

The menstrual cycle–mood disorder tandem: Screening, diagnosis, and treatment

➔ Distinguishing PMDD from an underlying mood disorder is just one of the challenges you face when a woman complains of depression, irritability, anxiety, or other mood changes

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The menstrual cycle and its attendant hormonal changes can exacerbate mental health disorders or trigger new disorders, such as premenstrual dysphoric disorder (PMDD) and perimenopausal depression. The mechanism is unclear, although it appears to be related to complex changes in the immune and endocrine systems.

As ObGyns, we are in a unique position to screen for menstrual cycle-related mood disturbances. Routine screening for mental health disorders is critical for accurate diagnosis and effective treatment. Management options include pharmacotherapy with antidepressant or anti-anxiety agents; hormonal suppression or supplementation; and

referral to, or consultation with, a mental health specialist.

Is it PMS or PMDD?

About 75% of women experience premenstrual symptoms at some point in their reproductive life. When these symptoms occur during the luteal phase only, they constitute premenstrual *syndrome* (PMS). The lifetime prevalence of PMS is thought to be 13% to 18% in women of reproductive age.¹ Common symptoms of PMS include anxiety, irritability, mood changes, acne, breast tenderness, fatigue, bloating, constipation or diarrhea, headache or backache, and food cravings. These changes are present during the luteal phase of the cycle and usually resolve completely with the start of menses.

Premenstrual *dysphoric disorder* (PMDD) is more severe than PMS, affecting only 3% to 6% of premenopausal women. To meet diagnostic criteria for PMDD, a woman must have at least five of the following mood symptoms (one of which must be depression, anxiety, lability, or anger), and they must be severe enough to interfere with social or occupational functioning, or both, for at least two consecutive menstrual cycles:

- depression, feelings of hopelessness, or self-deprecating thoughts

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- anxiety
- lability
- anger or irritability
- diminished interest in regular activities
- impaired concentration
- lethargy or excessive fatigue
- changes in appetite
- sleep disturbance
- somatic symptoms.^{2,3}

Women who have PMDD are typically symptom-free between menses and ovulation.

It is important to differentiate between PMDD and premenstrual exacerbation of an underlying mood disorder to develop the optimal treatment plan.

A preexisting anxiety disorder increases the probability of developing PMDD by a factor of 2.5.⁴ Of women given a diagnosis of PMDD, 30% to 70% have a history of a major mood disorder.⁵ PMDD may be triggered by life stressors, such as marital discord, smoking cessation, or hormonal changes.

Neuroimaging studies using functional magnetic resonance have found a diminished premenstrual response in the amygdala in women with PMDD, leading to enhanced processing of negative emotions, diminished processing of positive emotions, and reduced control of limbic activity (FIGURE).⁶

Is it new or preexisting depression?

During the luteal phase, there is an elevated risk of either a new depressive episode or worsening of ongoing depression.⁷

