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Menstrual cycle-related exacerbation of disease

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Abstract

Exacerbation of common medical and mental health disorders at specific phases of the menstrual cycle is a prevalent phenomenon. Although the precise cause is unclear, studies implicate complex interactions between the immune and neuroendocrine systems. The menstrual cycle also is a trigger for the onset of depressive disorders, including premenstrual dysphoric disorder, a disorder specific to the luteal phase of the menstrual cycle, and depression associated with the transition to menopause. This article discusses common mental health problems exacerbated by the menstrual cycle, with a particular focus on premenstrual dysphoric disorder and perimenopausal depression. Throughout the reproductive lifespan, routine screening and assessment for the presence of common psychiatric disorders are critical for accurate diagnosis and provision of effective treatment. Management options include referral or consultation with a primary care provider or psychiatrist; treatment options for premenstrual dysphoric disorder and perimenopausal depression include pharmacotherapy with antidepressant agents and/or psychotherapy. Hormones may be helpful.

Keywords

exacerbation; major depressive disorder; menstrual cycle; premenstrual dysphoric disorder; transition to menopause

Exacerbation of various medical and mental health conditions at specific phases of the menstrual cycle, particularly during the luteal and menstrual phases, is a common phenomenon (Table 1).¹ Approximately 50% of migraines in women are menstrually related,² catamenial epilepsy affects 10–70% of women with epilepsy,³ and premenstrual exacerbation of asthma has been reported in up to 40% of asthmatic women.⁴ Preexisting mental health disorders with premenstrual exacerbation include anxiety, and bipolar, psychotic, and eating disorders (Table 2). Lifetime prevalence rates for anxiety disorder are estimated at 30%.⁵ Generalized anxiety disorder (GAD) in women has a total lifetime prevalence rate of 7% with rates as high as 10% after age 45 years.^{5–7} In primary care settings, GAD is the most common anxiety disorder and the second most common psychiatric disorder after depression.^{7,8} The menstrual cycle appears to trigger the onset of premenstrual dysphoric disorder (PMDD), a mood disorder specific to the luteal phase of the menstrual cycle that affects up to 6% of premenopausal women,^{1,9} and depression associated with the transition to menopause.^{1,9} Although up to 50% of women may experience depressive symptoms during the menopausal transition, most are not diagnosed with depression.^{10–14}

Obstetrician-gynecologists often serve as a woman's primary health care provider during the reproductive and menopausal years and are therefore in a unique position to recognize the presence of disorders exacerbated or triggered by the menstrual cycle or transition to menopause. We describe the phenomenon of disease triggered or exacerbated by the menstrual cycle, examine potential underlying mechanisms to explain menstrual cycle-related effects, identify psychiatric disorders commonly exacerbated by the menstrual cycle with a particular focus on PMDD and depression associated with the transition to menopause, discuss the role of the obstetrician-gynecologist in identifying predictable patterns of symptom deterioration of psychiatric disorders exacerbated by the menstrual cycle, and review management options for psychiatric disorders exacerbated by the menstrual cycle.

Examining etiologic factors in menstrual cycle disease exacerbation

The precise cause and underlying mechanisms of menstrual cycle-related disease exacerbation are not clearly understood. Complex interactions between fluctuating and declining levels of ovarian hormones during the menstrual cycle have been associated with the immune and neuroendocrine systems. In some women with migraines, the sudden decline in levels of estrogen during the menstrual cycle appears to trigger migraine onset^{1,15}; after menopause, when estrogen levels are low with little fluctuation, migraines tend to improve.¹ Eighty percent of pregnant women with migraines without aura report no migraines during the third trimester; nearly all (94%) report return of migraines after delivery.¹⁶ Sudden estrogen withdrawal, in 98 women who received gonadotropin-releasing hormone as part of in vitro fertilization, was associated with migraines in 28 (28.6%) women, of whom 23 (82%) reported debilitating severity.¹⁷ Treatment for menstrual migraine treatment included therapy given shortly after the migraine begins as well as short-term preventive therapies with triptans (serotonin receptor agonists), nonsteroidal antiinflammatory drugs, and estrogen supplements given typically 2 days before menses and up to 3 days after the onset of menstruation.¹⁸ Long-term preventive therapy is recommended for recurrent migraines or a concomitant medical condition that could respond to migraine therapy. For those with migraines while taking low-dose 21-day cycle 20 or 30 μ g oral contraceptives (OCs), the addition of estrogen during the placebo week may alleviate menstrual migraine. Continuous OCs for 11 weeks to suppress ovulation and menses may also prevent the onset of menstrual migraine.¹⁸

