

Clinical Practice

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

POSTPARTUM DEPRESSION

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A woman visits the doctor for her six-week postpartum evaluation. She reports that she cannot sleep even if her baby sleeps. She cries daily and worries constantly. She does not feel hungry and is not eating regularly. Making decisions is overwhelming. She says she is not herself. How should this new mother be evaluated and treated?

THE CLINICAL PROBLEM

Postpartum depression, the most common complication of childbearing, occurs in 13 percent of women (one of every eight) after delivery.¹ Given that there are nearly 4 million births in the United States annually, a half-million women have this disorder every year.

STRATEGIES AND EVIDENCE

Definitions

Major depression is defined by the presence of five of the symptoms listed in Table 1, one of which must be either depressed mood or decreased interest or pleasure in activities. The symptoms reflect the physiologic dysregulation (disturbance of sleep, appetite, and cognition) that is characteristic of depression and must be present for most of the day nearly every day for two weeks or more. According to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV),² an episode of depression is considered to have postpartum onset if it begins within four weeks after delivery. However, onset within three

TABLE 1. SYMPTOMS OF MAJOR DEPRESSION WITH POSTPARTUM ONSET.*

Major depression is defined by the presence of five of the following symptoms, one of which must be either depressed mood or decreased interest or pleasure†:
Depressed mood, often accompanied or overshadowed by severe anxiety
Markedly diminished interest or pleasure in activities
Appetite disturbance — usually loss of appetite with weight loss
Sleep disturbance — most often insomnia and fragmented sleep, even when the baby sleeps
Physical agitation (most commonly) or psychomotor slowing
Fatigue, decreased energy
Feelings of worthlessness or excessive or inappropriate guilt
Decreased concentration or ability to make decisions
Recurrent thoughts of death or suicidal ideation

*From the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV).² Postpartum depression is defined in the DSM-IV as that which begins within four weeks after delivery.

†Symptoms must be present most of the day nearly every day for two weeks. A diagnosis of major depression also requires a decline from the woman's previous level of functioning and substantial impairment.

months after delivery is the time frame commonly used by investigators on the basis of epidemiologic studies.³ The patterns of symptoms in women with postpartum depression are similar to those in women who have episodes unrelated to childbirth.⁴ Difficulties in the interactions between caretakers who are under stress and infants increase the risk of insecure attachment and cognitive and behavioral problems in children. The consequences of parental mental illness, such as family discord, loss of income, and placement of children outside of the home, also affect child development.

Causes

The rapid decline in the levels of reproductive hormones that occurs after delivery is believed to contribute to the development of depression in susceptible women. In one study, such a decline after delivery was simulated in nonpregnant women with the use of leuprolide to induce a hypogonadal state, followed by treatment with supraphysiologic doses of estradiol and progesterone, and finally the withdrawal of both steroids under double-blind conditions.⁵ Five of eight women with a history of postpartum depression, but none of eight women without previous depression, had mood changes. Women with a history of postpar-

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tum depression appear differentially sensitive to the effects on mood of the withdrawal of gonadal steroids.

Although it is tempting to attribute postpartum depression to hormonal decline, several other factors may predispose women to this condition. Stressful life events,⁶ past episodes of depression (not necessarily related to childbearing), and a family history of mood disorders,^{1,7} all recognized predictors of major depression in women,⁶ are also predictors of postpartum depression. The likelihood of postpartum depression does not appear to be related to a woman's educational level, the sex of her infant, whether or not she breast-feeds, the mode of delivery, or whether or not the pregnancy was planned.⁷

Screening

The Edinburgh Postnatal Depression Scale (Supplementary Appendix 1, available with the full text of this article at <http://www.nejm.org>),⁸ a 10-item questionnaire that is easy to administer, is an effective screening tool. One example of an item on the questionnaire is the following statement: "I have looked forward with enjoyment to things," to which responses are scored from 0, for "as much as I ever did," to 3, for "hardly at all." A cutoff score of 9 or 10 has been recommended in the United Kingdom for first-stage screening⁹ and is a reliable indicator of the presence of postpartum depression in women in the United States as well.¹⁰ If a woman has a total score on the Edinburgh Postnatal Depression Scale of 10 or higher or indicates that "the thought of harming myself has occurred to me" either "sometimes" (a score of 2) or "quite often" (a score of 3), a brief clinical interview to review symptoms and establish the diagnosis of depression is warranted.

