

Reproductive Mood Disorders

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Focus Points

- Premenstrual dysphoric disorder (PMDD) differs from premenstrual syndrome (PMS) in that psychological symptoms of PMDD are more debilitating; symptoms of either disorder have an impact on social functioning.
- Symptoms of PMS and PMDD occur during the luteal phase and resolve completely by the cessation of menstrual flow.
- In postpartum depression, symptoms meet criteria for a major depressive episode within 4 weeks of delivery.
- Selective serotonin reuptake inhibitors are helpful in many women with reproductive mood disorders, indicating dysregulation of serotonergic activity as a potential etiology.
- Estrogen has been shown to modulate neurotransmission at multiple points in the serotonin pathway, including serotonin uptake, synthesis, receptor transcription and density, and response to serotonergic stimulation. Progestins counteract some of these effects.

Abstract

Reproductive events are associated with varying degrees of depressed mood in a significant number of women. Reproductive mood disorders linked to menstruation include premenstrual syndrome, premenstrual dysphoric disorder, and premenstrual exacerbation of mood disorders. Postpartum disorders include postpartum "blues" and postpartum depression with or without psychosis. Women are also more vulnerable to affective disorders during the perimenopausal period. Though similar to affective disorders without temporal relationship to hormonal changes, hormonally mediated mood disorders are distinct entities with many common features. They share potential etiologies, including onset with exposure to fluctuation in ovarian sex steroids and improvement in symptoms in response to treatment with selective serotonin reuptake inhibitors (SSRIs.) SSRIs are indeed the best-established class of medications for treating reproductive mood disorders.

Introduction

In the general population, affective disorders are approximately twice as common in women as in men, with a prevalence of depression in women $\leq 20\%$.¹ In addition to genetic and psychosocial factors, repeated dysphoric premenstrual or postpartum events may contribute to the greater lifetime prevalence of mood disorders in women. Affective disorders linked to hormonal

fluctuations are seen during premenstrual, postpartum, and perimenopausal periods. Hormonal fluctuations are also associated with increased risk of affective dysregulation or mood episodes in women with unipolar, bipolar, or perimenopausal depression.² During reproductive events, exposure to and withdrawal from progesterone, more specifically from the centrally acting metabolites of progesterone termed neurosteroids, could modulate

γ -aminobutyric acid (GABA)_A receptor functioning in a fashion similar to chronic stress, increasing the vulnerability to depressive disorders.

Premenstrual affective disorders, postpartum mood disorders, and perimenopausal symptoms are well-recognized syndromes. Care must be taken to perform a thorough history and physical examination, as well as to evaluate symptoms recorded by the patient, in order to avoid diagnosing a reproductive mood disorder in a patient whose symptoms might be better explained by a psychiatric or medical condition. Once a definitive diagnosis is made, various treatment strategies with documented efficacy can be undertaken. This article reviews the basis for these disorders, their clinical features, and updates in their formal diagnosis and treatment.

Premenstrual Affective Disorders: Premenstrual Syndrome and Premenstrual Dysphoric Disorder

Clinical Features and Formal Diagnosis

An estimated 50% to 80% of menstruating women experience physical and psychological symptomatology during the premenstrual period. In 3% to 5% of these cases, symptoms are of sufficient severity to disrupt social or psychological functioning.³ In premenstrual disorders, which include premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD), variations in ovarian hormone concentrations result in both somatic and psychosocial manifestations. Predominant physical complaints include bloating, mastalgia, and increased appetite; affective symptoms include irritability, anxiety, and

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Disclosure: The authors do not have an affiliation with or financial interest in a commercial organization that might pose a conflict of interest.

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depression. Confusion and poor concentration are the primary cognitive changes reported. Behaviorally, social withdrawal and increased argumentative behaviors are typically seen. By definition, the symptoms of PMS and PMDD begin after ovulation and may persist through the first 4 days of the follicular phase of the menstrual cycle. In anovulatory states, such as before menarche, during spontaneously anovulatory cycles, during pregnancy, or after the menopause, the rise and fall of ovarian sex steroids is aborted, and PMS symptoms fail to occur.⁴

PMS is diagnosed when one or more physical symptoms and at least one psychological symptom are present for ≤ 2 weeks prior to menses, with remission by the cessation of the menstrual flow.⁵ In clinically significant PMS, symptoms must be documented prospectively for at least two consecutive menstrual cycles, restricted to the luteal phase of the menstrual cycle, and result in functional impairment. Other medical or psychological diagnoses that might better explain the symptoms must be excluded. Affective and somatic symptoms used as diagnostic criteria for PMS by the American College of Obstetrics and Gynecology (ACOG) are listed in Table 1.⁵

PMDD is a more severe premenstrual disorder focused on the psychological symptoms. It has been estimated that approximately 79% of women diagnosed with severe PMS would also be given the diagnosis of PMDD.⁶ The diagnosis of either PMS or PMDD requires luteal phase timing of symptoms, and a symptom-free interval from approximately day 4 of menses to the onset of ovulation. The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)⁷ criteria for the diagnosis of PMDD are outlined in Table 2. A recent study noted a 6.3% prevalence of PMDD among a community-based sample of American women; other estimates have suggested a prevalence of 3% to 8% of women.⁸

