrual syndrome (PMS) encompasses a variety of emotional and physical symptoms that occur from several days to several weeks before the onset of menstrual flow. Although many women experience some premenstrual discomfort, most women do not consider these premenstrual changes severe, and they do not disrupt a woman's life. PMS is characterized by debilitating mood and behavioral changes in the week preceding menstruation that interfere with normal functioning.

The term PMS was first coined in 1953, but an American gynecologist, T. Frank, characterized the syndrome in 1931:

[These women] complain of indescribable tension from 10 to 7 days preceding menstruation which in most instances continues until the time that the menstrual flow occurs. The patients complain of unrest, irritability, like jumping out of their skin and a desire to find relief by foolish and ill considered actions. Their personal suffering is intense and manifests itself in many reckless and sometimes reprehensible actions. . . . Within an hour or two after the onset of the menstrual flow complete relief from both physical and mental tension occurs.

Frank's description of the severity and intensity of the symptoms that characterize women suffering from PMS holds true today. Since that time, many treatments have been proposed for PMS, with varying degrees of success, and the cause of the disorder has not yet been characterized. There has been progress in refining the diagnosis, identifying contributing factors, and demonstrating effective treatments for women who suffer from PMS. This article focuses on the clinical aspects of PMS: the current criteria for a diagnosis and an update on treatment.

IS PREMENSTRUAL SYNDROME A SOCIALLY CONSTRUCTED LABEL?

Generally, attitudes regarding menstruation are negative. As summarized by Speroff, this attitude can be traced back to times when menstruating women

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were thought to be possessed by evil spirits, and myths portrayed the menses as
detoxification or a time of magic, danger, or even poison. Ancient physicians such
as Pliny wrote extensively describing how a menstruating woman could kill crops,
drive animals mad, and even deter thieves. Aristotle wrote that a reflection of a
menstruous woman in a mirror would bewitch the next person who looked into
it. Some physicians argue that culture has conditioned women to expect symptoms
in the menstrual and premenstrual phase or that menstruation is associated with
a change in affect or even antisocial behavior. Disordered menstruation has been
used successfully in an English court of law as grounds for a plea of insanity.68

Given the prevalence of myths surrounding menstruation and the premen-
strual period, it is difficult to determine objectively, qualify, and quantify the
symptoms of women truly suffering from PMS. Investigators have shown that
some premenstrual symptoms are associated with the expectation of menstruation.
One study, using a bogus electroencephalogram that subjects believed could
predict the onset of menses, demonstrated that only women who were convinced
that they were premenstrual reported significantly higher symptom ratings of
pain, water retention, and altered eating habits.7

When controlling for the negative connotations of menstruation, however,
there still emerges a distinct and well-characterized group of women suffering
from PMS. These symptoms are mainly alterations of mood and behavior that
can be severe.57 There is evidence that PMS is a discrete mood disorder and not
simply the extreme end of a spectrum of menstrual symptoms.32 Although the
pathophysiology of PMS is still not defined, specific signs and symptoms can be
identified, and beneficial treatments do exist.

SYMPTOMS

The symptoms of PMS are varied and nonspecific. Many of the symptoms
of PMS overlap symptoms characteristic of other medical disorders. The symptoms
can be artificially divided into somatic and emotional complaints. Women who
suffer from severe PMS usually are most affected by the emotional symptoms.57

Emotional symptoms include emotional hypersensitivity, depressive symp-
toms, irritability, mood swings, anxiety, tension, fear of loss of control, and confu-
sion. Somatic complaints include feelings of bloating, body aches, breast tender-
ness, headaches, food cravings, and poor coordination. Often, somatic complaints
are out of proportion to physical findings, as illustrated by the discrepancy be-
tween the subjectivity of feeling bloated and objective measurements of weight
gain.13 Women with PMS may experience any number of these symptoms and to
varying degrees. Women who complain predominantly of physical symptoms
(breast tenderness, swelling, food cravings, aches) are less likely to meet current
criteria for severe PMS, which requires multiple symptoms that include emotional
symptoms such as irritability, depression, anxiety, tension, mood swings, and
fear of loss of control. Although patterns of symptoms can be identified in certain
subgroups of women who suffer from PMS,28 as yet there is no one group of
symptoms that is characteristic of PMS.

