

Depression in Pregnancy: Strategies for Primary Care Management

Dealing with an underdiagnosed and undertreated problem

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Major depression is a common disorder, with a lifetime prevalence of 17.3% and a 12-month prevalence of 10.3%.¹ Female sex is a significant risk factor for depression.² Epidemiologic studies in nonclinical populations have consistently shown that depression is about twice as common in women as it is in men.³⁻⁵ Gender differences in depression likely result from a variety of interacting factors, including biologic, psychological, and sociocultural influences (Table 1).²

For example, hormonal changes related to reproductive events (eg, menses, the postpartum period, and menopause) and exogenous hormonal therapy may trigger depressive episodes.⁶ (See “How the neuroendocrine system may affect mood” on page 492.) Vulnerability to the onset of depressive episodes and to the worsening of ongoing depression increases during the premenstrual phase of the cycle.⁷ Furthermore, in a study that examined prevalence rates of depression in 360 pregnant women, 25% of the women experienced depressive symptoms, and 10% of those who did

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ABSTRACT: Depression is more common in pregnant women than many clinicians believe. It not only impairs functioning and increases the suicide risk in the expectant mother but also may adversely affect maternal-infant bonding and the infant's cognitive and emotional development. Screening for depression during pregnancy is essential. Begin with a complete patient history. Remember that the symptoms of pregnancy and depression often overlap. Also, rule out medical disorders (eg, anemia and thyroid dysfunction) that can cause depressive symptoms. The therapeutic goals are to achieve mental stability without harming the fetus. Nondrug treatments are preferred during the first trimester. However, severe symptoms warrant antidepressant therapy, regardless of the pregnancy stage. (*Women Health Primary Care* 2000;3(7):490-498)

met the diagnostic criteria for depression.⁸

The consequences of depression include personal suffering, increased suicide risk, and impaired occupational and social functioning. If untreated, depression can significantly decrease life expectancy and can adversely affect the morbidity, mortality, and costs of comorbid med-

ical illnesses. When the costs of inpatient and outpatient care, pharmaceuticals, lost productivity, missed workdays, and lost lifetime earnings are combined, the total annual economic burden of major depression in the United States is approximately \$44 billion.⁹

Although depression usually first presents in a primary care setting, it tends to be underdiagnosed and is often undertreated.¹⁰ Various reasons for the underrecognition and undertreatment of depression have been proposed. Davidson and Meltzer-Brody¹¹ note that the providers, the patients, and the health care system all share responsibility:

- ◆ Physician education in the diagnosis and management of depression in medical schools and primary care postgraduate training is often inadequate.
- ◆ Patients often do not recognize that they are depressed, and those who do may be prevented from seeking help by the shame and stigmatization still associated with mental illness.
- ◆ Many current health care systems view depression as a single, short-term event and fail to recognize that

this disorder is often chronic and recurring.

Our focus in this article is depression during pregnancy. We will offer strategies to help you recognize depression in your pregnant patients and treat it effectively. We will discuss both nonpharmacologic and pharmacologic management techniques, including which antidepressants are safe for pregnant women and which are best avoided. We will also provide guidelines for when to refer the patient for a psychiatric consult.

HOW TO RECOGNIZE

Clinical lore has long posited that pregnancy is a time of emotional well-being, but few data are available to support the notion that pregnancy confers any protection against mental illness.¹² In fact, similar rates of depression are reported in gravid and nongravid women. Although the incidence of depression (both major and minor) in pregnant women is approximately 10% (comparable to that in non-pregnant women), certain factors may increase the risk in vulnerable subpopulations.¹³

RISK FACTORS

Among the risk factors for depression during pregnancy are a personal history of depression, including inadequately treated ongoing depression; a family history of depression; young age; marital discord; lack of social support; a first pregnancy or an unwanted pregnancy; and recent adverse life events, such as the death of a parent (Table 2).¹⁴⁻¹⁶ Depression during pregnancy also increases the risk of developing postpartum depression by approximately threefold.¹³

Untreated or undertreated depression in pregnancy can lead to poor nutrition; inadequate medical and prenatal care; worsening of comorbid medical illness; disrupted sleep patterns; increased exposure to alcohol, illicit drugs, or tobacco;

Table 1. Depression: Female-specific characteristics

Compared with men, women are more likely to:

- ◆ Experience depression (female-to-male prevalence ratio, 2:1).³⁻⁵
- ◆ Have depressive episodes triggered or exacerbated by hormonal shifts.^{6,7}
- ◆ Present with reverse vegetative symptoms (eg, increased appetite and weight gain) and report more somatic symptoms.^{46,47}
- ◆ Attempt suicide (but are less likely to succeed).^{48,49} (Men have a higher rate of completed suicide because they are more likely than women to use violent means, such as gunshots or hanging, and are less likely to seek help for depression.)
- ◆ Have episodes of depression that are longer and more likely to develop into a chronic and recurrent course of illness.⁵⁰⁻⁵²
- ◆ Be vulnerable to developing a seasonal pattern to depression.⁵³
- ◆ Report increased functional impairment, especially in the setting of marital and family discord.⁵⁴
- ◆ Have depression precipitated by identifiable stressful life events.⁵⁵

and suicide (Table 3).¹² Depressed pregnant women thus may be more likely to have low-birth-weight infants, preterm deliveries, and infants who are small for their gestational age.¹⁷ Maternal depression also appears to have an adverse impact on maternal-antenatal attachment, mother-infant attachment, and the cognitive and emotional development of the infant.¹⁸⁻²²

SCREENING

At present, in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, the diagnostic criteria for depression are identical in gravid and nongravid women. However, the diagnosis of antenatal depression can be confounded by the overlapping symptoms common to both depression and pregnancy, including changes in appetite, body weight, sleep, libido, and energy. In addition, comorbid medical disorders (eg, anemia, gestational diabetes, thyroid dysfunction) may cause depressive symptoms and further complicate the assessment of major depression during pregnancy.¹² Thus, when evaluating a pregnant patient for possible depression, the clinician must obtain a complete history (Table 4).

Several screening questions may assist the clinician in detecting depressive symptoms, including:

- ◆ Are you feeling sad, blue, or depressed?
- ◆ Have you lost interest and pleasure in most things you usually enjoy?
- ◆ Do you feel guilty about things in your life?
- ◆ Do you have difficulties concentrating or making decisions?
- ◆ How have things been at home or at work? (This simple question is particularly useful in the primary care setting, where clinicians monitor their patients regularly.)

When evaluating a new mother for depression, it is also important to inquire about neurovegetative symptoms, such as changes in sleep habits, appetite, and energy. Stowe and Nemeroff²³ believe that one of the most valuable screening questions for assessing postpartum distress addresses sleep disturbance. In their experience, new mothers may be tired but are easily able to rest and sleep when they are given the opportunity. In contrast, women with postpartum depression often have such high levels of anxiety that they are unable to rest or to return to sleep after getting up with the infant at night. Our clinical experience suggests that the same is true for depressed pregnant women.

Emotional distress in the family also should raise concern. Multiple somatic complaints without a

clear organic pathology are a common symptom of major depression in the general population; this is also likely to be true for depression in pregnant women.²³

Several screening instruments are available to detect depression in clinical and nonclinical populations.^{24,25} The main problem with these diagnostic questionnaires is that they do not distinguish the normative somatic experiences associated with pregnancy (fatigue, sleep and appetite disturbances) from symptoms of depression. At present, no screening tool for the assessment of depression specific to pregnancy is available. What is

needed is a simple and reliable diagnostic screening instrument to identify antenatal depression. Developing clinical instruments for the early detection of depression in pregnancy would enhance intervention strategies and benefit preventive efforts.²⁶

Certain existing tools, however, may be helpful in establishing the diagnosis. For example, the self-report Beck Depression Inventory has well-established validity and reliability among the general population.²⁴ This screening tool has also been validated among pregnant women²⁷; however, a higher cutoff score (at least 16) is

necessary to avoid false-positive results arising from the normative somatic experiences that are associated with pregnancy, which we described previously.

HOW TO TREAT

Treatment approaches for pregnant women with depression include nonpharmacologic and pharmacologic interventions. The goal is to maintain psychiatric stability while minimizing the risks to the developing fetus. Thus, when symptoms of depression are mild, nonpharmacologic methods take precedence over pharmacotherapy or electroconvulsive therapy (ECT). (Mor-

How the neuroendocrine system may affect mood

To date, no clear evidence supports a direct cause-and-effect relationship between depression and alterations in serum gonadal hormones. However, substantial data demonstrate that sex hormones modulate psychoactive neuroendocrine systems.⁴² Two important interconnected neuroendocrine systems that have been increasingly studied in both nongravid and gravid women are the hypothalamic-pituitary-adrenal (HPA) axis and the hypothalamic-pituitary-ovarian (HPO) axis.