In catamenial epilepsy, menstrual-cycle-linked, low levels of progesterone have been associated with decreased seizure threshold.¹⁹ Seizure frequency has been found to be elevated immediately preceding ovulation, corresponding to a rise in estrogen, as well as immediately preceding menses, corresponding to a rapid reduction in estrogen and progesterone.^{1,19} Catamenial epilepsy may be due in part to a decrease in corpus luteum progesterone-derived GABA (gamma-aminobutyric acid) steroids during menstruation.²⁰ Changing levels of estrogen and progesterone throughout the cycle may alter the metabolism of anticonvulsant drugs, via release of hepatic monooxygenase enzymes.^{1,21}

Estrogen has been shown to influence the development of B and T cells, as well as the differentiation and homeostasis of antigen-presenting cells.²² If estrogen acts as an immunomodulator, it may contribute to the higher incidence of autoimmune disease observed in women over men. Estrogen may mediate the expression and responsiveness of androgens, progesterone, prolactin, and gonadotropin-releasing hormone, all of which have been shown to have effects on B cell activities and tumor proliferation.²² The action of estrogens on inflammatory diseases may be antiinflammatory or proinflammatory depending on multiple factors such as the type of immune stimulus (foreign antigens or autoantigens), specific target organs, the pre- or postmenopausal status of the woman, variability in

estrogen receptors, differences in intracellular metabolism of estrogen and variable responses of the immune system.²³

Estrogen appears to act as a neuro-modulator with diverse effects on the central nervous system through its influence on neurotransmitter systems.²⁴ During the menopausal transition, fluctuating levels of estrogen are thought to result in variable functioning of serotonin, which may contribute in part to depression.^{25,26} Estrogen has been found to regulate various aspects of GABA and dopaminergic transmission, both important in the brain's response to hormones, by serving as inhibitory and excitatory neurotransmitters.²⁴ An example of the interaction between mood, neuroactive steroids, and the GABA system is PMDD,²⁰ in which a cluster of negative mood symptoms and physical symptoms occurs during the luteal phase of the menstrual cycle.⁹ The sequential addition of progestins or progesterone to postmenopausal estrogen treatment induces negative mood symptoms in some women, thought to be modulated through the GABA system.²⁷

Some women may have an abnormal central nervous system response to normal hormone levels.^{28,29} Schmidt et al²⁹ showed that in women with normal pituitary-gonadal function and premenstrual syndrome (PMS), symptoms of PMS occurred in response to normal hormonal changes during the menstrual cycle; thus in susceptible women, normal levels of gonadal hormones triggered an abnormal response (ie, worsening mood).²⁹ Lee et al²⁸ proposed that autonomic balance appears to shift toward sympathetic bias during the luteal phase of the menstrual cycle, resulting in direct modulation of T-helper cells in the lymphoid system.²⁸ By modulating the lymphoid system and activating the cortisol pathway, the sympathetic system selectively inhibited T-helper 1 functions while facilitating T-helper 2 responses.²⁸ This bias toward T-helper 2 immunity during the luteal phase favors maternal tolerance of the embryo and successful implantation²⁸ and may be an evolutionary adaptation designed to prepare the body for the immunologic and physiologic demands of a successful pregnancy but may also contribute to immune variance seen in systemic lupus or rheumatoid arthritis.^{22,28}