PREVALENCE

Women who seek treatment for PMS by definition must have menstrual
cycles. The mean age of clinical samples is the early 30s. Epidemiologic studies
of PMS have failed to show unequivocally an association between PMS and age,
socioeconomic status, parity, diet, exercise, stress, menstrual cycle characteristics, or personality.\textsuperscript{57}

Overall, approximately 75% of the general population complain of some premenstrual symptoms. The large range of prevalence reported in the literature (1% to 90\%)\textsuperscript{18} reflects a wide variety of criteria in assessing premenstrual symptoms and the variety of populations sampled. In most current reports, in which stringent, specific diagnostic criteria for PMS are used, 3\% to 8\% of cycling women can be diagnosed with PMS.\textsuperscript{18} Of those who seek medical treatment, approximately 40\% to 50\% meet criteria for PMS.\textsuperscript{49} If the requirements of the diagnosis include complete absence of symptoms postmenstrually only, 10\% to 20\% of women seeking medical treatment meet criteria for PMS.\textsuperscript{49}

**DEFINITION**

PMS is included as a provisional diagnosis in the DSM IV\textsuperscript{2} in which it is termed \textit{premenstrual dysphoric disorder} (PDD). For the diagnosis of PDD, 5 of the 11 listed symptoms must be severe premenstrually with postmenstrual remission. The five symptoms must include at least one dysphoric symptom (irritability, mood swings, anxiety, or depression), and multiple physical symptoms are counted as 1 symptom (Table 1). Although this is the one attempt to date to systematize a PMS diagnosis, some researchers believe that the PDD criteria are too restrictive, whereas others find the criteria too inclusive.\textsuperscript{43}

**DIAGNOSIS**

There is no pathognomonic symptom, no laboratory test, and no objective finding on physical examination to confirm a diagnosis of PMS. The diagnosis

**Table 1. CRITERIA FOR PREMENSTRUAL DYSPHORIC DISORDER**

| On prospective evaluation of patient symptom charting for 2 to 3 menstrual cycles, 5 (or more) of the following symptoms are present during the last week of the luteal phase, and were absent postmenstrually. At least 1 of the symptoms must be 1, 2, 3, or 4: |
|---|---|
| 1. Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts |
| 2. Marked anxiety, tension, feeling of being “keyed up” or “on edge” |
| 3. Marked affective liability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection) |
| 4. Persistent and marked anger or irritability or increase in interpersonal conflicts |
| 5. Decreased interest in usual activities (e.g., work, school, friends, hobbies) |
| 6. Subjective sense of difficulty in concentrating |
| 7. Lethargy, easy fatigability, or marked lack of energy |
| 8. Marked change in appetite, overeating, or specific food cravings |
| 9. Hypersomnia or insomnia |
| 10. A subjective sense of being overwhelmed or out of control |
| 11. Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of “bloating” or weight gain |

The disturbances must markedly interfere with work or school or with usual social activities and relationships with others (e.g., avoidance of social activities, decreased productivity and efficiency at work or school)

The disturbances must not be an exacerbation of the symptoms of another disorder (e.g., major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder)

*Adapted from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, ed 4. Washington, DC, American Psychiatric Association, 1994; with permission.*
of PMS depends on the patient’s subjective report of symptoms. The patient’s retrospective report or recall of these symptoms is insufficient, because many symptoms and behavior changes may be attributed to menstruation, which is a repetitive visible occurrence in a woman’s life. It is necessary to maintain a prospective symptom report in a daily record for at least two or three menstrual cycles. The clinician reviews the daily records to determine that the symptoms are related to the menstrual cycle: high in the week before menstruation and low in the week following menstruation. The symptoms must also be at a severity that disrupts normal function, with a clear increase from postmenstrual levels. Fewer than 50% of women who complain of PMS can be demonstrated to have such a pattern of mood changes and symptoms. Commonly used daily assessment measures include the Daily Rating Form, the visual analog scale, and modifications of the Moos Menstrual Distress Questionnaire and the Calendar of Premenstrual Experiences.