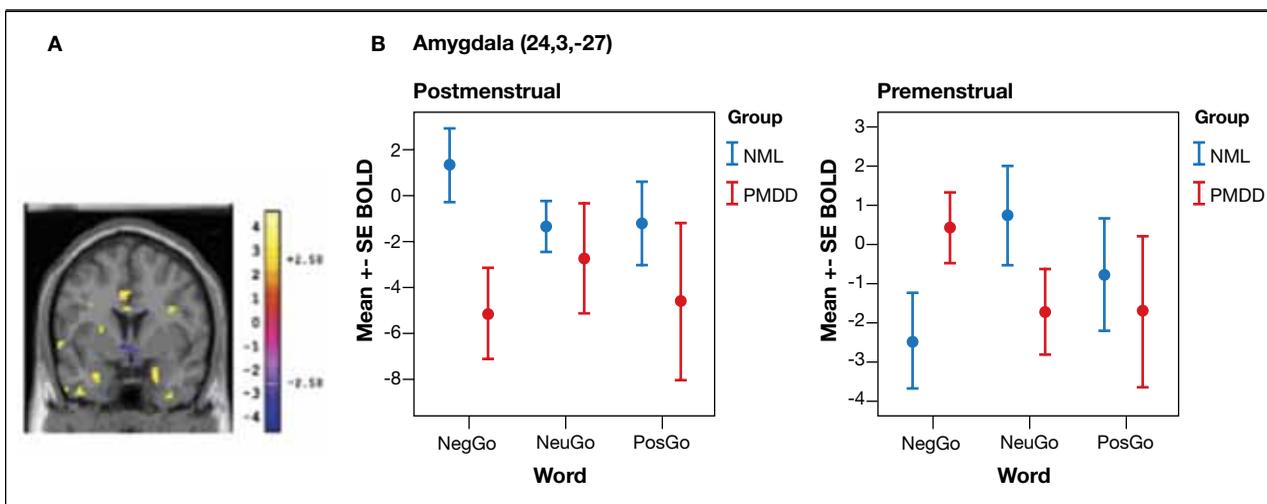
The fluctuating hormone levels seen during the menopausal transition have also been associated with a new onset of depression, affecting 15% to 50% of women.⁸⁻¹⁴ Although most women do *not* experience a significant mood disturbance during the menopausal transition, studies have shown that they are more vulnerable to depression at this time.¹¹⁻¹⁵ Cohen and colleagues found a twofold increase in the risk of developing depressive symptoms with the onset of perimenopause in women without a history of depression.⁹ Another study found a fourfold increase in the risk of depressive symptoms and an increase of 2.5 times in the risk of being given a diagnosis of depression.¹⁶

Fluctuations and variability in reproductive hormones were significantly associated with the onset of depression in perimenopausal women.¹⁶

Cardinal symptoms of major depressive disorder (MDD) are feelings of sadness or unhappiness and loss of interest in normal activities for at least 2 weeks.

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Functional MRI of the brain is revealing in PMDD



A. Coronal section shows enhanced processing of negative emotions in the amygdala of women with premenstrual dysphoric disorder (PMDD). Scale reveals study-specific *t* values. **B.** Bars show responses of women with PMDD (red) vs controls (blue) in postmenstrual and premenstrual phases. Stimulus was an emotional “Go/No-Go” task, with negative, neutral, and positive “Go” findings displayed. Source: Protopopescu et al.⁶

Fast facts for better care of menstrual cycle-related mood disorders

- **Preexisting mental health disorders** may be exacerbated by the menstrual cycle and hormonal changes.
- **Routine screening and assessment** for mental health disorders are critical for diagnosis and effective treatment.
- Screening for menstrual cycle-related mood disturbances should focus on the **history**, including psychiatric history, and the duration and intensity of her symptoms.
- Cardinal symptoms of **major depressive disorder** (MDD) are depressed mood and loss of interest in normal activities over a period of at least 2 weeks.
- Women who have a **history of depression** are more likely to experience depressive symptoms or be given a diagnosis of MDD, particularly if the earlier episode of depression was associated with a reproductive event, such as postnatal blues, postpartum depression, or premenstrual dysphoric disorder (PMDD).
- To meet diagnostic criteria for PMDD, a woman must experience **at least one mood symptom severe enough to interfere with social or occupational functioning**, or both, over at least two consecutive cycles.
- For **depression that worsens during the luteal phase or during perimenopause**, antidepressant agents can be increased during times of vulnerability, such as the luteal phase of the cycle, late perimenopause, or periods of high life stress.
- Although most women do not experience a significant mood disturbance during the **menopausal transition**, studies have found an increased vulnerability to depressive symptoms during this time.
- For perimenopausal women who experience depression as well as vasomotor symptoms, **hormone therapy** may help alleviate both.
- A woman who has depressed mood during the menopausal transition should be evaluated for an **underlying mood or stress-related disorder** rather than assumed to be experiencing menopausal symptoms only.
- **Treatment for anxiety** may improve both anxiety and depression.