An alternative to the Edinburgh Postnatal Depression Scale is to frame the required criterion for the diagnosis of depression as a screening question²: "Have you had depressed mood or decreased interest or pleasure in activities most of the day nearly every day for the past two weeks?" If the woman answers in the affirmative, the clinician can next determine whether at least five of the symptoms listed in Table 1 are present. The level of impairment and distress can be explored with the question "Has the depression made it hard for you to do your work, take care of things at home, or get along with people?"²

Evaluation and Differential Diagnosis

If the patient has considered a plan to act on suicidal thoughts or has thoughts about harming her infant, provisions for safety and urgent referral for psychiatric care are recommended. Women who have major functional impairment (as evidenced by the avoidance of family or friends, an inability to attend

to hygiene, or an inability to care adequately for the infant) and those with coexisting substance abuse are also candidates for rapid referral. Women who report depressive symptoms without suicidal ideation or major functional impairment (or score between 5 and 9 on the Edinburgh Postnatal Depression Scale) should be evaluated again two to four weeks later in order to determine whether an episode of depression has evolved or whether symptoms have subsided.

A careful history taking and a physical examination are warranted in all women with postpartum depression. Thyroid function should be assessed, since both hypothyroidism and hyperthyroidism are more frequent during the postpartum period and may contribute to mood changes. However, in women with hyperthyroidism or hypothyroidism, treatment of both thyroid and depressive disorders is usually required.⁷

Postpartum depression must be distinguished from the "baby blues," which occur in the majority of new mothers. In this syndrome, symptoms such as weeping, sadness, irritability, anxiety, and confusion occur, peaking around the fourth day after delivery, and resolving by the tenth day. This transient mood disturbance does not consistently affect the woman's ability to function.

Postpartum psychosis represents a psychiatric emergency that requires immediate intervention because of the risk of infanticide and suicide. Onset usually occurs within the first two weeks after delivery. This disorder differs from other psychotic episodes because it usually involves extreme disorganization of thought, bizarre behavior, unusual hallucinations (which may be visual, olfactory, or tactile), and delusions, all of which suggest an organic cause.⁴ Treatments for postpartum psychosis have been discussed in detail elsewhere.¹¹

Postpartum psychosis is usually a manifestation of bipolar disorder.¹² A depressive episode (with or without psychotic features) can occur during the course of bipolar disorder. Therefore, all patients with postpartum depression should be screened with the following questions²: "Have you ever had four continuous days when you were feeling so good, high, excited, or 'hyper' that other people thought you were not your normal self or you got into trouble?" and "Have you experienced four continuous days when you were so irritable that you found yourself shouting at people or starting fights or arguments?" Positive responses to these questions necessitate psychiatric referral.

Antidepressant Treatment

For women who are given a diagnosis of major depression with postpartum onset, treatment with antidepressant drugs is appropriate. A selective serotonin-

reuptake inhibitor should be tried initially because such agents are associated with a low risk of toxic effects in patients taking an overdose, as well as with ease of administration. However, if the patient has previously had a positive response to a specific drug from any class of antidepressants, that agent should be strongly considered.

The efficacy of antidepressant drugs for depression unrelated to childbearing supports their use for postpartum depression, and the available data confirm the assumption that they are effective against postpartum depression. Information about drugs used to treat depression¹³⁻¹⁸ is presented in Table 2. However, only one placebo-controlled trial and three open trials that specifically addressed postpartum depression

have been published. The selective serotonin-reuptake inhibitor fluoxetine was compared with psychotherapy, and both treatments were similarly effective.¹⁸ Fluoxetine was significantly more effective than placebo.¹⁸ Sertraline,¹⁹ venlafaxine,²⁰ and drugs grouped according to class (selective serotonin-reuptake inhibitors and tricyclic antidepressants²¹) were effective in open trials. Women with postpartum depression may be more likely to have a response to serotonergic agents, such as selective serotonin-reuptake inhibitors and venlafaxine, than to nonserotonergic tricyclic antidepressants.¹⁹⁻²¹

Because women who have recently given birth are often sensitive to the side effects of medications,²² treatment should be initiated at half the recommend-

TABLE 2. PHARMACOTHERAPY FOR POSTPARTUM DEPRESSION.