DIFFERENTIAL DIAGNOSIS

It is essential to differentiate PMS from other major mood and physical disorders. Because the nonspecific symptoms of PMS may overlap with psychiatric, endocrine, medical, or gynecologic disorders, a list of differential diagnoses should be carefully constructed. Each potential diagnosis should then be ruled out with the appropriate evaluations.

Association with Depression

PMS is associated with major affective disorders. The highest incidence of PMS is in the mid reproductive years, as is the 1-year and lifetime incidence of depression in women. A report noted that 59% of women presenting with PMS had a history of a DSM-III diagnosis of an anxiety or mood disorder (or both). Of women with PMS, 30% to 76% are noted to have a history of depression, which is greater than the 25% incidence noted in the general population. Owing to the similarity of the PMS symptoms of anxiety, mood swings, depression, tension, and loss of control to the symptoms of affective disorders, the diagnostic evaluation needs to include careful assessment of when these symptoms occur in the cycle. Screening questionnaires such as the Beck Depression Inventory or the Hopkins Symptom checklist are helpful in determining the extent of the depressive symptoms. Depression can be screened by clinician interview using the Hamilton Depression Rating Scale (Ham D). These instruments do not diagnose depression, but they do provide information on the degree of depressive symptoms that may signal a disorder.

It is important to conduct mood assessment in the postmenstrual (follicular) phase when the symptom levels are not confounded by PMS. High scores on mood measures in the follicular phase suggest that the problems extend beyond PMS. If it appears that there are other mood disorders, but the severity is unclear, further psychiatric interview may be appropriate.

Medical Conditions

Medical conditions, such as anemia, chronic fatigue syndrome, and collagen vascular disease as well as endocrine diseases such as early diabetes mellitus
or hypothyroidism, can present with nonspecific symptoms, such as feelings of lethargy, weight gain, abdominal pain, bloating, and feelings of altered mood. Although classic examples of these disorders should not present any diagnostic dilemma, atypical presentations can be confused with symptoms of PMS. If suspicion is high for any of these disorders, appropriate evaluations should be undertaken.

Physical pain associated with PMS requires investigation. For example, breast tenderness in PMS should not be confused with normal breast changes in the menstrual cycle or fibrocystic breast disease. Abdominal and pelvic pain are not characteristic of PMS.

**Gynecologic Conditions**

Perhaps the most common misdiagnosis of PMS is that of dysmenorrhea. The reason for this misdiagnosis is usually not because of confusion of the symptoms but instead confusion over definitions or inadequate history. Primary dysmenorrhea, by definition, is menstrual pain in the absence of pelvic pathology. The onset of dysmenorrhea is hours before menstruation and lasts up to 72 hours. Dysmenorrhea does not have prodromal affective symptoms. The pain of dysmenorrhea is characterized by intermittent crampy lower abdominal pain, concentrated in the midline (suprapubic) region, and may be associated with diarrhea, nausea, or vomiting. The etiology of primary dysmenorrhea is uterine prostaglandins causing painful uterine contractions. It is treated with nonsteroidal anti-inflammatory drugs or oral contraceptive pills.

Secondary dysmenorrhea is menstrual pain caused by an underlying pelvic pathology, most commonly uterine fibroids or endometriosis. If a patient presenting with complaints of PMS has an abnormal pelvic examination or has a suggestive history for gynecologic pathology, such as abnormal vaginal bleeding or severe dysmenorrhea, a more extensive workup may be necessary.

**CAUSE**

The list of proposed mechanisms for PMS is impressively long, but no specific deficiency or abnormality has been identified to explain the cause of PMS. PMS can be considered a consequence of complex interactions between ovarian steroid production, endogenous opioid peptides, central neurotransmitters, prostaglandins, and peripheral autonomic and endocrine systems. It is likely that the cause of PMS is due to alterations at the hypothalamic or suprahypothalamic level rather than alterations in ovarian activity. This theory is consistent with the current literature on PMS, which reports no abnormalities in hormone levels in the menstrual cycle (follicle-stimulating hormone [FSH], luteinizing hormone [LH], estrogen, progesterone, prolactin, sex hormone–binding globulin, testosterone). It also appears that there is no direct relationship between late luteal phase ovarian physiology and PMS. The truncation of the luteal phase of a menstrual cycle with the antiprogestrone RU 486 did not eliminate the predicted development of PMS symptoms, and luteal phase low-dose RU 486 was no better than placebo in treating PMS. It also appears that hormonal changes without ovulation and corpus luteum development can induce the symptoms of PMS. Therefore, it is possible or even likely that the elimination of cyclical fluctuations
in ovarian steroids, by whatever method, is responsible for its beneficial effect on PMS rather than prevention of ovulation per se.