Premenstrual exacerbation of preexisting mental health disorders

Anxiety disorders

A worsening of preexisting anxiety symptoms premenstrually has been reported. Breier et al³⁰ studied 43 menstruating women with agoraphobia and found that half experienced significant premenstrual exacerbation of anxiety symptoms. For panic disorder, premenstrual exacerbation may be associated with an increase in anxiety symptom severity or number of panic attacks. Breier et al³⁰ reported a higher number of panic attacks in 14 of 43 (33%) women with panic disorder, and Hsiao et al³¹ also reported premenstrual exacerbation of panic attack frequency in 30% of patients studied. Two studies^{32,33} of approximately 20 patients each with panic disorder, found no significant change in the frequency of panic attacks between the late luteal and follicular phases of the menstrual cycle. Premenstrual exacerbation of GAD has been reported by Hsiao et al³¹ in Chinese patients with chronic depression and coexisting GAD who had higher rates of premenstrual exacerbation, and by McLeod et al³⁴ with more severe anxiety symptoms in patients with both GAD and PMS, compared with nonaffected controls. Labad et al³⁵ reported some women with obsessive compulsive disorder (OCD) reported worsening of OCD premenstrually and postpartum and exhibited a greater history of mood symptoms, including premenstrual depression and major depression.

Bipolar disorder

Several studies have reported premenstrual exacerbation of psychiatric symptoms as described in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*

(DSM-IV)³⁶ in women who had bipolar disorder diagnosed.^{37–42} Exacerbation has been suggested related to rapid cycling,⁴³ but a relationship between mood and menstrual cycle in rapid cycle bipolar disorder is not clear.⁴⁴ Women with bipolar disorder appear more sensitive to negative life stressors⁴⁵ and more vulnerable to depressive episodes during certain phases of the reproductive cycle, such as during the transition to menopause⁴⁶ and during the postpartum period.⁴⁷ A retrospective study (n = 2524) of women with either major depressive disorder (MDD) or bipolar disorder found 20.9% reported postpartum symptoms and 26.4% reported perimenopausal symptoms.⁴⁸ Lifetime rates of mood symptoms were similar between women with MDD and bipolar disorder but significantly correlated in women with MDD (odds ratio [OR], 1.66 –1.82) compared with nonaffected women.⁴⁸

Psychotic disorders

Menstrual cycle-related exacerbation of psychotic disorders,³¹ including a worsening of psychiatric symptoms and clinical features of schizophrenia, have been reported,^{49,50} and hypothesized to be a concurrence of affective, behavioral, and somatic symptoms related to the premenstrual phase of the cycle.⁵¹ Hsiao et al³¹ reported that of 50 female Chinese patients with schizophrenia, 52% had PMS and 20% experienced premenstrual exacerbation (mild in 70%) of schizophrenia symptoms. Harlow et al⁵² using Swedish registry data (n = 612,306 women with live births, 1987–2001) found postpartum hospitalization incidences of 0.04% for psychotic and 0.01% for bipolar episodes in women with no previous psychiatric hospitalizations, compared with 9.2% and 4.5%, respectively, for women with any predelivery psychiatric hospitalization. More than 40% of women hospitalized during pregnancy for a psychotic or bipolar episode were rehospitalized during the postpartum period, with 90% of all postpartum psychotic or bipolar episodes occurring within the first 4 weeks' postpartum.⁵² Therefore, it is important to identify women with psychiatric histories early in pregnancy and to collaborate with psychiatrists to avoid the risks of hospitalization for postpartum psychosis or bipolar disorder in these women.⁵²

Eating disorders

Changes in appetite and eating behavior are common during the premenstrual phase of the menstrual cycle. Women with bulimia, characterized by binge eating and purging,³⁶ may be susceptible to increased appetite and cravings during the premenstrual phase. Leon et al⁵³ did not find evidence of menstrual cycle-related exacerbation of abnormal eating behavior in 45 women who had bulimia diagnosed; however, Gladis and Walsh⁵⁴ reported a modest statistically significant premenstrual increase in binge eating, particularly the 5 days preceding the menstrual period, among 15 normal-weight bulimic women. Other investigators have found an exacerbation of bulimic symptoms during the premenstrual phase of the cycle.^{55,56}

To date, no studies have been published examining menstrual cycle-related effects on the incidence and course of anorexia, in part, because amenorrhea is a DSM-IV diagnostic criterion for anorexia.⁵⁷ The review by Godart et al⁵⁸ of studies assessing the prevalence of mood disorders in patients with eating disorders (bulimia and anorexia) found most limited by the lack of controls and a lack of information about puberty and reproductive events. Estimated overall lifetime prevalence of MDD in anorexic inpatients and outpatients was 40%, double the rate in the general community with a correlation between severity of the eating disorder and severity of depression.⁵⁸