DRUG	RECOMMENDED RANGE OF DOSES (mg/day)*	SIDE EFFECTS	IMPLICATIONS FOR USE DURING BREAST-FEEDING
Selective serotonin-reuptake inhibitors			
Sertraline	50–200	Nausea, loose stools, tremors, insomnia, sexual dysfunction, possible drug interactions†	Drug and weakly active metabolite generally not detectable in infants; no reports of adverse events
Paroxetine	20–60	Nausea, drowsiness, fatigue, dizziness, sexual dysfunction, possible drug interactions†	No active metabolite; levels not detectable in infants; no reports of adverse events
Fluvoxamine	50–200	Nausea, drowsiness, anorexia, anxiety, sexual dysfunction, possible drug interactions†	No active metabolite; levels not detectable in infants; no reports of adverse events
Citalopram	20–40	Nausea, insomnia, dizziness, somnolence	One infant with a measurable level had colic; other infants had no problems and serum levels that were undetectable or just above the limit of detection
Fluoxetine	20–60	Nausea, drowsiness, anorexia, anxiety, sexual dysfunction, possible drug interactions†	Drug and active metabolite have comparatively long half-lives; serum levels similar to those in adults reported in some symptomatic infants; prenatal exposure adds to serum levels in breast-fed infants
Tricyclic antidepressants			
Nortriptyline	50–150	Sedation, weight gain, dry mouth, constipation, orthostatic hypotension, possible drug interactions‡; base-line ECG recommended‡	Drug and metabolites generally below or slightly above limit of detectability; no reports of adverse events in infants
Desipramine	100–300	Sedation, weight gain, dry mouth, constipation, orthostatic hypotension, possible drug interactions‡; base-line ECG recommended‡	Drug and metabolites below quantifiable level; no adverse effects
Serotonin–norepinephrine reuptake inhibitor			
Venlafaxine	75–300	Nausea, sweating, dry mouth, dizziness, insomnia, somnolence, sexual dysfunction	Undetectable or low serum levels of drug; metabolite usually measurable and levels similar to those in adults observed in some infants; drug level greater in breast milk than in maternal serum
Other			
Bupropion	300–450	Dizziness, headache, dry mouth, sweating, tremor, agitation, rare seizures, possible drug interactions†	Unknown
Nefazodone	300–600	Dry mouth, somnolence, nausea, dizziness, possible drug interactions†	No published data on serum levels in infants; sedation and poor feeding in a premature infant described
Mirtazapine	15–45	Somnolence, nausea, weight gain, dizziness	Unknown

*Treatment with any of these agents should be initiated at half of the lowest recommended therapeutic dose. Dosages are from the *Physician's Desk Reference*, 55th ed.¹³

†Drug interactions are possible because of the drug's inhibition of the following cytochrome P450 (CYP) enzyme systems^{17,18}: for sertraline, 2D6, 2C, and 3A4; for paroxetine, nortriptyline, desipramine, and bupropion, 2D6; for fluvoxamine, 1A2, 2C, and 3A4; for fluoxetine, 2D6, 2C, and 3A4; for nefazodone, 3A4.

‡If the electrocardiogram (ECG) shows conduction defects, consider a non-tricyclic antidepressant.

ed starting doses listed in Table 2 (e.g., 25 mg of sertraline per day or 10 mg of paroxetine per day) for four days, and doses should be increased by small increments (e.g., 25 mg of sertraline per week or 10 mg of paroxetine per week) as tolerated, until full remission is achieved. Slow increases in the dose are helpful in managing side effects. If the patient has a response to an initial trial of medication lasting six to eight weeks, the same dose should be continued for a minimum of six months after a full remission has been achieved, in order to prevent relapse.²³ If there is no improvement after six weeks of drug therapy, or if the patient has a response but then has a relapse, referral to a psychiatrist should be considered. The average duration of a postpartum episode of depression (without treatment) is seven months.²⁴ Fifty to 85 percent of patients with a single episode of major depression will have at least one more episode after the discontinuation of medication, and the risk increases with the number of previous episodes.²³ Therefore, long-term treatment for the prevention of recurrence should be considered for women who have had three or more episodes of severe depression.