Other literature investigating the cause of PMS has reported the following: no change in fluid regulation (renin-angiotensin, aldosterone); no change in the pituitary-hypothalamic axis or its relationship to the adrenal gland, thyroid gland, or ovaries; and no change in vitamin or mineral content (magnesium, zinc, vitamin A, vitamin E, thiamine, or vitamin B6). Investigations have focused on alterations in neurotransmitters and neuromodulators. These may be susceptible to steroid fluctuations in the menstrual cycle. The role of serotonin in the premenstrual feelings or irritability and dysphoria has been investigated.

Serotonin

As a result of the efficacy of serotoninergic reuptake inhibitors in the treatment of depression, relationship between PMS and the serotonin system has been investigated. Studies have reported reduced luteal whole-blood serotonin and reduced luteal serotonin platelet uptake in women with PMS. It has been shown that women with PMS have a heightened sensitivity of 5-HT1 receptors, which is further increased premenstrually. Plasma from women with PMS has also been shown to decrease serotonin uptake in rat brain. Other studies have demonstrated that women with PMS have a blunted growth hormone and cortisol response to an infusion of L-tryptophan. Additionally, others have postulated that increased androgen level (free testosterone levels) may influence the serotoninergic mechanism, resulting in irritability and dysphoria. Together these observations suggest that 5-HT, a serotonin receptor, may be important in the cause of PMS.

Other Proposed Causes

Other current areas of investigation into the cause of PMS have centered on the panic threshold and altered coping mechanisms and vulnerability factors. Studies have suggested that women who suffer from PMS have a lower threshold for the alarm for suffocation. This hypothesis suggests that as progesterone levels fall in the luteal phase and $P_{CO_2}$ rises, women with a low threshold for the suffocation alarm system may suffer panic symptoms.

A positive association has been demonstrated between the duration of a stressful experience and the severity of negative affect in patients with PMS. This association suggests that patients with PMS are particularly vulnerable to stressful life experiences.

An additional theory to explain the cause of PMS is that of learned helplessness. Menstruation may present itself to some women as an unpleasant repetitive event. In the animal model, administration of a repetitive stimulus over time can produce increasing effects and profound long-term changes in brain activity and behavior. A rat subjected to inescapable shocks develops behavioral and biologic changes. Although no empiric evidence exists in humans that supports this theory, sensitization as a result of premenstrual feelings might occur, thus explaining the gradual worsening of PMS both in severity and in duration of time that is observed in many individuals.

TREATMENT

When studying clinical trials investigating treatment for PMS, one should evaluate the literature critically. Consideration of the population enrolled in the
study, the definitions used for the diagnosis of PMS, the criteria for improvement, and the placebo effect are important. Subject selection differs in many studies, and pooling data from different populations may obscure or confound conclusions. Studies using objective, prospective charting of symptoms or strict diagnostic criteria allow better extrapolation of findings. Careful attention must also be given to the prevalence of comorbidity with other psychiatric diagnoses and to which symptoms respond to therapy. Finally, there is a placebo effect in the treatment of PMS, and while recognizing its importance in the treatment of PMS, it should be accounted for in a clinical trial. Open trials in particular are vulnerable to the placebo effect. Clinical trials should be long enough to identify patients that initially respond to the placebo effect. Well-controlled trials account for this effect.

A great variety of treatments have been proposed for PMS. Few of these treatments have been evaluated properly. There have been, however, well-designed, placebo-controlled clinical trials demonstrating benefit for women who suffer from PMS (Table 2). The treatment summarized next represents only a portion of the proposed treatments of PMS.