During perimenopause, the triggers of depression are many

Women who have a history of depression are more likely to experience depressive symptoms or be given a diagnosis of MDD during the menopausal transition than women without such a history—particularly if the earlier episode was associated with a repro-

ductive event, such as postnatal blues, postpartum depression, or PMDD.^{15,17}

In the Study of Women’s Health Across the Nation (SWAN), the risk of depressive symptoms was significantly increased during perimenopause and early menopause or when a woman used hormone therapy (HT), independent of potential confounding factors, such as poor perceived health or stressful events.¹⁸

Regardless of menopausal status, symptoms such as hot flashes, night sweats, sleep disturbances, mood swings, and impaired memory, have been related to an increased risk of perimenopausal depression in some, but not all, studies.^{9,10,19,20}

Symptoms of perimenopausal depression include:

- emotional flatness
- conversely, emotional lability
- “inability to cope”
- irritability
- social isolation
- tearfulness
- decreased energy
- weight gain
- sleep disturbances
- failure to enjoy normal activities.

Any woman who reports depressed mood during the menopausal transition should be evaluated for an underlying mood or a stress-related disorder.²¹

Some mood disorders may become worse premenstrually

For example, anxiety symptoms may worsen premenstrually, with increasing intensity during the perimenopausal transition. Some small studies have reported a premenstrual increase in panic attacks in women who have panic disorder,^{22,23} although other investigations have found no significant change in the frequency of panic attacks during the late luteal phase of the menstrual cycle, compared with the follicular phase.

Premenstrual exacerbation of generalized anxiety disorder has also been reported in women with and without chronic depression,^{23,24} as has worsening of obsessive-compulsive disorder.²⁵

Women who have bipolar disorder may be increasingly vulnerable to mood shifts during hormonal fluctuations, such as the postpartum period or perimenopause.^{26,27}

No clear evidence of worsening eating disorders has been found, but an increase in binge eating has been reported, particularly during the 5 days preceding menses. No studies have evaluated menstrual cycle effects on anorexia, although an association has been found between the severity of eating disorders and depression.²⁸

Exacerbation of schizophrenia in relation to the menstrual cycle has also been reported.²³ In one study, more than 40% of women who were hospitalized for a psychotic or bipolar episode during pregnancy were hospitalized again during the postpartum period—90% of them within the first 4 weeks after delivery.²⁹ Clearly, ObGyns need to identify women who have psychiatric illness or a history of mental disorders early in pregnancy and work with a psychiatrist to reduce the risk of postpartum hospitalization. We also need to recognize the risk of worsening of these disorders during the perimenopausal transition.

Screening tools are plentiful

When screening for menstrual cycle-related mood disorders, focus on the patient's history as well as the duration and intensity of symptoms. When taking a history, review not only the recent and distant medical history but also the psychiatric history. Screening tools are available to assess the number and type of mood symptoms, as well as their duration and associated impairment, during three critical reproductive phases: premenstrual, postpartum, and perimenopausal. For detail on specific screening tools, see my earlier article on menstrual cycle-related exacerbation of disease.³⁰

Because “many practitioners find the numerous case-finding and screening questionnaires for depression too cumbersome and time-consuming for routine use,”³¹ Arroll and colleagues proposed two simple, *verbal* questions for use in primary care:

“During the past month, have you often been bothered by feeling down, depressed, or hopeless?”

“During the past month, have you often been bothered by feeling little interest or pleasure in doing things?”