When the HPA axis is activated by stress, it has an inhibitory effect on the reproductive system.⁴³ Corticotropin-releasing hormone (CRH) inhibits gonadotropin-releasing hormone (GnRH) secretion; cortisol secreted from the adrenal cortex inhibits GnRH secretion, luteinizing hormone (LH) secretion, estrogen and progesterone biosynthesis, and estradiol actions.⁴³ Estrogen, derived mainly from the ovaries, stimulates the HPA axis by inciting CRH synthesis and cortisol-binding globulin secretion and also potentiating norepinephrine action.⁴³ Lindholm and Schultz-Moller⁴⁴ showed that pregnant women and women receiving high-dose estrogen therapy had elevated plasma levels of free cortisol in the morning and evening.

Throughout a woman's reproductive life cycle, monthly fluctuations in estradiol influence the secretion of central nervous system CRH and adrenocortical catecholamines. Evidence suggests that menstrual cycle-associated changes in the develop-

ment and severity of depressive syndromes or disorders may be indirectly related to CRH plasma levels.⁷ Decreasing estrogen levels during the late luteal phase, for example, lead to decreased CRH secretion and secondarily diminish norepinephrine secretion, which may play a role in premenstrual dysphoric disorder.⁴³ Similarly, the perimenopausal interval is characterized by a progressive lowering of estrogen levels and decreased CRH activity. This may explain the increased vulnerability to depression during this time of a woman's life cycle.

During pregnancy wide hormonal changes occur. As the pregnancy progresses, levels of progesterone, estradiol, CRH, adrenocorticotrophic hormone (ACTH), and cortisol increase. The latter half of pregnancy is associated with a state of hypercortisolism, which is caused by the placental production of CRH.⁴³ What is unclear is whether these hormonal changes are associated with the development of depression during pregnancy. Although pregnancy does not precipitate depression, it also does not protect women from the disorder.²⁶ Furthermore, when it is present and left untreated or undertreated, depression in pregnancy increases the risk for postpartum depression. It may be that the abrupt post-delivery decreases in estradiol, progesterone, CRH, ACTH, and cortisol levels lead to a significantly increased risk for the development of postnatal psychiatric disturbances, such as postpartum blues, postpartum depression, and postpartum psychosis.⁴⁵

bidly depressed gravid women may benefit from ECT. However, discussion of this therapy is beyond the scope of this article; Miller²⁸ has reviewed the potential risks and benefits of ECT in this setting.)

NONPHARMACOLOGIC INTERVENTIONS

When depressive symptoms are mild to moderate, it is preferable to choose nonpharmacologic interventions, especially in the first trimester, when organogenesis is most active.¹³

Elimination of caffeine and alcohol: Caffeine can lead to sleep disturbance and thus can contribute to the development of depressive symptoms or worsen them. Alcohol is a depressant, and it has been implicated in depression. (Also, alcohol use during pregnancy can lead to the development of fetal alcohol syndrome.)

Adequate sleep: Although sleep disturbance is common during a normal pregnancy, sleep deprivation exacerbates psychiatric symptoms. Therefore, pregnant women with depression should attempt to maximize the opportunity for adequate rest.

Relaxation techniques: Anxiety symptoms are often comorbid with depression. Relaxation techniques can be helpful for managing these symptoms.

Cognitive-behavioral therapy: This treatment has been shown to be effective in patients who are suffering from depression or anxiety disorders.

Support groups: Participation in a support group allows patients to identify with other persons who may be experiencing similar difficulties. This may provide the patients with both emotional and practical support.

Education: It is important to educate patients and their families about the symptoms of depression as well as about the increased risk of postpartum depression when de-

Table 2. Risk factors for depression during pregnancy

- ◆ Personal history of depression
- ◆ Inadequately treated ongoing depression
- Family history of depression
- ◆ Younger age
- ◆ Marital discord
- ◆ Lack of social support
- ◆ First pregnancy
- ◆ Unwanted pregnancy
- ◆ Recent adverse life events

pression is not treated adequately during pregnancy.

Conjoint therapy: This treatment may be helpful during pregnancy if marital difficulties are a primary stressor in a pregnant woman's life. Marital difficulties may increase the risk for postpartum depression.

Reduction of psychosocial stressors: Evidence indicates that life stressors play a role in the development of depression in women. By minimizing stressors (eg, decreasing the number of hours they work each week), pregnant women may help improve their depressive symptoms.