A significant number of women with premenstrual disorders are also affected by other mood disorders. In women with PMS or PMDD, the lifetime prevalence of major depressive disorder (MDD) varies between 30% and 76%, depending on the diagnostic criteria and the population under scrutiny.⁹

Prospectively screened women who met criteria for PMDD were found to have concurrent psychiatric disorders in 20% of cases, as assessed by the Schedule for Affective Disorders and

Schizophrenia interview. Psychiatric diagnoses included depression, anxiety disorder, phobic disorder, schizophrenia, schizoaffective disorder, and substance abuse.⁹

Table 1
ACOG Diagnostic Criteria for Premenstrual Syndrome

PMS is diagnosed when all of the following criteria have been met:

- The patient prospectively documents at least one of the affective and somatic symptoms listed below.
- Symptoms present during the 5 days before menses for three menstrual cycles.
- Symptoms are of significant severity to impact social or economic performance.
- Symptoms abate during the first 4 days of the menstrual cycle and do not recur until at least cycle day 13.
- There is no concomitant pharmacologic therapy, hormone ingestion, or drug or alcohol abuse.

Affective Symptoms

- Depression
- Angry outbursts
- Irritability
- Anxiety
- Confusion
- Social withdrawal

Somatic Symptoms

- Breast Tenderness
- Abdominal bloating
- Headache
- Swelling of extremities

ACOG=American College of Obstetricians and Gynecologists; PMS=premenstrual syndrome. Adapted from m: ACOG Practice Bulletin: Premenstrual Syndrome. *Compendium of Selected Publications*. Washington, DC: American College of Obstetricians and Gynecologists; 2000:1-9.

Rapkin AJ, Mikacich JA, Moatakef-Imani B. *Primary Psychiatry*. Vol 10, No 12. 2003.

Table 2
DSM-IV Criteria for PMDD

PMDD is diagnosed when the following criteria has been met for most of the preceding 12 cycles:

1. The patient experiences five or more of the following symptoms, including at least one core symptom:
 - Markedly depressed mood, hopelessness, self-deprecating thoughts*
 - Marked anxiety, tension*
 - Marked affective lability*
 - Persistent and marked anger or irritability*
 - Decreased interest in usual activities
 - Subjective sense of difficulty in concentrating
 - Subjective sense of being out of control
 - Lethargy, easy fatigability
 - Marked change in appetite
 - Hypersomnia or insomnia
 - Other physical symptoms, such as breast tenderness, headache, bloating
2. The patient reports symptoms during the last week of the luteal phase, with remission within a few days of onset of menses
3. The patient documents absence of symptoms during the week following menses
4. The patient demonstrates marked interference of symptoms with work, school, or usual social activities and relationships
5. Symptoms are not an exacerbation of another disorder
6. Prospective daily ratings confirm three of the above criteria during at least two consecutive symptomatic menstrual cycles

*Core symptom.

DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; PMDD=premenstrual dysphoric disorder.

Adapted from: *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994:715-718.

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The diagnosis of PMS or PMDD is hampered by the presence of a wide range of symptoms, many shared with other syndromes. In addition, certain psychiatric or medical conditions may worsen during the luteal phase of the menstrual cycle. The focus of the first visit to the physician should be a complete history and physical, in order to exclude other diagnoses. The differential diagnosis of PMS and PMDD includes various conditions subject to menstrual magnification or premenstrual exacerbation, including depressive disorders, generalized anxiety disorder, panic disorder, hypothyroidism, irritable bowel syndrome, endometriosis, anemia, chronic fatigue syndrome, fibromyalgia, lupus, perimenopause, drug or alcohol abuse, and domestic violence.

A clinical diagnosis of PMS or PMDD relies on the patient's subjective recounting of symptoms. Nightly recording is essential to document a cyclical nature of the complaints, helping to differentiate a premenstrual disorder from a psychological or medical condition. Patients should chart their symptoms throughout at least two successive menstrual cycles. When the woman returns with her diaries, dividing them into three phases—premenstrual, menstrual, and postmenstrual—demonstrates the temporal relationship between symptoms and menses. Cyclical symptoms confined to the latter half of each menstrual cycle and resolving by day 4 of menses, as well as a clearly symptom-free interval from menses until ovulation, are critical to the diagnosis of PMDD. Severe cases of PMS and all cases of PMDD are disabling syndromes that interfere with work, social relationships, or both. Consistent postmenstrual timing of symptoms suggests an underlying affective disorder, as does the presence of physical symptoms relating only to appetite, energy, and sleep, and not including breast tenderness and/or bloating.

Etiologic Hypotheses

Potential explanations for the symptoms in premenstrual mood disorders involve dysregulation of serotonergic activity and/or of GABAergic receptor functioning.¹⁰ Decreased serotonin transmission in the brain is thought to contribute to depressed mood, irritability, anger and aggression, poor impulse control, and increased carbohydrate craving. Most, but not all, serotonergic

parameters which have been evaluated are altered only during the symptomatic luteal phase in women with PMS or PMDD.¹¹ Furthermore, serotonergic, not noradrenergic antidepressants, are effective in PMS and PMDD.