They then validated the questions in 15 practices in Auckland, New Zealand. If the answer to either question was “Yes,” the test was considered positive. Of the 157 patients who screened positive, 28 (18%) were determined, via composite interview, to be depressed, whereas only one of the 264 patients who screened negative was found to be depressed. The relatively high false-positive rate is not a concern in depression screening, the investigators point out, because “further clarification can be obtained by asking more questions (the reference standard)” or by referring the patient to another health professional.³¹

Anxiety is common in women who have PMDD and generalized depression and may worsen or intensify during perimenopause. Tools to identify anxiety disorders are available as hand-scored or Web-based tests.³⁰

Before a diagnosis of PMDD can be made, prospective daily ratings of mental health symptoms for at least one consecutive menstrual cycle are essential; there must be a symptom-free period after menses begin until the time of ovulation.³

How to manage anxiety and depression

Anxiety and depression are the two most commonly clustered symptoms. In many cases, anxiety is the presenting complaint for women who have both depression and anxiety.³¹ Decisions about treatment should be made on an individual basis.

Treatment for anxiety may improve both anxiety and depression. For generalized anxiety disorder and MDD, serotonin-norepinephrine reuptake inhibitors (SNRIs) and serotonin reuptake inhibitors (SRIs) are options. These agents have approval from the US Food and Drug Administration (FDA)



Treatment for anxiety may improve both anxiety and depression

to treat a broad spectrum of disorders, including MDD, panic disorder, social anxiety disorder, and post-traumatic stress disorder.

Psychotherapy also appears to be beneficial when used in combination with pharmacotherapy for major mood disorders. During perimenopause, stress-management skills and coping strategies are very helpful for significant midlife stressors, such as aging parents, teenage children, employment, marital or partner issues, and financial concerns.

Psychiatric consultation may be most appropriate for generalized anxiety disorder, bipolar disorder, eating disorders, and complicated or severe depression.

For depression that worsens during the luteal phase or perimenopausal transition, antidepressant agents are recommended as first-line therapy. The dosage can be increased during times of vulnerability, such as the luteal phase, late perimenopause, and periods of high stress.

In perimenopause, hormone therapy (HT) may be helpful, particularly in improving or accelerating the response to antidepressants.³²⁻³⁴ In the absence of contraindications, and if benefits outweigh risks, short-term HT may be an option, although it lacks FDA approval for this indication.³⁵ Psychiatrists may request gynecologic consultation for addition of HT when antidepressants alone are not effective.

Complementary and alternative therapies may also be beneficial, although they are not regulated by the FDA for safety or efficacy. Black cohosh and St. John's wort have demonstrated short-term benefits, as have light therapy, S-adenosylmethionine, and folate.³⁶

Regular exercise, a healthy diet, regular sleep, and decreased caffeine and alcohol consumption are all recommended and may help improve premenstrual mood symptoms. However, a recent large longitudinal study found that the risk of depression decreased with increasing consumption of caffeine.³⁷

Consider lifestyle changes

For PMS or mild PMDD, changes in lifestyle or diet may be helpful, including regular

exercise, smoking cessation, reduced alcohol intake, regular sleep, and the eating of small, frequent, regular meals. Over-the-counter products may provide some relief, as well. Short-term benefits have been found with vitamin B6, vitamin E, calcium carbonate, magnesium, tryptophan, evening primrose oil, and chaste tree berry. However, these products lack FDA approval or oversight and have limited efficacy data.

OCs and antidepressants are the main medical therapies for PMDD

The only FDA-approved *hormonal* therapy for PMDD is drospirenone/ethinyl estradiol (Yaz), which is approved to treat PMDD symptoms in women who need contraception. Other cyclic or continuous oral contraceptives (OCs) help maintain consistent hormone levels through ovarian suppression and are considered acceptable alternatives. The choice of OC depends on the patient; some progestins have been associated with negative mood effects. In postmenopausal women, medroxyprogesterone has more negative mood effects than norethindrone, with micronized progesterone appearing to have the least negative effects on mood.³⁸

Also approved for PMDD are three SRIs: fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft). These agents may be given intermittently (during the luteal phase) or continuously.

Other effective agents for PMDD (but that lack that FDA indication) are citalopram (Celexa), clomipramine (Anafranil, a tricyclic agent), and venlafaxine (Effexor, an SNRI), as well as the anxiolytic agents alprazolam (Xanax) and buspirone (Buspar).