PMDD

PMDD, a severe form of PMS, affects an estimated 3–6% of premenopausal women⁹ and is characterized by severe mood symptoms confined to the luteal phase of the menstrual

cycle,⁵⁹ followed by a symptom-free period after menses begin and before ovulation.^{59,60} By definition, a patient must report at least 1 mood symptom severe enough to interfere with social and/or occupational functioning for at least 2 consecutive cycles to meet DSM-IV diagnostic criteria for PMDD: dysphoria, tension, mood lability, or anger/irritability (Table 3).^{36,60} A history of anxiety or mood disorder is common among women with PMDD. In a prospective cohort study (n = 1488, 4 years), Perkonig et al⁶¹ found preexisting anxiety disorder associated with 2.5 times higher probability of PMDD developing. Patients with PMDD, 30–70% have a lifetime history of MDD.⁶² Those without a lifetime history of depression have an elevated risk of later having an episode of MDD.⁶² The onset of PMDD may be related to life stressors or environmental factors, including marital disruption,⁶³ cigarette smoking,⁹ a low level of education,⁹ and working outside the home.⁹

Neuroimaging studies that use functional magnetic resonance have shown differences between patients with and without PMDD.^{64,65} Protopopescu et al⁶⁴ found decreased premenstrual response in amygdala to negative stimuli during the premenstrual phase in women with PMDD that included enhanced negative emotional processing, diminished positive emotional processing, and diminished control of limbic activity. Inoue et al⁶⁵ showed that PMDD subjects, compared with controls and those with PMS, had fluctuating serotonergic function with higher serotonergic function during the follicular phase and lower serotonergic function during the luteal phase.

Perimenopausal depression

During the premenstrual phase, the risk of a new depressive episode is elevated and ongoing depression may worsen.⁶⁶ The transition to menopause may be a trigger for new onset depression in up to 15–50% of women,^{10,11,13} due in part to the fluctuating levels of estradiol and follicle-stimulating hormone (FSH) levels and irregular menstrual cycles.^{14,67,68} Mood swings and irritability have been shown to be significantly inversely associated with levels of FSH during the menopausal transition.⁶⁹ Although the majority of women do not experience mood disturbance during the transition to menopause,^{70,71} an increased vulnerability to depressive symptoms for some women has been reported by several community-based surveys and prospective observational studies.^{10,12,14,68,72–74}

Two large longitudinal studies suggest that in women without a depression history, the risk of new onset of MDD may be 2-fold or more during the perimenopause.^{11,67} Cohen et al¹¹ in a prospective cohort study of women without depression history found almost double the risk of significant depressive symptoms developing for those entering perimenopause (n = 326) compared with pre-menopausal women (n = 95) (OR, 1.8; 95% confidence interval [CI], 1.0–3.2), and a 2-fold risk (OR, 1.9; 95% CI, 0.9–4.0) of severe first onset of depressive symptoms. Another prospective cohort study (n = 231) of women without history of depression⁶⁷ that used the Center for Epidemiological Studies of Depression scale [CES-D]⁷⁵ scores ≥ 16 and new onset of a diagnosed depressive disorder that used the Primary Care Evaluation of Mental Disorders [PRIME-MD],⁷⁶ found that those entering the menopausal transition (43%) were 4 times more likely to have new onset of depressive symptoms develop (OR, 4.29; 95% CI, 2.39–7.72; $P < .001$) and 2.5 times more likely to have depression diagnosed (OR, 2.50; 95% CI, 1.25–5.02; $P = .01$).⁶⁷ Fluctuations and variability in levels of reproductive hormones, including estradiol, FSH, and luteinizing hormone, were significantly associated with new onset depressed mood.⁶⁷