The GABA_A receptor is considered a primary regulator of cognitive function and affect. Its expression and pharmacologic effect is modulated by various factors, including ovarian sex steroids.¹² Allopregnanolone is a neuroactive steroid produced by the ovary, the adrenal gland, and *de novo* in the brain as a metabolite of both cholesterol and progesterone. Similar to benzodiazepines and barbiturates, allopregnanolone binds to the chloride channel of the GABA_A receptor and has anxiolytic and anticonvulsant effects.¹³ Rodent studies of exposure to and withdrawal from progesterone after metabolism to allopregnanolone reveal decreased sensitivity of GABA_A receptors to GABA agonists, resulting in insensitivity to endogenous anxiolytic neurosteroids or to benzodiazepines.¹⁴ The finding of decreased sensitivity was attributed to alterations in GABA_A receptor subunit composition. Women with PMS or PMDD may also be less sensitive to the anxiolytic, sedating effects of neurosteroids during the luteal phase.¹⁵ Diminished levels of or sensitivity to allopregnanolone and/or altered GABAergic transmission could contribute to symptoms of anxiety, irritability, and depression in women with PMS or PMDD.

Lower allopregnanolone concentrations have also been found in the luteal phase in women with PMS^{16,17} in some published studies.^{18,19} Additionally, in women with premenstrual mood disorders, an appropriate increase in neuroactive steroid levels in response to stress may not occur.¹³ Fluoxetine and paroxetine, two selective serotonin reuptake inhibitors (SSRIs), increase brain allopregnanolone content in rats²⁰ and possibly in individuals with depression. The increase of allopregnanolone concentrations in the brain acting via GABA receptors may contribute to the rapid anxiolytic and antidepressant clinical action of this class of drugs.²⁰

The consistent finding of diminished serotonergic activity limited to the luteal phase in women with premenstrual mood disorders, as well as the rapid therapeutic response to the administration of

SSRIs and the alteration in neurosteroid concentration or reactivity, suggest that the interaction between ovarian sex steroids, the GABA_A receptor, and/or the central serotonergic system, differ in women with PMS/PMDD compared with asymptomatic women or those with an affective disorder.

Treatment Strategies

SSRIs are considered the treatment of choice in premenstrual affective disorders, such as severe PMS or PMDD. Many placebo-controlled trials have demonstrated a 50% to 70% response rate at standard daily antidepressant doses, with significant improvement compared to placebo using various SSRIs, including fluoxetine,^{21,22} sertraline,^{23,24} citalopram,²⁵ and the serotonin norepinephrine reuptake inhibitor venlafaxine.²⁶ Unlike the treatment of affective disorders, in which a clinical response requires 3–6 weeks of exposure to a drug, the response to SSRIs in PMS and PMDD patients occurs within the first days of exposure.

The shorter response interval in premenstrual affective disorders is the basis of intermittent treatment with SSRIs during the luteal phase, which has also proven effective in many studies.^{24,25,27} More recently, weekly luteal-phase dosing of enteric-coated fluoxetine in two 90-mg doses was shown to be efficacious and well-tolerated.²⁸ In addition to improvement in mood, other aspects of PMS and PMDD may be relieved by treatment with SSRIs. SSRIs have been shown to reduce the most common physical symptoms, such as bloating and breast tenderness, associated with PMDD,²⁷ whereas treatment with another antidepressant, bupropion,²¹ has not shown significant effectiveness compared to placebo. In a recently published study,²⁷ intermittent luteal phase dosing of sertraline failed to demonstrate significant improvement in physical symptoms, but did effectively reduce complaints of premenstrual cognitive disturbance, increased appetite, increased sleep, and lethargy. Another recent placebo-controlled study showed that fluoxetine 20 mg/day or 60 mg/day reduced symptoms that negatively impact work capacity within the first cycle of treatment.²⁹

Unfortunately, premenstrual symptoms rapidly recur following discontinuation of SSRI therapy in women with

premenstrual symptoms versus women with depression, who generally experience a prolonged remission. A retrospective analysis of two previous clinical trials of fluoxetine in PMDD demonstrated that symptoms recur within the first cycle after discontinuation following three treatment cycles.³⁰

Historically, oral contraceptive pills (OCPs) have not proven uniformly beneficial in PMS/PMDD. However, a newer OCP containing the progestin drospirenone, a spironolactone derivative, has shown promise in the treatment of PMDD in at least one study.³¹ The antiandrogenic and antiminerocorticoid effects of drospirenone combined with the ovulation inhibition of an OCP may be the basis of the suggested efficacy. The same OCP was found to improve health-related quality of life and general well-being and relieve several physical symptoms during the premenstrual period in women who experience PMS.³² Twenty-four-day active pills with 4-day placebo pill cycles, allowing for more complete hormonal suppression, are under study for the treatment of PMDD with the drospirenone-containing OCP.