Long-acting gonadotropin-releasing hormone GnRH agonists and danocrine (Danazol) also have been shown to be effective, but lack that FDA indication.

For women who experience significant mood changes that fail to respond to hormonal suppression or an antidepressant, it may be appropriate to combine an OC with

an SRI/SNRI, but data supporting this approach are limited. 

References

- Halbreich U, Borenstein J, Pearlstein T, Kahn LS. The prevalence, impairment, impact, and burden of premenstrual dysphoric disorder (PMS/PMDD). *Psychoneuroendocrinology*. 2003;28(Suppl 3):1-23.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
- Ling FW. Recognizing and treating premenstrual dysphoric disorder in the obstetric, gynecologic, and primary care practices. *J Clin Psychiatry*. 2000;61(suppl 12):9-16.
- Perkonig A, Yonkers KA, Pfister H, et al. Risk factors for premenstrual dysphoric disorder in a community sample of young women: the role of traumatic events and posttraumatic stress disorder. *J Clin Psychiatry*. 2004;65(10):1314-1322.
- Soares CN, Cohen LS, Otto MW, Harlow BL. Characteristics of women with premenstrual dysphoric disorder (PMDD) who did or did not report history of depression: a preliminary report from the Harvard Study of Moods and Cycles. *J Womens Health Gend Based Med*. 2001;10(9):873-878.
- Protopopescu X, Tuescher O, Pan H, et al. Toward a functional neuroanatomy of premenstrual dysphoric disorder. *J Affect Disord*. 2008;108(1-2):87-94.
- Yonkers KA. The association between premenstrual dysphoric disorder and other mood disorders. *J Clin Psychiatry*. 1997;58(suppl 15):19-25.
- Bromberger JT, Meyer PM, Kravitz HM, et al. Psychologic distress and natural menopause: a multiethnic community study. *Am J Public Health*. 2001;91(9):1435-1442.
- Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during the menopausal transition: The Harvard Study of Moods and Cycles. *Arch Gen Psychiatry*. 2006;63(4):385-390.
- Freeman EW, Sammel MD, Liu L, Gracia CR, Nelson DB, Hollander L. Hormones and menopausal status as predictors of depression in women in transition to menopause. *Arch Gen Psychiatry*. 2004;61(1):62-70.
- Freeman EW, Sammel MD, Lin H, et al. Symptoms associated with menopausal transition and reproductive hormones in midlife women. *Obstet Gynecol*. 2007;110(2 pt 1):230-240.
- Steinberg EM, Rubinow DR, Bartko JJ, et al. A cross-sectional evaluation of perimenopausal depression. *J Clin Psychiatry*. 2008;69(6):973-980.
- Avis NE, Brambilla D, McKinlay SM, Vass K. A longitudinal analysis of the association between menopause and depression. Results from the Massachusetts Women's Health Study. *Ann Epidemiol*. 1994;4(3):214-220.
- Schmidt PJ, Haq N, Rubinow DR. A longitudinal evaluation of the relationship between reproductive status and mood in perimenopausal women. *Am J Psychiatry*. 2004;161(12):2238-2244.
- Woods NF, Smith-DiJulio K, Percival DB, et al. Depressed mood during the menopausal transition and early postmenopause: observations from the Seattle Midlife Women's Health Study. *Menopause*. 2008;15(2):223-232.
- Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Arch Gen Psychiatry*. 2006;63(4):375-382.
- Gregory RJ, Masand PS, Yohai NH. Depression across the reproductive life cycle: correlations between events. *Prim Care Companion J Clin Psychiatry*. 2000;2(4):127-129.
- Bromberger JT, Matthews KA, Schott LL, et al. Depressive symptoms during the menopausal transition: The Study of Women's Health Across the Nation (SWAN). *J Affect Disord*. 2007;103(1-3):267-272.