### Surgery

Since early medical times, it has been surmised that the cause of PMS is related to the cyclicity of hormones in the menstrual cycle. Therefore, the majority of treatments have been aimed at correcting a hormonal deficiency or abnormally high hormone level. Historically the definitive treatment for severe PMS included total hysterectomy with oophorectomy or radiation to eliminate ovarian function.39 It has been noted that a hysterectomy without removing the ovaries was not effective in the elimination of PMS.39 Although this type of radical treatment has been reported to be successful in extreme recalcitrant cases, surgical therapy for PMS should only be a last resort and should always be preceded by “medical” oophorectomy.45

### Table 2. MEDICATIONS SHOWING EFFICACY FOR PREMENSTRUAL SYNDROME IN PLACEBO-CONTROLLED TRIALS

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Reference</th>
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<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20 mg/d</td>
<td>Stone et al, 199046</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20 mg/d</td>
<td>Wood et al, 199273</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20 mg/d</td>
<td>Menkes et al, 199237</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>25–75 mg/d</td>
<td>Sundblad et al, 199271</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>25–75 mg/d, luteal phase</td>
<td>Sundblad, 199370</td>
</tr>
<tr>
<td><strong>Anxiolytics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.25 mg TID, luteal phase</td>
<td>Smith et al, 198756</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>2.25 mg/d (TID) mean dose,</td>
<td>Harrison et al, 199011</td>
</tr>
<tr>
<td></td>
<td>luteal phase</td>
<td></td>
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<tr>
<td>Alprazolam</td>
<td>1.5 mg/d (QID) mean dose,</td>
<td>Freeman et al, 199521</td>
</tr>
<tr>
<td></td>
<td>luteal phase</td>
<td></td>
</tr>
<tr>
<td>Buspirone</td>
<td>25 mg/d, mean dose</td>
<td>Rickels et al, 198956</td>
</tr>
<tr>
<td><strong>Ovulation suppressors</strong></td>
<td></td>
<td></td>
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<tr>
<td>Histralin</td>
<td>100 μg/d plus HRT</td>
<td>Mortola et al, 199144</td>
</tr>
<tr>
<td>Luprolide depot</td>
<td>3.75 mg/mo</td>
<td>Brown et al, 19948</td>
</tr>
<tr>
<td>Leuprolide depot</td>
<td>3.75 mg/mo plus HRT</td>
<td>Mezrow et al, 199438</td>
</tr>
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Medical Oophorectomy

A medical oophorectomy is now possible with the advent of gonadotropin-releasing hormone (GnRH) agonists. GnRH agonists function by suppressing the gonadotropin levels at the level of the pituitary, thus disrupting the normal pulsatility of FSH and LH and eliminating ovulation and sex steroid production. They can be administered subcutaneously (Lupron), intramuscularly (Depo-Lupron), or intranasally (buserelin). Successful treatment of PMS by eliminating the menstrual cycle in this fashion has been demonstrated. Other studies have confirmed this finding, while demonstrating that GnRH therapy is not successful in patients with concurrent major depression. The disadvantages of this therapy include a prolonged hypoestrogenic state with its associated side effects of menopausal symptoms, such as hot flashes and vaginal dryness, as well as the risk of osteoporosis. The use of these agents alone is therefore recommended for no longer than 6 consecutive months. By adding back estrogen and progesterone, one can theoretically protect against the long-term consequences of ovarian steroid deficiency and therefore prolong the use of these agents. Studies investigating adding back estrogen and progesterone to GnRH agonist therapy note a small but not significant increase in daily symptom ratings for PMS. Symptoms were still significantly improved from pretreatment levels.

Oral Contraceptives

Both the avoidance and the use of combined oral contraceptive pills (OCPs) have been recommended for the treatment of PMS. Overall the efficacy of OCPs in the treatment of PMS has not been proved. OCPs may be beneficial to women with PMS because they suppress ovulation. The suppression of ovulation, however, is not uniform for all brands of pills. The avoidance of OCPs in patients with PMS is due to the prevalence of depression and irritability some patients experience secondary to the progesterone OCPs. One report demonstrated that triphasic oral contraceptives were helpful for premenstrual breast pain and edema but not for emotional symptoms. Because physical symptoms usually do not constitute the main cluster of symptoms in severe PMS, the use of OCPs may actually be treating dysmenorrhea. Other reports on OCPs have not demonstrated an improvement of PMS beyond a few cycles, and one report noted that OCPs prolonged or delayed premenstrual dysphoria. Although there is some evidence that a subset of patients with PMS may improve with OCPs, this is not considered a first-line therapy for PMS.

