

Premenstrual Disorders: Epidemiology and Disease Burden

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Abstract

Many women of childbearing age experience a variety of symptoms related to the menstrual cycle that may be limited to mild discomfort or extend to premenstrual syndrome or, depending on the degree of emotional and somatic impairment, to the most severe premenstrual dysphoric disorder (PMDD). With PMDD, women experience markedly compromised quality of life and ability to function in several settings, leading to higher direct medical costs for increased physician visits and laboratory tests, and higher indirect costs to employers through lower productivity at work. Diagnostic criteria established for premenstrual disorders may now enable physicians to evaluate their patients' complex symptoms more precisely and recommend a form of treatment that can alleviate the original complaint and improve healthcare for women.

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During a woman's reproductive years, premenstrual symptoms can significantly disrupt her quality of life (QOL) as well as present difficult diagnostic and management challenges for clinicians. Premenstrual disorders primarily occur in women who have ovulatory menstrual cycles; however, premenstrual syndrome (PMS) symptoms have also been described in oligo-ovulatory women, for example, in women with polycystic ovary syndrome and those in perimenopause, who may have bleeding without ovulation. Also, some women on oral contraceptives have persistent PMS symptoms. The disturbing symptoms of PMS or premenstrual dysphoric disorder (PMDD) occur during the luteal (premenstrual) phase of ovulatory cycles (the last 14 days before menstruation) and disappear shortly after the onset of menstruation. Normal, manageable symptoms associated with premenstrual molimina (signs of impending menstruation) that most ovulatory women experience

include breast tenderness, food cravings, and bloating or pelvic heaviness.¹ These symptoms do not adversely affect a woman's ability to function during daily activities. PMS is characterized by disturbing physical and/or mood-related symptoms that occur during the late luteal phase of the menstrual cycle and usually disappear within 3 days after the onset of menses. The most severe type of premenstrual disorder, PMDD, formerly known as late luteal-phase dysphoric disorder, causes significant functional impairment and greatly diminishes a woman's QOL.

Development of Diagnostic Criteria for PMS and PMDD

Premenstrual symptoms are characterized in terms of their type, severity, and timing. Until relatively recently, PMS research was limited by the lack of a clinically meaningful definition for this disorder. Clinical management guidelines for PMS that include diagnostic criteria were published in 2000 by the American College of Obstetricians and Gynecologists (ACOG).² These guidelines were based on an earlier publication by Mortola and colleagues, who first noted the distinction between endogenous depression and depressive episodes occurring only during the luteal phase of cycles of women with PMS.³

ACOG practice guidelines for a diagnosis of PMS specified that one or more disturbing affective or somatic symptoms (**Table 1**) must have occurred during the 5 days before menses in each of 3 previous menstrual cycles. These symptoms must be relieved within 4 days of the onset of menses and must not recur until at least day 13 of the

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Table 1. Symptoms of PMS

Somatic	Affective
Headache	Irritability
Breast tenderness	Depression
Abdominal bloating	Angry outbursts
Swelling of extremities	Confusion
	Anxiety
	Social withdrawal

PMS indicates premenstrual syndrome.
Sources: References 2,3.

Table 2. Research Criteria (Diagnostic Criteria) for PMDD

<p>Essential Symptoms</p> <p>Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts</p> <p>Marked anxiety, tension, feelings of being “keyed up” or “on edge”</p> <p>Marked affective lability—feeling suddenly sad or tearful, or increased sensitivity to rejection</p> <p>Persistent and marked anger or irritability or increased interpersonal conflicts</p> <p>Additional Symptoms</p> <p>Decreased interest in usual activities—work, school, friends, hobbies</p> <p>A subjective sense of difficulty in concentrating</p> <p>Lethargy, easy fatigability, or a marked lack of energy</p> <p>A marked change in appetite, overeating, or cravings for specific foods</p> <p>Hypersomnia or insomnia</p> <p>A subjective sense of being overwhelmed or out of control</p> <p>Physical symptoms—headaches, breast tenderness and/or swelling, joint and/or muscle pain, a sensation of “bloating,” and weight gain</p>

PMDD indicates premenstrual dysphoric disorder.
Source: Reprinted from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (Copyright 2000). American Psychiatric Association.

woman’s cycle.² The symptom most often associated with PMS is irritability.