Women with a lifetime history of depression have been found to be significantly more likely to experience depressive symptoms and be diagnosed with MDD during the menopausal transition than those without a history of depression.^{12,14,69,72} Higher rates of depressive symptoms in perimenopause are found in women with a history of depressive symptoms or a mood disorder specifically associated with a reproductive-related event, such as postnatal

blues, postpartum depression, or PMDD.^{74,77} Bromberger et al⁷¹ in the Study of Women's Health Across the Nation (SWAN), a community-based, multicenter, longitudinal, observational study of 3302 multiethnic women aged 42–52 years at entry, found that although most did not experience high depressive symptoms (CES-D score ≥ 16), the risk of high depressive symptoms was significantly increased during early peri-, late peri-, postmenopause, or when using hormone therapy (OR ranged from 1.30–1.71), compared with those premenopausal,⁷¹ independent of potentially confounding factors, such as difficulty paying for basics, negative attitude, poor perceived health, and stressful events.⁷¹

The presence of climacteric symptoms, regardless of menopausal status, has been associated with the development of depression. Hot flashes, night sweats, sleep disturbances, mood swings, and memory problems have been shown, in some but not all studies, to be associated with increased risk of perimenopausal depression.^{11,13,78,79} Woods et al⁷⁰ reported in the Seattle Midlife Women's Health Study (n = 164) that the majority of women for the majority of time experienced the menopausal transition without a high severity of depressed mood; a small group of women had labile mood worsening over time, whereas others improved. The finding of a depressed mood in women during the menopausal transition should not be automatically attributed to the menopausal transition, but should be further evaluated.⁷⁰ Psychosocial and environmental factors may contribute to the development of perimenopausal depression, including unemployment, health problems, empty nest syndrome, aging parents, marital discord, financial concerns, and overall life stress.^{67,74,80,81} Furthermore, perceived stress strongly correlates with the severity of menopausal mood symptoms, including irritability, mood swings, anxiety, and concentration difficulties.⁶⁹

There is no specific diagnostic entity for depression during the transition to menopause.³⁶ The cardinal symptoms of MDD are depressed mood and loss of interest in normal activities for at least 2-weeks (Table 4).³⁶ Trouble sleeping and weight gain are associated with both the transition to menopause and with major depression.^{57,78,79} Women may present with physical complaints such as pain or multiple unexplained symptoms.⁸² One international study reported that 69% of patients who met criteria for major depression presented with only physical symptoms, including backaches, gastrointestinal disturbances, and pain in the joints and limbs.⁸² Certain physical illnesses, such as fibromyalgia, migraines, and diabetes, are commonly comorbid with MDD,^{83,84} and may suggest an underlying depressive disorder.

Screening and assessment of PMDD and perimenopausal depression

Screening for the presence of PMDD and perimenopausal depression should focus on overall number and type of mood symptoms, duration of symptoms, and associated impairment as well as current and past medical and psychiatric health.^{77,85} Arroll et al⁸⁶ proposed 2 simple, validated screening questions based on DSM-IV diagnostic criteria for MDD that can easily be integrated into practice: (1) During the past month, have you often been feeling down, depressed, or hopeless? and (2) During the past month, have you felt little interest or pleasure in doing things?⁸⁵ (Table 4). Maintaining psychiatric histories can help identify patients at higher risk for mood disturbance associated with reproductive-related events.⁷⁷ Lifetime psychiatric illness is common in PMDD with mood disorders most common, followed by anxiety disorders in up to 50%.^{87,88} Women with a history of depression are twice as likely to report symptoms of anxiety.⁶⁹ Thus it is important to screen for the presence of anxiety disorders in women presenting with PMDD or perimenopausal depression (Table 5).^{76,87,89–91}

The symptoms of PMDD overlap with those of MDD, particularly atypical depression (ie, depressed mood, sensitivity to interpersonal rejection, appetite increase or weight gain, and

hypersomnia).⁵⁷ However, in contrast to MDD, PMDD is marked by a symptom-free period after menses begins and before ovulation.^{59,60} Prospective daily ratings of mental health symptoms for at least 2 consecutive menstrual cycles are essential to confirm a preliminary diagnosis of PMDD (Table 6).^{60,86,92–97} Validated, patient-rated questionnaires⁹⁸ can be used to assess the presence and severity of depression during the transition to menopause (Table 7).^{99–101}