- Avis NE, Crawford S, Stellato R, Longcope C. Longitudinal study of hormone levels and depression among women transitioning through menopause. *Climacteric*. 2001;4(3):243-249.
- Bosworth HB, Bastian LA, Kuchibhatla MN, et al. Depressive symptoms, menopausal status, and climacteric symptoms in women at midlife. *Psychosom Med*. 2001;63(4):603-608.
- Woods NF, Mariella A, Mitchell ES. Depressed mood symptoms during the menopausal transition: observations from the Seattle Midlife Women's Health Study. *Climacteric*. 2006;9(3):195-203.
- Breier A, Charney DS, Heninger GR. Agoraphobia with panic attacks. Development, diagnostic stability, and course of illness. *Arch Gen Psychiatry*. 1986;43(11):1029-1036.
- Hsiao MC, Hsiao CC, Liu CY. Premenstrual symptoms and premenstrual exacerbation in patients with psychiatric disorders. *Psychiatry Clin Neurosci*. 2004;58(2):186-190.
- McLeod DR, Hoehn-Saric R, Foster GV, Hipsley PA. The influence of premenstrual syndrome on ratings of anxiety in women with generalized anxiety disorder. *Acta Psychiatr Scand*. 1993;88(4):248-251.
- Labad J, Menchon JM, Alonso P, Segalas C, Jimenez S, Vallejo J. Female reproductive cycle and obsessive-compulsive disorder. *J Clin Psychiatry*. 2005;66(4):428-435.
- Freeman MP, Smith KW, Freeman SA, et al. The impact of reproductive events on the course of bipolar disorder in women. *J Clin Psychiatry*. 2002;63(4):284-287.
- Marsh WK, Templeton A, Ketter TA, Rasgon NL. Increased frequency of depressive episodes during the menopausal transition in women with bipolar disorder: preliminary report. *J Psychiatr Res*. 2008;42(3):247-251.
- Godart NT, Perdereau F, Rein Z, et al. Comorbidity studies of eating disorders and mood disorders. Critical review of the literature. *J Affect Disord*. 2007;97(1-3):37-49.
- Harlow BL, Vitonis AF, Sparen P, Cnattingius S, Joffe H, Hultman CM. Incidence of hospitalization for postpartum psychotic and bipolar episodes in women with and without prior prepregnancy or prenatal psychiatric hospitalizations. *Arch Gen Psychiatry*. 2007;64(1):42-48.
- Pinkerton JV, Guico-Pabia CJ, Taylor HS. Menstrual cycle-related exacerbation of disease. *Am J Obstet Gynecol*. 2010;202(3):221-231.
- Arroll B, Khin N, Kerse N. Screening for depression in primary care with two verbally asked questions: cross sectional study. *BMJ*. 2003;327(7424):1144-1146.
- Schmidt PJ, Nieman L, Danaceau MA, et al. Estrogen replacement in perimenopause-related depression: a preliminary report. *Am J Obstet Gynecol*. 2000;183(2):414-420.
- Soares CN, Almeida OP, Joffe H, Cohen LS. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. *Arch Gen Psychiatry*. 2001;58(6):529-534.
- Rasgon NL, Dunkin J, Fairbanks L, et al. Estrogen and response to sertraline in postmenopausal women with major depressive disorder: a pilot study. *J Psychiatr Res*. 2007;41(3-4):338-343.
- Gyllstrom ME, Schreiner PJ, Harlow BL. Perimenopause and depression: strength of association, causal mechanisms and treatment recommendations. *Best Pract Res Clin Obstet Gynaecol*. 2007;21(2):275-92.
- Geller SE, Studee L. Botanical and dietary supplements for mood and anxiety in menopausal women. *Menopause*. 2007;14(3Pt1):541-549.
- Lucas M, Mirzaei F, Pan A, et al. Coffee, caffeine, and risk of depression among women. *Arch Intern Med*. 2011;171(17):1571-1578.
- Oinonen K, Mazmanian D. To what extent do oral contraceptives influence mood and affect? *J Affect Disord*. 2002;70(3):229-240.