For a diagnosis of PMS, a woman who experiences these symptoms must suffer from notably impaired function in her social activities or work-related performance. In addition, her symptoms must occur consistently during 2 cycles of prospective recording and in the absence of pharmacotherapy, hormone administration, or use of drugs or alcohol.

For PMDD, the American Psychiatric Association has established criteria for diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*.⁴ A woman must experience at least 5 of the symptoms listed in **Table 2**, including 1 or more of the core symptoms, to have PMDD. These symptoms must have been present during most of the last week of the luteal phase in a majority, if not all, of the woman’s menstrual cycles during the previous year. Also, symptoms must begin to remit within a few days of the start of the follicular phase of her cycle, and they must not recur during the week after menses.

Collectively, the symptoms must be severe enough to disrupt a woman’s ability to function at work or school, during household or social activities, or in interpersonal relationships. However, they must not be indicative merely of an exacerbation of on-going anxiety or depressive disorders, with which they may share common features. Prospective daily recording of symptoms during at least 2 consecutive symptomatic cycles is necessary for confirmation of the diagnostic criteria. Because of the cyclic nature of depressive symptoms in PMDD, it should be possible to differentiate this premenstrual disorder from depressive disorders that occur throughout the cycle.⁴

Epidemiology of Premenstrual Disorders

Approximately 70% to 90% of women of childbearing age in the United States experience at least some uncomfortable symptoms during the premenstrual phase of their cycles; this percentage can be extrapolated to approximately 43 million to 55 million women (annual estimates).⁵ Between 20% and 40% of this group, or approximately 12 million to 25 million women (annual estimates), believe that they have symptoms sufficiently bothersome to qualify as PMS.⁵ In addition, an estimated 3% to 8% of US reproductive-age women, numbering 2 million to 5 million (annual estimates), have symptoms of sufficient severity to be classified as PMDD.⁵

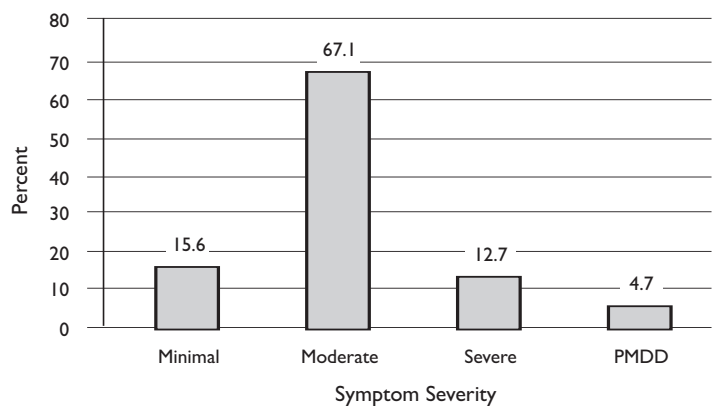
Premenstrual disorders can affect a woman at any stage in her reproductive life—beginning around age 14, or about 2

years after menarche, and persist until around age 51, when menopause typically occurs.⁶ According to Halbreich and colleagues, US women have approximately 481 menstrual cycles during this age span.⁶ With an average adjustment of 22 months for 2 pregnancies and postpartum periods, many women actually experience about 459 cycles during their childbearing years. In addition, US women with PMDD experience an average of 6.4 days of severe symptoms per menstrual cycle⁷; this extrapolates to a lifetime total of roughly 2938 days, equivalent to approximately 8 years with severe symptoms. Thus PMS/PMDD can cause distress or even impairment of functioning over a significant fraction of a woman's lifetime. Even after treatment that alleviates the symptoms of PMDD, the underlying physiologic abnormality remains, so that symptoms may recur after discontinuation of treatment.⁸

In addition to the projections listed earlier for numbers of women with PMS/PMDD, recently published studies regarding diagnostic and treatment approaches for women with premenstrual disorders were evaluated.⁶ For example, Kraemer and Kraemer analyzed the experience of women who reported seeking medical attention for their premenstrual symptoms from an average of 3.75 physicians over an average of 5.33 years before being diagnosed with PMS.⁹ Similarly, 85% of women respondents to a survey by Campbell and colleagues had tried 1 or more treatments for PMS, and 45% reported that they wanted additional help.¹⁰ In a survey of 445 US women reporting premenstrual symptoms, 138 (31%) met the criteria for PMS.⁷ Less than half (45%) of the group with severe premenstrual symptoms had sought medical treatment, and 58% did not think any treatment would help.⁷ It appears likely that many women with PMS and PMDD may be misdiagnosed, because symptoms can mimic organic disorders or worsen existing psychiatric conditions (known as premenstrual magnification), and often they may not receive adequate counseling to assuage their concerns.