Management options for PMDD and perimenopausal depression

Effective short- and long-term management of depression is critical to achieve sustained remission and complete functional recovery.⁵⁷ Consultation with or referral to a mental health specialist should be assessed for each individual case.^{102–104} However, anxiety, and bipolar and eating disorders, as well as complicated cases of depression, such as atypical, bipolar, or severe depression, are most appropriately managed by consultation with or referral to a specialist (Table 8).¹⁰⁵ Anxiety and depression symptoms are 2 of the most commonly clustered psychiatric symptom domains, and anxiety is often the chief presenting complaint for patients with depression and concomitant anxiety.¹⁰⁵ Treatment options for anxiety disorders may improve symptoms of both depression and anxiety.⁶ Serotonin-norepinephrine re-uptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) are first-line, US Food and Drug Administration (FDA)-approved treatment agents for GAD.^{6,105,106} Agents from both classes have demonstrated efficacy and safety across the spectrum of depressive and anxiety disorders, including MDD, panic disorder, social anxiety disorder, and PTSD.⁶

PMDD

First-line pharmacologic management of PMDD is typically an SSRI agent.¹⁰⁷ SSRIs, which are FDA-approved for treatment of PMDD include fluoxetine, paroxetine, and sertraline, continuous or intermittent dosing regimens. Agents that have demonstrated efficacy in treatment of PMDD but are not FDA-approved include the SSRI citalopram, the tricyclic antidepressant (TCA) clomipramine, the SNRI venlafaxine, and the anxiolytic agents alprazolam and buspirone.¹⁰⁷

Cyclic or continuous contraceptives provide consistent hormone levels through ovarian suppression and are an acceptable first-line treatment option for women with PMDD, particularly for those who desire hormonal contraception. One OC is FDA-approved for the treatment of PMDD, containing the progestin drospirenone (3 mg) and ethinyl estradiol (20 µg) in a 24-day active pill, followed by 4-day placebo pill regimen.¹⁰⁷ A continuous contraceptive patch, such as the estradiol patch has been shown to improve symptoms of severe PMS and may be beneficial for the treatment of PMDD, but is not FDA approved.¹⁰⁷

The choice of type of contraceptive (oral or patch), and formulation depends on the patient. Some progestins in contraceptives have been associated with negative mood effects.¹⁰⁷ Non-FDA- approved hormonal therapies with demonstrated efficacy for PMDD in randomized, controlled trials include depo leuprolide depot (3.75 mg/mo intramuscularly for 3 cycles), goserelin (3.6 mg subcutaneously for 6 cycles), and danocrine (200 mg/d for 2 cycles).^{107–110} For women with significant mood changes who have not responded to either an SSRI or contraceptive used alone, it may be appropriate to combine a contraceptive with an SSRI, although limited data are available to support this recommendation.¹⁰⁷

Nonpharmacologic interventions for PMDD include regular exercise, cessation of smoking, limited alcohol, and regular sleep.¹¹¹ Stress management, anger management, self-help support groups, individual and couples therapy, cognitive-behavioral therapy (CBT), patient education, and light therapy may be beneficial.¹¹¹ Dietary recommendations include eating

small, frequent, regular, nutritionally balanced meals. Vitamins B6 and E, calcium carbonate, magnesium, and tryptophan have demonstrated short-term benefits,¹¹¹ as have herbs, evening primrose oil, and chaste tree berry.¹¹² Herbal and dietary supplements are not regulated by the FDA and have not been studied in a rigorous or systematic manner.¹¹³

Perimenopausal depression

Antidepressant agents are recommended as first-line therapy for moderate-to-severe major depression, including during the menopausal transition.⁵⁷

For mild-to-moderate depressive symptoms in symptomatic perimenopausal women, estrogen therapy may be helpful.^{114,115} Serotonin and norepinephrine systems involved in mood regulation may become dysregulated during depressive episodes during periods of estrogen fluctuation or decline.^{11,73} Transdermal estradiol therapy (50–100 µg/d) has demonstrated efficacy for the treatment of perimenopausal depression in short-term, double-blind trials.^{114,115} Concerns about the safety of hormone therapy were raised by the Women's Health Initiative (WHI) estrogen plus progestin trial (EPT),¹¹⁶ with increased coronary heart disease (CHD) and breast cancer in healthy postmenopausal women after an average of 5 years.^{116–118} The estrogen-alone component of the WHI trial,¹¹⁹ (conjugated equine estrogen) did not significantly affect the incidence of CHD¹²⁰ or breast cancer¹²¹ over an average of 7 years in healthy post-menopausal women with prior hysterectomy. Additional analyses of WHI found cardiovascular risks not significantly elevated in women less than age 60 or within 10 years of menopause, with a reduced risk of CHD seen in women under age 60.^{122–124} Concern exists about increased incidence of breast cancer after 5 years of use with EPT,¹²⁵ and after longer term (≥15 years of use) of unopposed estrogen.¹²⁶