The use of a gonadotropin-releasing hormone (GnRH) agonist to suppress ovarian sex steroids provides symptomatic relief in a majority of women with PMS.³³⁻³⁵ Response rates to GnRH agonist therapy were not noted in all documented studies, but in two reports, 50% to 55% of women with PMS responded with a reduction in symptom severity by 50% to 75%. In at least one trial of GnRH agonist therapy with low dose (menopausal replacement doses) of estrogen and progesterone addback, the symptomatic improvement vaginal health and estrogen withdrawal persisted over the course of 12 months.³⁵ A GnRH agonist can be used alone or to augment treatment with an SSRI. With addback therapy, bone density, cardiovascular health, and vaginal health can theoretically be maintained and vasomotor symptoms can be prevented. However, long-term studies are lacking. Therefore, GnRH analog even with addback therapy remains a third-line therapy if psychotropics have failed or if there is a concurrent gynecologic indication for its use, such as cyclic pelvic pain or endometriosis.

GnRH agonist with estrogen addback alone for two to three cycles is also recommended as a preoperative

strategy for women with severe PMS/PMDD who have completed childbearing and who may not have responded adequately to psychotropics. These women may be candidates for hysterectomy and bilateral salpingoophorectomy, which would be followed by addback of estrogen alone. It is reasonable, therefore, to suggest that in these select cases, prior to performing the surgery, both the treating physician and the patient are confident that the hormonal mediated therapy afforded by hysterectomy and bilateral oophorectomy with estrogen addback would be satisfactory for their symptomatology. Bilateral oophorectomy with estrogen addback is effective for severe PMS/PMDD, but should be reserved for extreme cases in which other methods have failed, preliminary treatment with GnRH agonist with addback has indeed been successful, and reproduction is completed.

Several complementary and alternative medicine approaches have demonstrated some efficacy in premenstrual disorders, although studies of these therapies were not well-controlled. These include light therapy, certain herbal and nutritional supplements, the use of exercise, and mind-body approaches.^{36,37} Active bright white light therapy, administered according to a protocol used effectively in seasonal affective disorder, significantly improved mood symptoms in patients with PMS, although one third of the subjects were taking OCPs during the study.³⁶ L-tryptophan, a serotonin precursor, given at a dose of 6 g/day, was significantly more effective than placebo in the control of extreme mood swings, dysphoria, irritability, and tension in patients with PMDD.³⁸ Calcium carbonate 1,200 mg/day in divided doses has also shown efficacy in two randomized controlled trials for PMS.³⁹ Initiation of or increase in exercise, particularly the aerobic variety, may reduce premenstrual mood symptoms and has other obvious potential health advantages. Psychological counseling employing cognitive-behavioral therapy (CBT), in comparison to fluoxetine administration or combined CBT with fluoxetine, showed significant improvement in premenstrual symptoms after 6 months of treatment, and CBT demonstrated longer maintenance of treatment effects.⁴⁰

Mood Disorders in Pregnancy

The prevalence of depression during pregnancy is estimated to be between 10% and 16%. Pregnancy is not considered protective against relapses in women with recurrent MDD. Thus, in women who are treated in the nonpregnant state with SSRIs or tricyclic antidepressants (TCAs) for severe depression or depression with prior recurrences, the same antidepressants are usually continued. SSRIs, although category C drugs, are well-studied in pregnancy, and equivalent rates of major malformations compared to nonexposed controls have been noted. In women taking SSRIs in various stages of pregnancy, rates of neonatal complications and congenital anomalies were within general population rates.⁴¹ Children of women who received either TCAs or fluoxetine were evaluated between 16 and 86 months of life, and there were no significant differences in intelligence quotient, temperament, mood, activity levels, distractibility, or behavior, in any of the children.⁴² Recent research suggests that SSRI-exposed infants may have adverse serotonergic effects during the first 4 days of life. Observed symptoms, including tremor, restlessness, and rigidity, are similar to serotonergic overstimulation in adults, rather than an SSRI withdrawal syndrome.⁴³ Nevertheless, the use of SSRIs in order to avoid severe, disabling depression in pregnant women is recommended.

Postpartum Affective Disorders

Postpartum affective disorders, ranging from postpartum "blues" to severe depression with psychosis, pose a major public health problem affecting 10% to 20% of women in the first few months after delivery. Aside from the adverse consequences for women who become depressed while going through a major life transition, there are additional concerns for the family unit. Maternal depression has an adverse effect on the relationship between mother and child and on the child's emotional, behavioral, and cognitive development.⁴⁴ Expedient treatment is usually effective and allows mother-infant attachment to develop. However, though women often have contact with healthcare professionals during the postpartum

period, many women experiencing depression after birth do not seek professional attention and are relatively unwilling to disclose emotional problems, particularly depression.⁴⁵ Almost 50% of women do not seek help from family members or friends.⁴⁶

Treatment is based on optimizing social support and counseling or antidepressants as indicated. Referral for psychiatric care is indicated with severe depression, suicidal ideation, or evidence of psychosis. Such women require a comprehensive approach to treatment, including crisis intervention, pharmacotherapy, psychotherapy, and intensification of their social support system.