In an investigation of pretreatment psychosocial functioning of women with PMDD and their response to treatment, scores on several psychosocial functioning scales dur-

Figure. Severity of Premenstrual Symptoms in Women* Aged 21 to 45 Years



*N = 1194.

PMDD indicates premenstrual dysphoric disorder.

Source: Adapted with permission from Sternfeld B. *Obstet Gynecol.* 2002; 99:1014-1024.

ing the follicular phase in these women were similar to community norms, whereas scores during the luteal phase were similar to scores of women with depressive disorders.¹¹

The spectrum of premenstrual symptom severity was examined by Sternfeld et al in a large, diverse sample of women from members of a large health maintenance organization in northern California.¹² Eligibility criteria included: (1) aged 21 to 45, (2) no psychiatric diagnoses in the past 2 years, (3) no psychotropic medication in the past 6 months, (4) no history of hysterectomy or bilateral oophorectomy, and (5) no pregnancy in the previous year. The 1194 women who qualified for the study rated their symptoms' severity during each day of the premenstrual phase of their cycles: 186 had minimal symptoms, 801 had moderate symptoms, 151 had severe symptoms, and 56 met the criteria for PMDD. The percentage of women in each category is shown in the **Figure**. Each woman experienced a relatively constant degree of symptom severity—particularly for emotional symptoms—over 2 consecutive cycles.

Premenstrual Disorders: The Disease Burden

The high prevalence of premenstrual disorders and their negative impact on women's QOL has been an ongoing concern

for patients and their physicians. Because the symptoms are so varied, and because no specific endocrine diagnostic test exists, a premenstrual disorder may go unrecognized or be misdiagnosed as another condition. However, diagnostic criteria developed for PMS and PMDD have made it possible to consider more objectively the somatic, emotional, and behavioral symptoms that cause long-term distress for so many women. Overcoming this barrier to understanding the complexity of women's menstrual-related complaints is a major step toward ameliorating patients' impaired daily functioning and achieving adherence with physician recommendations.

In addition to interfering with a woman's QOL, PMS and PMDD can have both direct and indirect economic consequences. Direct costs take the form of fees for outpatient office visits (including possible referrals to specialists), laboratory tests, and treatment. Indirect costs, which are considerably more difficult to quantify, are usually viewed in terms of lost productivity at work (sometimes termed "presenteeism") and lost wages because of absenteeism.

Borenstein and colleagues analyzed women aged 18 to 45 years who were enrolled in a medical group in southern California in a cross-sectional cohort study.¹³ Women who completed the screening survey and who met eligibility criteria

were asked to complete 2 screening tools in a telephone interview: the Medical Outcomes Study Short Form-36 (SF-36) and the 10-item Center for Epidemiological Studies-Depression Scale. Of the 436 women who completed and returned the survey, 125 were identified as having PMS and 311 served as controls. The women with PMS scored significantly lower on the mental ($P < .001$) and physical ($P = .04$) scales of the SF-36 in comparison with controls. In addition, women with PMS reported decreased productivity at work, greater interference with hobbies, and a greater number of workdays missed for health-related reasons (each $P < .001$) compared with the control group. Women with PMS also made more frequent visits to ambulatory-care providers and were more likely to accrue an excess of \$500 in visit costs over 2 years. It was concluded that PMS has a significant impact on a woman's health-related QOL and may lead to reduced productivity at work and increased healthcare costs.¹³

This same group of women was also asked to maintain a symptom diary using the Daily Record of Severity of Problems (DRSP) during 2 consecutive menstrual cycles.¹⁴ A total of 125 participants were identified as having PMS; of these, 78 women had symptoms for 1 cycle and 47 women had symptoms for 2 cycles; the 311 women without PMS again served as controls. **Table 3** shows the percentages of controls and women with 2 cycles of PMS who had high health-related absenteeism (>2 workdays/month missed), high productivity loss (>5 days/month with a 50% decrease in productivity), and a high degree of impairment (>14 days/month) in occupational and social activities and other settings. The women with 2 cycles of PMS were significantly more likely to experience general impairment on more days per month compared with controls (22 ± 6.5 days/month vs 9.6 ± 7.9 days/month; $P < .0001$).