In the absence of contraindications, hormone therapy is a potential option for short-term treatment of perimenopausal depression in patients for whom the benefits outweigh the risks, although not FDA approved for this indication.¹²⁷

Estrogen therapy, oral or patch, may accelerate response to antidepressants.¹²⁸ Twenty-two postmenopausal women with MDD who received sertraline and either estrogen therapy (0.1-mg estradiol patch) or placebo, had similar response at the end of 10 weeks, but estrogen therapy was associated with significantly greater early improvement (at weeks 2–4) compared with placebo.^{128,129} Little data are available about the influence of menopausal status on response to antidepressants, and efficacy of some antidepressants may vary depending on menopausal status. Kornstein et al¹³⁰ showed that premenopausal women both responded and tolerated the SSRI antidepressant sertraline significantly better than the TCA imipramine, whereas postmenopausal women showed similar response and tolerability to the 2 antidepressants. Pinto-Meza et al¹³¹ found perimenopausal women significantly less likely to respond to 6-month treatment with an SSRI than premenopausal women. In contrast, Cassano et al¹³² reported no significant differences in response or remission rates in pre-, peri-, and postmenopausal women with MDD treated with fluoxetine for 8 weeks. SNRI agents have consistent and improved efficacy compared with other classes of antidepressants for the treatment of MDD in women of different age groups approximating pre-, peri-, and postmenopausal status.^{133,134} Psychotherapy, including Interpersonal therapy and CBT, may be beneficial as it is effectively used in combination with pharmacotherapy for MDD.⁵⁷

Complementary and alternative therapies have limited safety and efficacy data and do not undergo regulation by the FDA.¹¹³ Black cohosh and St. John's wort have demonstrated short-term benefits for perimenopausal depression,¹¹³ whereas light therapy, S-adenosylmethionine, and folate have shown benefits for major depression in women.¹³⁵ A

healthy lifestyle of exercise and a diet limited in caffeine may improve mood symptoms.^{79,135}

Conclusion

The majority of women do not experience menstrual-related exacerbation of disease, although for some women there is an increased vulnerability. Obstetrician-gynecologists are in unique positions to screen for the presence of mental health issues in potentially at-risk patients. Mental health issues may be difficult to identify; however, certain factors are associated with an elevated risk. Identification of pregnant women with previous psychiatric illness early in pregnancy is essential to preventing postpartum hospitalizations for psychosis and bipolar disease. Throughout the reproductive lifespan, routine screening and assessment for the presence of common psychiatric disorders are critical for accurate diagnosis and effective treatment. Consultation with or referral to a mental health specialist may be necessary and should be assessed for each individual case. Treatment options for PMDD and perimenopausal depression include pharmacotherapy with antidepressant agents, and psychotherapy. Hormones may be of benefit.

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TABLE 1

Common medical conditions exacerbated by the menstrual cycle

Condition
Acne
Acute appendicitis
Acute intermittent porphyria
Aphthous ulcers
Asthma
Diabetes
Endocrine allergy and anaphylaxis
Epilepsy
Erythema multiforme
Glaucoma
Hereditary angioedema
Irritable bowel syndrome
Migraines
Multiple sclerosis
Paroxysmal supraventricular tachycardia
Rheumatoid arthritis
Uticaria

Data from Case et al.¹

TABLE 2

Common mental health disorders exacerbated by the menstrual cycle

Disorder
Anxiety
Bipolar disorder
Eating disorders
Menopausal transition-related depression
Premenstrual dysphoric disorder (PMDD)

Data from Case et al.¹

TABLE 3

Criteria for diagnosis of premenstrual dysphoric disorder (DSM-IV)