Breast-Feeding

All antidepressants are excreted in breast milk. Optimal clinical management dictates the use of the lowest effective dose of antidepressants in a lactating mother. Observation of the infant's behavior before the mother is treated permits clinicians to avoid misinterpreting typical behavior as potentially drug-related.

The serum levels of antidepressants in infants of breast-feeding mothers have been evaluated in multiple studies.²⁵⁻⁴¹ The selective serotonin-reuptake inhibitor sertraline has been recommended as the first-line treatment for breast-feeding mothers on the basis of multiple case series by several investigators that suggest that this agent may be used with little risk.⁴² Epperson and colleagues²⁷ evaluated the functional effects of very low levels of sertraline in breast-fed infants by assessing the platelet serotonin level. In humans, platelet and central neuronal serotonin transporters are identical. The expected marked decline in serotonin levels was observed in mothers after treatment, but there was minimal change in the infants who were exposed to small amounts of sertraline through breast milk. No reports of adverse effects in breast-fed infants whose mothers were treated with sertraline, paroxetine, or fluvoxamine have been published.

Colic has been reported in three infants who were breast-fed by mothers taking fluoxetine; when tested, the infants were shown to have serum levels of fluoxetine and norfluoxetine (the active metabolite of fluoxetine) that were in the therapeutic range for

adults.^{31,32} Chambers et al.⁴³ reported that breast-fed infants of fluoxetine-treated mothers gained significantly less weight after birth, although the mothers did not report unusual behavior in these infants. Unlike most antidepressants, fluoxetine has a highly active metabolite (norfluoxetine), and both agents have very long half-lives (84 and 146 hours, respectively).⁴¹ Continuous exposure to fluoxetine through breast milk is more likely than exposure to other selective serotonin-reuptake inhibitors to lead to measurable serum levels of the antidepressant agent.⁴¹ Prenatal exposure to fluoxetine may also contribute to measurable serum levels in infants of mothers who take this medication. In one report, "uneasy sleep" was described in an infant with a measurable serum level of citalopram, a selective serotonin-reuptake inhibitor with a shorter half-life³⁵; however, this report is inconsistent with data on other selective serotonin-reuptake inhibitors that have similar half-lives. An unusually high level of sertraline was reported in one infant,²⁵ although the authors believed it to be a spurious finding. However, some infants may have particularly poor metabolism of antidepressants.⁴¹

Tricyclic antidepressants are not typically found in measurable amounts in nursing infants.⁴¹ Since these agents are not first-line drugs for depression, only the representative drugs nortriptyline and desipramine (which have fewer side effects than others in the class) are listed in Table 2. Of the drugs in this class, nortriptyline has been studied the most as a treatment for breast-feeding women. The only adverse outcome reported with any tricyclic antidepressant, respiratory depression and sedation, occurred in an infant whose mother was taking doxepin.⁴¹ Data are lacking on other classes of antidepressants.

Children who were exposed to tricyclic antidepressants through breast milk have been followed through preschool and compared with children who were not exposed to such drugs, and no developmental problems have been found.⁴⁴ However, there are no published long-term evaluations of infants exposed to selective serotonin-reuptake inhibitors through breast milk, and effects of antidepressants on developing neurotransmitter systems cannot be ruled out. Although substantial data have been published on antidepressant levels in infants exposed through breast milk, they reflect effects in full-term infants. Close clinical monitoring and measurement of serum levels are warranted for premature or sick newborns. In the cases of women who have a response only to drugs for which data are unavailable, decisions regarding treatment during breast-feeding must take into account this uncertainty. The importance of caretaking by capable parents, which is compromised by depression, and the benefits of breast-feeding should also be weighed in the decision-making process.