In conjunction with the preceding study, Borenstein and colleagues also quantified the economic impact of PMS on the employer by looking at direct medical costs (based on administrative claims and the Medicare fee schedule) and indirect costs (based on the woman's self-report of workdays missed

Table 3. Work-productivity Loss and Functional Impairment Associated With PMS Over 2 Menstrual Cycles

Measurements	Controls (%)	2 Cycles PMS (%)	P Value
>2 days/month missed due to health reasons	16.7	35.6	.006
>5 days/month with 50% reduction in work productivity	21.2	61.7	<.0001
>14 days/month with impairment in:			
Work/school/household activities	14.9	68.1	<.0001
Social activities/hobbies	21.0	66.0	<.0001
Relationship with others	10.7	61.7	<.0001

PMS indicates premenstrual syndrome.

Source: Dean BB, Borenstein JE. *J Occup Environ Med.* 2004;46:649-656.

and decreased work productivity).¹⁴ The population was composed of 374 women with regular menses who had used the DRSP to record daily symptoms for 2 consecutive menstrual cycles. Based on the DRSP, 111 (29.6%) women were diagnosed with PMS. This group had increased direct medical costs of \$59 per year ($P = .003$) and increased indirect costs of \$4333 per year compared with women who did not have PMS ($P < .0001$). It was concluded that a diagnosis of PMS was associated with modest increases in direct medical costs and a considerable increase in indirect costs stemming from missed workdays and lower productivity when the women were at work.¹⁴

Etiology of Symptoms in Premenstrual Disorders

Work by a number of investigators suggests that reproductive hormones are normal in women with PMS/PMDD, but women with these syndromes have higher sensitivity to the changing levels of reproductive hormones that occur during the menstrual cycle. Recently, Halbreich and Monacelli¹⁵ reviewed concepts on the pathobiology of premenstrual disorders and noted that these disorders involve multifaceted interactions between processes of the central nervous system, hormones, and other modulators. Women who have a genetic predisposition to premenstrual disorders (although no specific genes have yet been identified) may experience abnormally severe responses to normal cyclic fluctuations of gonadal hormones that may contribute to symptom expression.

Ovulation and gonadal hormones can mediate changes in neurotransmitters, such as serotonin and gamma-aminobutyric acid, which are involved in regulating mood, behavior, and cognitive functions,¹⁶ and in neurohormonal systems, such as the renin-angiotensin-aldosterone system (RAAS), which controls sodium and water retention and potassium excretion, and any resulting abnormalities can lead to premenstrual symptoms. For example, estrogen and progesterone affect the RAAS in different ways to influence electrolyte and fluid balance in the body. Estrogen has a mineralocorticoid

effect by inducing the synthesis of angiotensinogen in the liver, and this, in turn, increases aldosterone and stimulates the RAAS to increase fluid retention, bloating, and breast tenderness—all premenstrually related symptoms. Progesterone, however, exhibits antimineralocorticoid activity by competing with aldosterone at the aldosterone receptor. The end result of these hormonal changes is an increase in fluid excretion and a reduction in the bloating and breast tenderness that frequently occur in the late luteal phase of the menstrual cycle.¹³ Therefore, a woman who experiences significant water retention, bloating, and breast tenderness in the late luteal phase of her cycle has an altered response to changes in levels of gonadal hormones that contributes to her premenstrual symptoms.¹⁶

Another study evaluated the episodic release of progesterone and luteinizing hormone (LH) in the luteal phase of the cycles of 14 women with PMS and in 14 controls without PMS.¹⁷ The Moos' Menstrual Distress Questionnaire was used to prospectively confirm PMS in 2 consecutive menstrual cycles. Blood samples were drawn every 10 minutes for 12 hours, and the Detect program was used to determine the presence of significant progesterone and LH pulses. The increased pulse frequency and decreased amplitude of LH in women with PMS compared with controls reflects changes in neurotransmitters, supporting the concept of PMS as a neuroendocrine disorder.¹⁷