Progesterone

An altered level of progesterone in PMS patients and progesterone supplementation as a possible treatment of PMS date back to 1938. Many open trials have reported successful treatment of PMS with luteal phase supplementation of progesterone. Controlled clinical trials, however, have failed to demonstrate the effectiveness of progesterone treatment in a variety of preparations and dosages. Currently, there is no evidence from controlled studies that either natural progesterone, administered in either suppository or micronized oral form during the luteal phase, or the closely related progestins are more effective than placebo in PMS treatment. Despite no evidence of its efficacy in controlled trials, some clinical programs described success in using progesterone therapy for PMS, and
many women as well as clinicians maintain their strong advocacy of this treatment. Natural progesterone appears to be a benign treatment without major side effects. There are no long-term safety data on progesterone in PMS therapy, however, and consequently, progesterone does not have Food and Drug Administration approval for PMS treatment. With the advent of treatments with proven effectiveness for PMS, the support for progesterone as a treatment is likely to wane.

Thyroid Hormone

Early open-label trials suggesting the benefit of thyroid replacement therapy for PMS have not been substantiated in blinded control clinical trials. If a thyroid abnormality is suspected, this should be investigated and treated as a separate condition.

Bromocriptine

Bromocriptine, a dopamine-receptor agonist, has been used to treat PMS based on the theory that prolactin can alter fluid and electrolyte balance. Daily bromocriptine administered from day 10 of the cycle to menses, however, was effective only in relieving the somatic premenstrual symptoms, consistent with earlier studies that bromocriptine is not helpful for premenstrual mood and anxiety symptoms. Bromocriptine is a treatment for premenstrual mastalgia.

Anxiolytics

Because some of the most troubling symptoms of PMS are emotional, another approach to PMS treatment is the psychotropic compounds. Treatment with the anxiolytic alprazolam in the luteal phase has met with some success, although not all studies showed effectiveness. The largest study investigating the effectiveness of alprazolam (started at 0.25 mg three times a day with increase to a maximum of 4 mg/day, with an average dose of 2.25 mg) demonstrated modest efficacy for the total symptoms of PMS. Alprazolam is the only effective medication that can be administered only in the luteal phase. The initial side effect of drowsiness usually subsides in a short time. Dependence, which is always a concern when treating with benzodiazepines, has not been demonstrated in patients carefully diagnosed with PMS when dosage is limited to the luteal phase.

Effective treatment of PMS has also been noted with buspirone (10 mg three times a day), a nonbenzodiazepine anxiolytic. Results from a large trial are needed to confirm or refute these preliminary findings.

Tricyclic Antidepressants

An open label trial evaluating the use of nortriptyline (50 to 125 mg daily), a noradrenergic antidepressant, demonstrated a reduction of premenstrual symptoms. There was a high rate of adverse side effects, however. A double-blind, placebo-controlled trial of clomipramine hydrochloride (25 to 75 mg a day) also demonstrated reduced symptoms. Additional trials are currently investigating the role of tricyclic antidepressants in the treatment of PMS as well as studies
confirming the benefit of the use of clomipramine (25 to 70 mg daily) solely in
the luteal phase.70

Selective Serotonin Reuptake Inhibitors

Serotonergic antidepressants are now considered a first-line drug treatment
for PMS because of their apparent efficacy and easy tolerability. Preliminary
placebo-controlled trials have demonstrated the efficacy of fluoxetine 20 mg daily
in the treatment of PMS symptoms.37 Notably the emotional symptoms of PMS
were much more reduced than somatic PMS symptoms, further lending support
to the theory that altered serotoninergic function is present in women with PMS.55
These findings have been repeated69 (demonstrated in larger, double-blind, pla-
cebo-controlled trials73) and supported in long-term use of fluoxetine.51

Other serotoninergic reuptake inhibitors, such as nefazodone,70 have also
been shown to be effective in the treatment of PMS. It is likely that others, such
as sertraline, paroxetine, venlafaxine, and fluvoxamine, which are all currently
under study, will prove to have efficacy in the treatment of PMS as well.