Close communication with the obstetric service: Primary care clinicians should maintain close com-

Table 3. Results of untreated or undertreated depression

- ◆ Poor nutrition
- ◆ Inadequate medical and prenatal care
- ◆ Worsening of comorbid medical illness
- ◆ Disrupted sleep patterns
- ◆ Increased exposure to alcohol, illicit drugs, tobacco
- ◆ Suicide
- ◆ Increased risk for low-birth-weight infants, preterm deliveries, and infants small for gestational age
- ◆ Postpartum depression
- ◆ Adverse impact on maternal-antenatal attachment, mother-infant attachment, and the cognitive and emotional development of the infant

munication with their pregnant patients' obstetricians. In this way, all parties involved in a woman's care will be informed if her psychiatric condition worsens.

PHARMACOLOGIC INTERVENTIONS

Drug treatment should be considered when symptoms of depression are severe (eg, the patient is suicidal, psychotic, or functionally impaired) because the risks of medication to the mother and fetus are outweighed by the effects of the illness. The decision to use a medication during pregnancy is best made after the risks and benefits have been thoroughly explained and discussed with the patient, close relatives, and other treating clinicians. Medication dosages should be maintained at the minimum level necessary to control symptoms.^{29,30}

Medication exposure during pregnancy poses five main categories of potential risk to the fetus:

- ◆ Intrauterine fetal death.³⁰
- ◆ Teratogenicity or morphologic toxicity.³⁰ A medication is considered teratogenic when prenatal exposure to it significantly increases the risk of congenital malformations over the baseline risk.³¹
- ◆ Growth impairment.³⁰
- ◆ Neonatal toxicity.³⁰ The physical and behavioral symptoms that develop at the time of delivery and shortly after birth are caused by drug use at or near the time of delivery and are usually of limited duration.³²
- ◆ Behavioral teratogenicity.³⁰ This category includes potential neurobehavioral abnormalities in children following in-utero medication exposure.^{33,34}

Other considerations include possible direct toxicity to the maternal-fetal unit and possible adverse interactions between psychotropic agents and medications needed during obstetric care (eg, terbutaline, a tocolytic medication

given to prevent preterm labor).

Tricyclic antidepressants (TCAs): According to the growing literature on TCAs in pregnancy, these agents do not appear to pose an increased risk of congenital anomalies, even when used during the first trimester. A recent meta-analysis assessing the risk of congenital malformation with prenatal exposure to TCAs reveals that these antidepressants appear to have a rela-

tively safe profile.²⁹ In newborns exposed to TCAs during labor and delivery, reversible perinatal syndromes with symptoms of jitteriness, irritability, hypotonia, lethargy, convulsions, and anticholinergic effects (eg, functional bowel obstruction and urinary retention) have been reported.

Selective serotonin reuptake inhibitors (SSRIs): Among the SSRIs, fluoxetine has been studied most

extensively for use in pregnancy. First trimester exposure to fluoxetine does not appear to be associated with major congenital anomalies,^{35,36} and fluoxetine exposure at the time of labor and delivery does not seem to cause perinatal toxicity.³⁷

Chambers et al³⁶ reported an increased risk of at least three minor anomalies (ie, having no cosmetic or functional importance) and higher rates of perinatal complications (eg, premature delivery, admission to special-care nurseries, neonatal toxicity, lower birth weight, and shorter birth length) following exposure to fluoxetine in the later stages of pregnancy. However, Robert³⁸ noted that weaknesses in this study may have confounded the results. Specifically, the data were from a nonrandomized prospective study; the role of depressive illness on birth outcome was not excluded; and maternal age was higher in the fluoxetine group. The frequency of minor malformations observed in the fluoxetine group is similar to the rate found in the general population. Clinicians should remember that depression itself is associated with a poor obstetric outcome.

A recent study compared long-term outcomes in children who had been exposed in utero to fluoxetine or a TCA and in children who had not been exposed in utero to any known teratogens.³⁹ No significant differences in temperament, mood, distractibility, behavior, global IQ, or language development in children age 7 or younger were noted.