Diagnosis of PMS and PMDD

To establish a diagnosis of PMS or PMDD, symptoms must: (1) be characteristic of common mood or physical symptoms, cognitive disturbances, and/or behavioral consequences; (2) be limited to the luteal phase of the cycle; (3) cause discomfort for the woman and, in the case of PMDD, greater impairment; and (4) not be readily explained by another diagnosis.¹⁷

During the initial visit of a woman presenting with premenstrual symptoms, several issues should be addressed. Based on the patient's history and a physical examination, the physician should determine whether 1 or more other diagnoses should

Table 4. Premenstrual Symptoms Self-assessment Tools

<p>Premenstrual Symptoms Screening Tool (PSST) 19-item questionnaire that allows the patient to rate the severity of the symptoms used to diagnose PMDD (Steiner M, et al. <i>Arch Women Ment Health.</i> 2003;6:203-209.)</p> <p>Calendar of Premenstrual Experiences (COPE) Includes 22 symptoms that are divided into 4 factors: mood reactivity, autonomic/cognitive, appetitive, and related to fluid retention (Feuerstein M, et al. <i>J Reprod Med.</i> 2002;47:279-289.)</p> <p>Visual analogue scale (VAS) (to quantify subjective factors) In a study of mood symptoms, Steiner et al (1999), a VAS was used for each of the 4 core symptoms for PMDD: irritability, tension, depression, and mood swings. The scale consisted of a 100-mm vertical line labeled 0 or “no symptom” at the left end and 100 or “severe” at the right end. (Steiner M, et al. <i>Arch Women Ment Health.</i> 2003;6:203-209.)</p> <p>Daily Record of Severity of Problems (DRSP) Consists of 24 items—21 individual items grouped into 11 distinct symptoms and 3 functional impairment items. The items are rated from 1 (not at all) to 6 (extreme). Available at: Daily Record of Severity of Problems. Available at: www.pmdd.factsforhealth.org/drsp_month.pdf. Accessed October 18, 2005.</p>
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PMDD indicates premenstrual dysphoric disorder.

be considered and, if indicated, should order appropriate laboratory tests or consultations to assess any other possibilities. If the patient is experiencing vegetative symptoms, significant suicidal ideations, or frequent inability to function, a psychiatric or psychologic referral should be considered.¹⁸

At least 2 months of prospective daily symptom recording using an established assessment tool provided by the physician are required for a diagnosis of PMS or PMDD. Examples of tools to evaluate premenstrual symptoms appear in **Table 4**.

At the second visit, the physician should critically review the pattern of the patient’s symptoms in her daily record. For example, is the menstrual pattern consistent with ovulation? Are the symptoms confined to the luteal and early menstrual phases of the cycle? If the assessment tool and the overall clinical evaluation are consistent with a premenstrual disorder, the clinician should then select an appropriate form of treatment.¹⁸

Additional daily symptom recording can help the physician and patient assess response to recommended treatments. For example, if symptoms are relatively mild, lifestyle modifications, dietary and other nutritional approaches, and nonprescription remedies may be tried and their effects documented over several cycles. Not all patients are willing and able to invest the time required for long-term symptom recording, however.

Conclusion

Most women of childbearing age experience some cyclic menstrually related symptoms, the severity of which can range from being relatively mildly problematic to causing serious premenstrual distress and interfering with occupational and social functioning. Across their entire constellation, premenstrual symptoms have been shown to have an adverse impact on a woman’s QOL and productivity and to lead to increased direct and indirect medical costs.

The proposed etiology of premenstrual disorders is multifaceted and includes an underlying genetic predisposition (although no genes have yet been identified) that makes a woman more susceptible to changes in gonadal hormones that interact with neurotransmitters and neurohormonal systems, resulting in symptoms that occur only in the luteal phase of the menstrual cycle.¹⁶

Diagnostic criteria have been developed for the diagnosis of PMDD that require (1) at least a 30% increase in at least 5 symptoms from the follicular to the luteal phase over 2 menstrual cycles based on daily prospective records; (2) the occurrence of menstrually related symptoms that cause dysfunction or impairment; (3) confirmation that symptoms occur only premenstrually; and (4) laboratory testing and/or consultations to rule out or identify other likely causes for the symptoms. These objective measures increase the likelihood of evaluating patient symptoms more accurately on presentation and recommending treatment approaches to alleviate symptoms, restore function, and optimize overall health for women with premenstrual disorders.

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