Postpartum "Blues"

A transitory state of unstable emotional reactivity that affects up to 85% of all postpartum women, the postpartum "blues" are characterized by affective lability with rapid onset and resolution.⁴⁷ Symptoms include crying spells, sadness, confusion, insomnia, and anxiety, and can begin as early as the first postpartum day, but most commonly occur after 3–5 days. Affective symptoms are self-limited and rapidly remit, usually within 7–14 days. Treatment consists of supportive care, along with education regarding newborn care. In those women whose symptoms continue and/or worsen, a diagnosis of postpartum depression is often made.

Several theories have been advanced to explain postpartum blues. The abrupt withdrawal of estrogen and progesterone may play a role. The likelihood of developing postpartum blues has been shown to depend upon the change between gestational and postpartum hormone levels, rather than the absolute level of these hormones.⁴⁸ Additionally, allopregnanolone and pregnanolone, anxiolytic metabolites of progesterone, were found to be significantly lower in patients with postpartum blues.⁴⁹ These neuroactive steroids may behave like other GABA_A agonists (eg, benzodiazepines), producing withdrawal symptoms after rapid discontinuation.

The development of postpartum blues is unrelated to parity, breastfeeding, prior psychiatric history, environmental stressors, or cultural context.⁵⁰ However, these factors may influence whether the blues lead to a major postpartum depressive episode.

Postpartum Depression

Postpartum depression, which affects 10% to 20% of women, is defined as an MDD episode within 4 weeks of delivery. Patients meet *DSM-IV* criteria for MDD, including presence of five or more of the following symptoms for at least 2 weeks: depressed mood, loss of interest or pleasure (anhedonia), significant weight loss or gain/change in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness, inappropriate/excessive guilt, diminished ability to think or concentrate, and recurrent thoughts of death or suicide.⁷ Sleep disturbance and excessive irritability are common. There may be feelings of guilt and inadequacy in caring for the infant, as well as a sense of detachment from the newborn. A small percentage of women with postpartum depression develop egodystonic thoughts of harming their infants.⁵¹ The quality of these thoughts may be obsessive, though they are generally acted upon only in the presence of psychosis.

The etiology of postpartum depression remains unclear. Prospective studies do not definitively link postpartum depression to the presence of hormonal abnormalities.⁵² However, some women may be more sensitive to the mood-destabilizing effect of gonadal steroid withdrawal. Other studies have concluded that cultural factors, including role identification, community support, and rituals, may explain the discrepancies in the incidence of postpartum depression.⁵³ Factors associated with postpartum depression include history of a prior MDD episode, history of PMDD, family history of mood disorders, psychosocial stress including low socioeconomic status, and inadequate social support.^{54,55} Operative delivery, adverse pregnancy outcome, and neonatal hospitalization are also risk factors.⁵⁶

An important first step in the treatment of postpartum depression is accurate diagnosis followed by encouraging the patient to optimize social support. Support from the partner has been shown to be of significant benefit for women experiencing postpartum depression.⁵⁷ Family and friends, as well as home-based help with nannies or housekeepers, can provide assistance with newborn care and allow sleep to be maximized and other responsibilities minimized during the postpartum transition.

Other nonmedical options in the treatment of postpartum depression include individual counseling with interpersonal psychotherapy (IPT), CBT, or group therapy. IPT has been shown to be as effective as pharmacologic therapy for the treatment of mild to moderate postpartum depression.⁵⁸ Six sessions of CBT also reduced postpartum depressive symptoms.⁵⁹ Group IPT may be more cost effective than individual IPT. Furthermore, the group approach allows participants to meet other women facing similar challenges, thereby normalizing their experiences as mothers of newborn infants.⁶⁰

The use of antidepressants is recommended for moderate to severe depression or for resistant depression. SSRIs and TCAs have been well studied and do not need to be discontinued during breastfeeding.⁶¹ Because of their preferable side-effect profile, the SSRIs are considered first-line agents. Sertraline is the best-studied SSRI and is therefore the drug of choice in breastfeeding mothers with postpartum depression.⁶² Althuler and colleagues⁶² demonstrated that low concentrations of sertraline were detected in breast milk, and infant serum concentrations were very low or nondetectable. Paroxetine is also a highly effective SSRI, with no drug detected in breast milk or infant serum.⁶³ Fluoxetine, an SSRI with a longer half-life, is also an effective antidepressant. In women who breastfeed, data demonstrate that if doses do not exceed 20 mg/day, there will not be an adverse effect in infants even after 2 months of therapy.⁶⁴ Citalopram is an acceptable alternative SSRI, as the drug enters the mother's milk in small amounts.⁶⁴ The TCAs nortriptyline and imipramine have been used effectively in the treatment of postpartum depression.⁶¹ In some, the management of postpartum depression is similar to the treatment of nonpuerperal depression and includes medication and/or psychotherapy.

Estrogen therapy using 17- β -estradiol has been shown to rapidly reduce postpartum depressive symptoms.⁶⁵ The medical risks preclude use in most cases; however, thromboembolic events are increased if estradiol is utilized within the first 6 weeks, and endometrial hyperplasia can result from unopposed estrogen use.