Criteria
A. In most menstrual cycles during the past year, 5 (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week postmenses, with at least 1 of the symptoms being either (1), (2), (3), or (4).
Cardinal symptoms
1. Markedly depressed mood, feeling of hopelessness, or self-deprecating thoughts.
2. Marked tension, feelings of being “keyed up” or “on edge.”
3. Marked affective lability (eg, feeling suddenly sad or tearful or increased sensitivity to rejection).
4. Persistent and marked anger or irritability or increased interpersonal conflicts.
Other associated symptoms
5. Decreased interest in usual activities (eg, 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.
B. The disturbance markedly interferes with work or school or with usual social activities and relationships with others (eg, avoidance of social activities, decreased productivity and efficiency at work or school).
C. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder (although it may be superimposed on any of these disorders).
D. Criteria A, B, and C must be confirmed by prospective ratings during at least 2 consecutive symptomatic cycles. (The diagnosis may be made provisionally before this confirmation.)

Reproduced, with permission, from the American Psychiatric Association.³⁶

TABLE 4

Criteria for diagnosis of major depressive disorder (DSM-IV)

Criteria
Five or more of the following symptoms must be present during the same 2-wk period; at least 1 of the symptoms is either (1) or (2).
Cardinal symptoms
1. Depressed mood most of the day, nearly every day.
2. Loss of interest or pleasure in most activities, nearly every day.
Other associated symptoms
3. Significant weight loss or gain (>5% of body weight in 1 mo).
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (not merely feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive guilt nearly every day.
8. Diminished concentration, or indecisiveness, nearly every day.
9. Recurrent thoughts of death (not just fear of dying) or suicidal ideation.

Adapted from the American Psychiatric Association.⁵⁷

TABLE 5

Screening tools for primary care providers to identify anxiety disorders

Tool
1. PRIME-MD, a 2-stage rapid screening and interview assessment screens for MDD, GAD, and panic disorder. ⁷⁶
2. The Symptom-Driven Diagnostic System, ⁸⁹ brief, patient-rated screening, handscored.
3. The Mini-International Neuropsychiatric Interview, ⁹⁰ brief, patient-rated screening assessments handscored.
4. The Web-based Depression and Anxiety Test—a free, internet-based for GAD, panic disorder, social anxiety disorder, and posttraumatic stress disorder (PTSD). ⁹¹

TABLE 6

Daily ratings for perimenopausal depression screening

Rating
1. The Daily Record of Severity of Problems (DRSP) Questionnaire 21 symptom items grouped within 11 psychologic and physical symptom domains measure DSM-IV PMDD criteria and changes associated with treatment. ⁹²
2. PMS questionnaires include the Daily Symptom Report, ⁹³
3. The Calendar of Premenstrual Symptom Experiences, ⁹⁴
4. The Moos Menstrual Distress Questionnaire, ⁹⁵
5. The Premenstrual Syndrome Diary, ⁹⁶ and
6. The Premenstrual Assessment Form. ⁹⁷

TABLE 7

Screening questionnaires for perimenopausal depression

Questionnaire
1. Patient Health Questionnaire, ⁹⁸ scores the 9 DSM-IV depression criteria.
2. The 16-item Quick Inventory of Depressive Symptomatology (QIDS) clinician-rated (QIDS-C ₁₆) and self-report (QIDS-SR ₁₆) forms. ⁹⁹
3. An adaptation of Edinburgh Postnatal Depression Screening tool. ¹⁰⁰
4. An adaptation of the Antenatal Psychosocial Health Assessment. ¹⁰¹

TABLE 8

Referral to a specialist

Referral
Anxiety disorder
■ Panic disorder
■ Generalized anxiety disorder
■ Social anxiety disorder
Bipolar disorder
Eating disorder
■ Bulimia nervosa
■ Anorexia nervosa
Psychotic disorder
Complicated cases of depression
■ Depression with psychotic features
■ Depression associated with substance abuse
■ Depression comorbid with panic disorder
■ Atypical depression (agitated depression)
■ Severe depression
■ Bipolar depression
■ Depression with active suicidality
■ Chronic relapsing depression needing long-term treatment
■ Double depression and chronic dysthymic depression

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