Prophylactic Treatment

Women who have a history of depression are justifiably concerned about recurrence after childbirth. After one postpartum episode, the risk of recurrence (defined as a return of symptoms that fulfill the DSM-IV criteria for major depression) is 25 percent.¹⁰ Preventive therapy after delivery should be considered for women with any previous episode of depression.¹⁰ The drug to which the patient previously had a response or a selective serotonin-reuptake inhibitor are reasonable choices; the tricyclic antidepressant nortriptyline did not confer protection, as compared with placebo.¹⁰ At a minimum, postpartum management should include monitoring for recurrence, with a plan for rapid intervention if indicated.

Psychotherapy

In a study involving 120 women who had recently given birth, interpersonal psychotherapy, a 12-session treatment that focuses on changing roles and important relationships, was effective for the relief of depressive symptoms and improvement in psychosocial functioning in treated women as compared with controls who were on the waiting list for such therapy.²⁴ A group intervention based on interpersonal psychotherapy and delivered during pregnancy prevented postpartum depression in 35 economically disadvantaged women.⁴⁵ However, psychotherapy in addition to fluoxetine did not improve outcomes more than fluoxetine alone.¹³

Hormonal Therapy

Estradiol⁴⁶ has been evaluated as a treatment for postpartum depression. In a study comparing transdermal 17 β -estradiol (200 μ g per day) with placebo, the estradiol-treated group had a significant reduction in depression scores during the first month. However, nearly half the women also were treated with antidepressants, so the effect of estradiol alone remains uncertain. Prophylactic administration of a progestogen after delivery increased the risk of postpartum depression as compared with placebo.⁴⁷

AREAS OF UNCERTAINTY

Antidepressants are effective for postpartum depression; however, it is not certain whether specific antidepressants or classes of antidepressants are more beneficial than others. The optimal approach to prophylaxis in high-risk patients is also unclear. The role of psychotherapy for patients with a partial response or no response to medication has not been explored. More data are needed on predictors of the response to therapy so that patients may be systematically matched with therapies. The role of gonadal steroids in causing postpartum depression remains unclear. In

addition, data are needed about long-term physical and mental development in infants exposed to antidepressants through breast-feeding as well as prenatally.

GUIDELINES

To our knowledge, there are no treatment guidelines available that are specific to postpartum depression. Clinical-practice guidelines developed by the American Psychiatric Association for major depression in adults apply²³ (they are available at <http://www.psych.org>). The severity of symptoms, the preferences of the patient, and the response to treatment during previous episodes influence the recommendations for psychotherapy, antidepressants, or electroconvulsive therapy.

CONCLUSIONS AND RECOMMENDATIONS

Physicians must expect that one out of eight new mothers will have postpartum depression. In women with previous episodes of postpartum depression, the risk of recurrence is one in four. Since identification of postpartum depression is the first step, we recommend that women be screened after delivery with the Edinburgh Postnatal Depression Scale, which is brief, is highly acceptable to patients, and reliably detects the presence of postpartum depression (indicated by a score of 10 or higher).⁸ Alternatively, women should be asked about depressed mood and other associated symptoms. Once depression has been identified, rapid implementation of treatment is advisable, because episodes may be long and the number and severity of sequelae increase with the duration of the episode. Depressed women should be asked about any intention to harm themselves or their children, which necessitates urgent referral for psychiatric care.

A selective serotonin-reuptake inhibitor should be the first-line drug because such agents carry a low risk of toxic effects in patients who take an overdose, are easy to administer, and have been used relatively frequently in breast-feeding women. Any drug should be initiated at half the usual starting dose. We administer medication for at least six months after full remission in order to prevent relapse,²³ and we consider long-term maintenance therapy for women with three or more episodes or episodes that featured serious disability. Women with postpartum depression may also respond to interpersonal psychotherapy. The goal of treatment is complete normalization of mood and physiologic and social functioning.

Women with this disorder need not feel alone in their suffering. They may find useful information in Marie Osmond's book *Behind the Smile: My Journey Out of Postpartum Depression*⁴⁸ and on the Web sites of the National Women's Health Information Center (<http://www.4woman.gov>) and groups such as Postpartum Support International (<http://www.chss>).

iup.edu/postpartum) and Depression after Delivery (<http://www.depressionafterdelivery.com>).

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