The use of preventive measures in postpartum depression is dependent

upon the patient's history. All women are at risk for postpartum depression and should be screened at 4–6 weeks postpartum with the Edinburgh Postnatal Depression Scale.⁶⁶ In primiparas with a history of depression or PMDD, very close observation for the first sign of postpartum depression is recommended and a 1–2-week postpartum visit should be scheduled. For multiparas with a history of postpartum depression, treatment should begin immediately after the birth of the child, before evidence of depression is seen. Antidepressants can be initiated during the third trimester if the patient is at very high risk of developing MDD after delivery. Postpartum depression increases the vulnerability to future episodes of MDD and PMDD.

Postpartum Depression with Psychosis

Postpartum psychosis is the most rare postpartum mood disorder, occurring in only 0.1% to 0.2% of all pregnancies.⁶⁷ Episodes typically begin abruptly between days 3 and 14 of the postpartum period, but they may occur anytime between the day 1 and week 6 postpartum.⁶⁸ Major symptoms include restlessness, sleep disturbance, anxiety, paranoid symptoms, hallucinations with or without delusions, catatonic excitement, and labile or depressed mood.⁶⁸ The extreme severity of symptoms represents a significant risk to both mother and infant. Compared with episodes of nonpsychotic depression, women with postpartum psychosis who harbor thoughts of harming their infants are more likely to act on these thoughts.⁶⁹

Postpartum psychosis has an uncertain etiology, although rapidly declining estrogen levels may be a contributing factor.⁷⁰ Thyroid dysfunction may play a role in a small subgroup of patients; thyroid abnormalities, notably thyroiditis, are slightly higher in postpartum women than in the general population.⁷¹ Other organic etiologies, such as Sheehan's syndrome, human immunodeficiency virus infection, drug or alcohol-related intoxication, and withdrawal conditions, may also be causes of psychosis.⁷²

Postpartum psychosis can be the first manifestation of a recurrent psychiatric illness, such as unipolar or bipolar depression. Postpartum mania is the most common cause of postpartum psychosis, affecting 25% to 35% of

women with previously diagnosed bipolar disorder.⁷³ Some studies suggest that psychotic disorders with postpartum onset are recurrent illnesses in the majority of cases.⁶⁸ According to the *DSM-IV*, the specifier "with postpartum onset" can be applied to the current or most recent major depressive, manic, or mixed episode in MDD, bipolar I or bipolar II disorder, or brief psychotic disorder, if the onset of the episode is within 4 weeks postpartum.⁷⁴

Aggressive treatment of postpartum psychosis is critical. The risk of infanticide necessitates careful supervision of the psychotic mother and her infant. Hospitalization is often required, especially if the mother appears to be dangerous to herself or to the infant.⁴⁷ Medication is indicated in the treatment of postpartum psychosis when the psychosis is deemed to be a manifestation of bipolar disorder and in cases where there is an increased risk of bipolar disorder, such as in the presence of a positive family history. Recommended treatments consist of mood stabilizers, such as lithium and neuroleptics. High-potency antipsychotics, such as haloperidol, are preferred over low-potency antipsychotics and are often necessary for the acute phase of psychosis.⁷⁵ However, in cases where postpartum psychosis is a diathesis of bipolar disorder, mania in particular, typical antipsychotics with antimanic properties, such as olanzapine, risperidone, and quetiapine, are indicated.⁷⁴ In addition, there is empiric support for the use of antidepressants, such as SSRIs or TCAs.^{72,74}

Issues related to breast feeding must be addressed, including whether or not breast feeding is advisable in a mother with postpartum psychosis. Sleep and stress reduction are certainly important for patients with postpartum psychosis, and breast feeding may not be conducive. In addition, lithium is present in breast milk at approximately 50% of the maternal serum levels and can be potentially toxic to the infant.⁷⁵ Therefore, breastfeeding is not recommended in women who are being treated with lithium. Lamotrigine, along with atypical antipsychotics, such as clozapine, olanzapine, risperidone, and quetiapine, are also not compatible with breast feeding.⁷⁵ Some mood stabilizers, such as valproic acid and tegretol, which have traditionally been used in the treatment

of epilepsy, have been determined to be safe in breastfeeding mothers.⁷⁵ However, no information exists regarding gabapentin and topiramate.

Puerperal psychosis can be resistant to neuroleptic medications, especially when the symptoms emerge long after delivery.⁷⁶ Electroconvulsive therapy (ECT) is an important alternative therapy for patients resistant to medication or whose symptoms threaten to escalate. Numerous reports indicate that severe depression, including that with postpartum onset, responds well to ECT. This form of therapy might be the treatment of choice for severe postpartum depression with or without suicidal and/or homicidal ideation, as well as in postpartum psychosis, where psychopharmacologic intervention may not provide rapid enough restoration of the patient's function.⁷⁷

The frequency of relapses during puerperium is approximately 25%. Prophylactic lithium immediately following delivery in nonlactating women who have previously suffered from either puerperal psychosis or bipolar disorder has been suggested.⁷⁸