The data on the use of newer SSRIs in pregnancy are sparse but expected to grow as the use of these agents increases. In one relatively small (267 subjects and 267 controls), prospective, multicenter, controlled cohort study of fluvoxamine, paroxetine, and sertraline, exposure to these drugs during pregnancy did not appear to be associated with major anomalies or

Table 4. Patient history for evaluating depression

<p>Current psychiatric</p> <ul style="list-style-type: none"> Depressive symptoms Depressed mood Diminished interest or pleasure in activities Significant weight change Insomnia or hypersomnia Fatigue or loss of energy Feelings of worthlessness or excessive guilt Psychomotor agitation or retardation Poor concentration or indecisiveness Thoughts of suicide Psychosocial stressors (eg, marital difficulties, financial problems) Current history of other psychiatric disorders (eg, mania, psychosis, eating disorder) <p>Past psychiatric</p> <ul style="list-style-type: none"> Past depression Associated with pregnancy Associated with postpartum Non-reproductive-related depression Past history of other psychiatric disorders Prior treatment for depression with medications (note antidepressants used, doses, lengths of treatment, and responses) Past use of psychotherapy (type, duration, response) Previous psychiatric hospitalizations Prior suicide attempts <p>Family psychiatric</p> <ul style="list-style-type: none"> Mental illness (including depression during pregnancy or postpartum) Suicides Use of psychotherapy or antidepressant drugs <p>Current medication</p> <ul style="list-style-type: none"> Prescribed medications Over-the-counter medications Herbal preparations 	<p>Substance abuse</p> <ul style="list-style-type: none"> Current use (note frequency of use, amount used, and symptoms of substance withdrawal) Alcohol Tobacco Cocaine Heroin Hallucinogens Phencyclidine hydrochloride Other illicit drugs Past history of substance abuse or dependence <p>Past medical</p> <ul style="list-style-type: none"> Anemia Head injury Seizures Thyroid abnormalities Medical problems during pregnancy Gestational diabetes Preeclampsia Eclampsia Other medical disorders <p>Reproductive</p> <ul style="list-style-type: none"> Prior pregnancies (including number of live births and spontaneous or elective abortions) Complications during pregnancies and delivery Complications during the postpartum period Infertility problems <p>Social</p> <ul style="list-style-type: none"> Supports (eg, marital status, family, friends) Employment and financial history Living situation (including all household members) History of physical and/or sexual abuse Level of education
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increased rates of miscarriage, stillbirth, or prematurity.⁴⁰


Monoamine oxidase inhibitors (MAOIs): There is a relative contraindication to the use of MAOIs during pregnancy. Animal studies have associated these agents with an increased risk of congenital anomalies.¹³ In the offspring of a small group of women exposed to an MAOI (tranylcypromine or phenelzine) during pregnancy, Heinonen et al⁴¹ noted a higher than normal rate of congenital malformations. Also, when used with terbutaline, MAOIs increase the risk of a hypertensive crisis.¹³

Other antidepressants: No studies have yet assessed in-utero exposure to bupropion, citalopram, trazodone, venlafaxine, or nefazodone.

WHEN TO REFER

A question often asked by primary care clinicians is when to refer the patient to a psychiatrist. The following guidelines may assist in making this decision. Conditions that warrant referral to a psychiatrist include:

- ◆ Suicidal or homicidal thoughts.
- ◆ Severe functional impairment.
- ◆ Depression comorbid with psychotic features, substance abuse, or panic disorder.
- ◆ Bipolar depression.
- ◆ Chronic relapsing depression.
- ◆ Failure to respond to a therapeutic trial of one or more antidepressants.

Alternatively, the primary care clinician may choose to manage the case in consultation with a psychiatrist, or the psychiatrist may treat the patient (while maintaining ongoing contact with the primary care clinician) until she is psychiatrically stable. We strongly support referral and consultation whenever a primary care clinician is uncomfortable treating a pregnant patient with depression. 

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PRIMARY POINTS

Depression in Pregnancy

About 25% of women experience depressive symptoms during pregnancy, and 10% of those who do meet the diagnostic criteria for major depression.

Depression that develops during pregnancy is associated with a threefold increase in the risk of postpartum depression.

Untreated or undertreated depression in pregnancy can lead to poor nutrition, inadequate medical and prenatal care, worsening of comorbid medical illness, disrupted sleep patterns, substance abuse, and suicide. Maternal depression also may have an adverse impact on maternal-antenatal attachment, mother-infant attachment, and the cognitive and emotional development of the infant.

The diagnosis of depression in pregnancy can be confounded by overlapping symptoms common to both depression and pregnancy (eg, changes in appetite, body weight, sleep, libido, and energy); it can also be complicated by the presence of depressive symptoms due to comorbid medical disorders (eg, anemia, gestational diabetes, and thyroid dysfunction).

Nonpharmacologic interventions for depression are preferred in the first trimester (when organogenesis is most active) and when symptoms are mild to moderate. However, when the symptoms are severe (eg, the patient is suicidal, psychotic, or functionally impaired), pharmacologic treatment should be considered.

Both tricyclic antidepressants and selective serotonin reuptake inhibitors appear to be safe for pregnant women.

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