In contrast to the tricyclic antidepressants, fluoxetine and the other selective
serotonin reuptake inhibitors do not have anticholinergic, hypotensive, or sedative
effects. Dependency is not a concern for this class of drug, and they have no
particular cardiovascular or serious toxic effects. The side effects of dizziness,
nausea, headache, and insomnia are usually transient and mild. Important drug
interactions may occur with monoamine oxidase inhibitors, tricyclic antidepres-
sants, and some other drugs.26 Therefore, selective serotonin reuptake inhibitors
should not be prescribed with other antidepressants. Although one must be con-
cerned regarding accidental pregnancy while taking these agents, one study inves-
tigating fluoxetine48 did not show any increase in teratogenicity.

Patients can have idiosyncratic responses to these agents. A patient’s response
to a given agent should be evaluated for at least three cycles. When relief is not
sufficient, another agent or treatment approach should be attempted. Given the
effectiveness and easy tolerability of this class of drugs, selective serotonin reup-
take inhibitors are rapidly becoming the first-line therapy for patients with se-
vere PMS.

Diuretics

Diuresis has long been proposed as a treatment for PMS. Many types of
diuretics have been evaluated, including ammonium chloride, thiazides, metola-
zeone, chlorthalidone, triamterene, and spironolactone.39 Results suggest that
weight gain and bloating can be improved in women who gain weight premenstru-
ally, but that diuresis is not effective for treating all types of premenstrual symp-
toms. Treatment with diuretics can lead to hypotensive episodes and electrolyte
abnormalities. Therefore, because there is no proven benefit for their use in patients
with PMS, they are not recommended.

Atenolol

Atenolol, by affecting aldosterone secretion via the renin system or by having
an effect in treating anxiety disorders, has also been theorized as a possible
treatment of PMS. In a double-blind trial, atenolol (50 mg daily for the 10 days
before menses) was effective “to a limited extent” in reducing irritability and preventing a decrease in vigor, elation, and “friendliness” in women who had PMS for 5 years or longer. This finding, however, was not confirmed in a subsequent prospective placebo trial. Currently, research does not support the use of atenolol in the treatment of PMS.

Prostaglandin-Related Treatments

Prostaglandins are implicated as a causative agent in primary dysmenorrhea, are involved in fluid balance, and act as neurotransmitters centrally. Therefore, theoretically, prostaglandins could play a role in PMS. Prostaglandin inhibitors, such as mefenamic acid and naproxen sodium, given in the luteal phase have been demonstrated to reduce many of the somatic symptoms associated with PMS. Affective and emotional symptoms, however, were improved inconsistently or not at all. Therefore, the use of prostaglandin inhibitors should be restricted to the treatment of dysmenorrhea.

Diet

There is no evidence that nutritional deficiencies cause PMS. Poor dietary habits, however, may exacerbate symptoms. A variety of nutritional factors have been examined for their role in PMS, including investigation of appetite changes; glucose tolerance; intake of carbohydrates, salt, and caffeine; and vitamin and mineral deficiencies.

Abnormalities in glucose metabolism, affected by cycling estrogen levels, have been postulated as a causative factor for the hypoglycemic-like symptoms of PMS, such as increased food cravings, irritability, nervousness, and fatigue. There has been no evidence, however, of associations between these symptoms and any changes in glucose tolerance or metabolism in women with PMS. Consuming meals that are high in carbohydrate-rich foods and low in protein, particularly during the premenstrual symptomatic time, may improve mood symptoms of PMS, including depression, tension, anger, confusion, fatigue, and alertness. This recommendation is contrary to the dictum to resist carbohydrate cravings and consume proteins, fruits, and vegetables. A possible link with biologic plausibility may be found in the association between serotonin and carbohydrates cravings. Serotonin has been shown to play a role in carbohydrate intake as well as the intake of its precursor, tryptophan. Thus, the changes in appetite and cravings noted in women with PMS may be as a result of abnormal or altered serotonin metabolism.

Salt Restriction

Salt intake has been theoretically associated with the bloating and edema of PMS. Although there is no evidence to support excess salt as the cause of PMS, because increased salt intake can dramatically produce weight gain, it is sensible to restrict salt intake in hopes of decreasing the sensation of water retention. Salt restriction has not been shown to be an effective treatment of PMS.