Perimenopausal Affective Disorders

Perimenopause is the period of transition from regular menstrual cycles to amenorrhea. By definition, the perimenopausal transition begins at the end of ovulatory cycles with reproductive potential and ends with the beginning of menopause. During this time, menses become irregular due to intermittent anovulatory cycles. Estradiol concentrations rise and fall in a chaotic pattern. The absence of menstrual bleeding for 12 months represents menopause. Menopause usually occurs at 45–55 years of age, with an average onset age of 51.4 years. Also known as the climacteric, perimenopause can last 5–7 years. Recent studies have supported the hypothesis that perimenopausal women experience increased vulnerability toward mood disorders.^{79–81} Among perimenopausal women, a psychiatric morbidity prevalence of 49.5% has been noted, with nearly one third meeting criteria for a depressive disorder.⁸¹ A lengthy perimenopause was found to be associated with higher rates of depression.⁸²

The primary physiologic changes associated with the ensuing menopause

are the degeneration of ovarian follicles (apoptosis) and resulting decrease in circulating estrogen. Premenopausal women have mean serum estradiol concentrations of approximately 5–35 ng/dl (50–350 pg/mL); levels after the menopause reach a nadir of approximately 1.3 ng/dl (13 pg/mL). Estrone levels fall from approximately 40–110 ng/dl to 3 ng/dl.⁸³ Testosterone and the adrenal androgen, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) concentrations also gradually decline. During the perimenopausal transition, hormone levels fluctuate erratically due to intermittent ovulation. As a result, women may experience both physical and psychological symptoms. Common physical complaints include hot flashes, vasomotor symptoms, insomnia, palpitations, headache, vaginal dryness, and pain with intercourse secondary to vaginal atrophy. Prominent mood complaints include irritability, anxiety, and depression.

There has been considerable controversy in the literature regarding the direct impact of decreasing estrogen levels on perimenopausal mood symptoms. Recent studies, however, have suggested that as estrogen levels decline, susceptibility to MDD increases.⁸⁴ Other studies do not show a direct correlation between estrogen concentrations and severity of depressive symptoms.⁸⁵ A few studies correlated menopausal well-being to DHEA or DHEAS levels.⁸⁶ The vulnerability for depression increases if risk factors are present, including family history of mental illnesses or affective disorders, impaired health, or social stress.⁸⁷ It remains unclear whether mood symptoms are related to the gradual decline in estrogen or to the abrupt fluctuations in estrogen concentrations due to intermittently ovulatory cycles.⁸⁸ Furthermore, large population-based studies recently noted >50% of the variance for the development of depression in the population can be explained by previous depression or cognitive and social factors.⁸⁹

Several depression screening instruments have been applied to the study of perimenopausal women. The Edinburgh Depression Scale (EDS) is effective and user-friendly in the detection of depressive symptoms and is not influenced by menopause-related somatic symptoms.⁹⁰ The Beck Depression Inventory (BDI) and State Trait Anxiety Inventory (STAI)

I and II have also been utilized.⁹¹ However, certain criteria identified by these scales may overlap in depressed individuals and those in perimenopause, making diagnosis difficult. For example, the BDI assesses for loss of interest in sex, which is a feature of both perimenopause and depression.⁹² One inventory has been developed specifically for perimenopausal women.⁹³ The Menopause-Specific Quality of Life Questionnaire assesses both physical and psychological menopausal symptoms and is self-administered.⁹⁴

It is important to distinguish between perimenopausal mood changes and symptoms and depressive disorder as defined by the *DSM-IV*.^{7,91} MDD as operationalized in the *DSM-IV* is defined as decrease in mood, performance, and drive, in addition to hopelessness; reduced self-esteem, guilt, suicidality, and changes in appetite, weight, libido, psychomotor activity, and sleep. The symptoms must continue for ≥ 2 weeks and be present most of the time during the episode. The symptoms also must represent a change compared to previous mood and functioning.

Most perimenopausal women do not develop MDD but have mild depressive symptoms. Menopause itself has not been thought to be a major cause of depression. Irritability is a very prevalent symptom in perimenopause and is reported as frequently as hot flashes.⁹⁴ The degree of premenstrual symptomatology, such as irritability, anxiety, fatigue, and depression, can be correlated with similar symptoms that occur during perimenopause, reinforcing the psychological impact of alterations in concentration of sex steroids in susceptible women.⁹⁵

Proposed Etiologies

A growing body of evidence demonstrates the impact of sex steroids on neuroregulatory systems that affect mood. Receptors (estrogen receptors α and β for sex steroids) have been identified in the amygdala, hippocampus, cingulate cortex, locus ceruleus, midbrain raphe nuclei, and central gray matter.⁹⁶ Estrogen impacts neuronal function through the serotonergic, noradrenergic, dopaminergic, γ -aminobutyric, and cholinergic systems. In particular, estrogen has been shown to modulate neurotransmission at multiple points in the serotonin pathway including serotonin

uptake, synthesis, receptor transcription and density, and response to serotonergic stimulation. Progestins counteract some of these effects.