Caffeine Restriction

Caffeine has been associated with both the prevalence and the severity of PMS symptoms. Caffeine can increase anxiety, tension, depression, and irritability.
Although caffeine intake is not the cause of PMS and its associated symptoms, women with PMS should avoid or decrease caffeine consumption. Care must be taken when stopping consumption of caffeine because an abrupt cessation of caffeine can be associated with withdrawal symptoms of irritability, nervousness, lethargy, and headache.

**Vitamin E**

Interest in vitamin E in treating PMS symptoms grew from its use in the treatment of fibrocystic breast disease. Although high-dose treatment (400 IU daily) with vitamin E was associated with reducing mood symptoms and food cravings, no reduction was noted in physical symptoms, including breast tenderness. Low-dose vitamin E supplementation (150 to 300 IU) was not effective in reducing PMS symptoms. Although toxicity has not been noted with high-dose treatment with vitamin E, little evidence exists demonstrating its effectiveness as a treatment for PMS.

**Vitamin B₆**

Vitamin B₆ deficiency has been suggested as a cause in PMS by altering liver metabolism of estrogen, lowering dopamine or serotonin levels, and lowering production of essential fatty acids. Vitamin B₆ supplementation in the treatment of PMS has been advocated since the 1940s. Although there are open label trials supporting its use, well-conducted and controlled double-blind trials failed to support consistently the use of vitamin B₆ in the treatment of PMS. There is no good evidence supporting the causative factors involving vitamin B₆ in PMS or supporting that women with PMS are vitamin B₆ deficient. There is a direct dose and time relationship for the development of neurologic symptoms in the use of vitamin B₆ at pharmacologic doses (>500 mg/day). Therefore, in the absence of proven benefit, the use of vitamin B₆ is not recommended for the treatment of PMS.

Although evidence for nutritional treatments is inconsistent, many clinicians recommend a nutritional approach in the initial treatment of PMS. Dietary changes that enhance nutritional status and promote good health are often recommended. This approach is relatively safe and has the added advantage that it is patient controlled. Dietary approaches can modify or alleviate symptoms in some women, and maintaining a healthy, well-balanced diet is highly likely to maximize well-being. A PMS diet consists of 60% complex carbohydrate, 20% protein, and 20% fat. If premenstrual food cravings are a predominant symptom, particular care not to increase caloric intake but to eat at more frequent intervals should be taken. Caffeine, salt, sugar, and alcohol consumption should be reduced or omitted.

**Exercise**

The effect of exercise on PMS has not been fully elucidated. Increasing aerobic exercise has been demonstrated to reduce some of the physical symptoms and negative affect in women with PMS in an open trial possibly via endorphins, whereas another study reported that aerobic exercise was superior to strength training in reducing premenstrual symptoms in normal women. Further research is needed to confirm these observations.
Behavioral Modification

Cognitive, behavioral, relaxation techniques and reflexology have been suggested as a treatment modality for PMS. Preliminary controlled studies have suggested efficacy for these techniques. Many successful behavioral modification treatments (diet, exercise, weight loss) reflect a greater control over the patients' lives and hence produce a positive impact. Large well-controlled trials with well-defined criteria for PMS are needed to evaluate these treatments fully.

SUMMARY

Many women have menstrual symptoms, but relatively few have severe PMS. PMS is a well-defined premenstrual cluster of predominantly affective symptoms that disrupt a woman's daily functioning. PMS is diagnosed with prospective charting of symptoms and should be differentiated from nondisruptive menstrual symptoms, major affective disorders, and other common medical and gynecologic conditions.

Most women with PMS can be helped. The serotonin reuptake inhibitors are becoming the first line of therapy for PMS because they are effective, easily tolerated, and free of major side effects. There is also evidence supporting the role of other antidepressants, anxiolytics, and GnRH agonists in the treatment of PMS. Although increasing control of one's life, promoting a healthy diet, the avoidance of salt and caffeine, vitamin supplementation, and exercise have not been proved as effective treatment for PMS, they should be promoted for their obvious general health benefits.

No one treatment fits the heterogeneous PMS population. A trial of medication should be continued for two or three menstrual cycles with appropriate dose adjustments. If relief is not sufficient, other agents or other treatments should be initiated.

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