Estrogen and progesterone may be important modulators of circadian rhythm. Reproductive changes in these hormones may cause impaired mental health in susceptible individuals, and a pilot study demonstrated that estradiol and progesterone may help to maintain circadian rhythm stability, thereby enhancing the effect of antidepressants.⁹⁷ Estradiol restores normal sleep electroencephalogram pattern and lessens nocturnal movement arousals.^{92,96,98}

Treatment Strategies

Psychosocial therapy with or without pharmacotherapy is the main treatment approach for the treatment of depression or depressive symptoms.⁹¹ Severe depression requires pharmacotherapy with antidepressants. Hormonal therapy alone or supplementation is discussed below.

A randomized, placebo-controlled study⁹⁹ described treatment of depressed perimenopausal women with 100 μ g transdermal 17- β -estradiol patches showing decrease in both depressive and somatic symptoms. The transdermal route was chosen for more steady state serum levels of estradiol over the study period. Depressive symptoms remained significantly decreased in women who received estrogen during the 4-week washout period. Patients who had discontinued placebo reported symptoms as severe as prior to treatment. Somatic complaints in those who were treated with estradiol returned during the washout period, whereas those who discontinued placebo had insignificant changes. In another placebo-controlled trial,¹⁰⁰ transdermal 17- β -estradiol 50 mcg improved mood in perimenopausal women with both minor and major depression. Full or partial therapeutic response was seen in 80% of those treated with estradiol alone, while only 22% of those receiving placebo reported improvement. Response occurred after 3 weeks of therapy and did not improve after an additional three weeks. The addition of medroxyprogesterone acetate after 3 or 6 weeks of estrogen treatment did not significantly alter the mood improvement. Reduction of depressive symptoms

occurred even in women who did not report vasomotor symptoms.

Estradiol levels are important factors in quality of sleep, as reported by perimenopausal women.¹⁰¹ Depressive symptoms have a strong association with poor sleep quality, and this association persisted in one study¹⁰¹ after adjusting for age, vasomotor symptoms, estradiol concentrations, caffeine consumption, and anxiety. The study suggests the importance of estrogen therapy during the perimenopause for women with poor sleep and concomitant depression.

SSRIs have been shown to be particularly useful for perimenopausal/menopausal women with affective disorders. The addition of estrogen has a role in augmentation of antidepressants. Significant improvement has been reported in depressed perimenopausal women with unipolar MDD after treatment with 0.3 mg of daily estradiol.¹⁰² Approximately 50% of the subjects were also receiving fluoxetine, but were nonresponders. Both groups had statistically significant responses to estrogen therapy by the first week of the 8-week trial. Mood ratings were maintained throughout the treatment period. It appears that the addition of estrogen to an SSRI may augment or accelerate therapeutic response to SSRIs.

Combined OCPs have also been shown to be effective in the treatment of perimenopausal mood and physical symptoms. A placebo-controlled, double-blind, randomized trial^{103,104} demonstrated the efficacy of a low-dose OCPs in symptomatic perimenopausal women. The treatment group showed improved cycle control, decreased bleeding severity, and improved quality of life, as measured by the Menopausal Symptoms-Specific Questionnaire, as well as improvement in physical and emotional roles, energy, social function, sleep, and depression. The OCP treatment was well-tolerated.

DHEA, a neurosteroid formed not only in the periphery of the adrenal but also in the brain, has been suggested as a treatment for MDD on the basis of small, early studies, but results are mixed.^{105,106} There may in fact be synergism with hormone-replacement therapy, but this has not been well studied.⁹⁴

Aside from pharmacologic therapy, other therapeutic modalities have been

proposed, including increasing physical activity, stress reduction, support groups, and psychotherapy. In particular, IPT is useful for short-term treatment of depressive disorders. IPT involves adaptation to the change of roles in the perimenopausal state, improvement in the patient's self-esteem, and acceptance of autonomous power.¹⁰⁷

Conclusion

Mood symptoms accompany physical symptoms and may significantly affect well-being and quality of life in a large proportion of premenstrual, postpartum women and menopausal women. A previous history of depression is highly associated with the occurrence of PMDD, postpartum depression, and perimenopausal depression. Recent research efforts support the use of serotonergic antidepressants in the treatment of symptomatic premenstrual women and estrogen and traditional antidepressants for postpartum and perimenopausal women.

Relief of vasomotor symptoms and improved sleep quality in menopausal women could underline a large part of the improvement in depressed mood, as most studies of perimenopausal women included those with vasomotor symptoms. OCPs may also be helpful in PMDD and perimenopausal affective disorders, though further research is needed to validate their effectiveness. **PP**

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2004 Association and Society Meeting Schedule

February

International Neuropsychological Society
32nd Annual Meeting
February 4-7
Baltimore, MD

American Association for Geriatric Psychiatry
17th Annual Meeting
February 21-24
Baltimore, MD

March

NEI Global Psychopharmacology Congress
March 12-14
San Diego, CA

2nd World Congress on Women's Mental Health
March 17-20, 2004
Marriott Wardman Park Hotel
Washington, DC

Anxiety Disorders Association of America
24th Annual Conference
March 11-14, 2004
Miami, FL

May

American Psychiatric Association
157th Annual Meeting
May 1-6
New York, NY

June

44th Annual New Clinical Drug Evaluation Unit (NCDEI)
Meeting
June 1-4
Phoenix, AZ

CINP XXIV Congress
June 20-24
Paris, France

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