Depression During Pregnancy: Diagnosis and Treatment Options

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Women often seek clinical consultation for antidepressant use both prior to conception and during pregnancy. Some women experience a new onset of symptoms during pregnancy, while those with a history of depressive symptoms are at increased risk. Nevertheless, clinicians are faced with the challenge of treating the mother without posing risks to the fetus. This review discusses risk factors for depression during pregnancy and the consequences of untreated depression. Nonpharmacologic and pharmacologic treatment options are reviewed, and guidelines for treating depression during pregnancy are presented. *(J Clin Psychiatry 2002;63[suppl 7]:24–30)*

Mood disorders are common in women and typically emerge during the childbearing years.[1] While pregnancy has traditionally been considered a time of emotional well-being, recent data indicate that about 10% of women experience clinically significant depressive symptoms during pregnancy (antenatal depression). Furthermore, women with histories of major depression appear to be at high risk for recurrent depression during pregnancy, particularly in the setting of antidepressant discontinuation.

Frequently, women with histories of major depression seek consultations regarding the use of antidepressant medications during pregnancy, either prior to conception or early in the course of pregnancy. In other cases, women present with recurrent or new onset of depressive symptoms during pregnancy. In both of these settings, the clinician faces certain challenges when making recommendations regarding the treatment of depression during pregnancy. All antidepressant medications readily diffuse across the placenta, and no psychotropic drug has yet been approved by the U.S. Food and Drug Administration (FDA) for use during pregnancy. Although data accumulated over the last 30 years suggest that some medications may be used safely during pregnancy,[2–4] our knowledge regarding the risks of prenatal exposure to psychotropic medications is incomplete. Thus, it is common for patients to avoid pharmacologic treatment during pregnancy.

The clinical challenge for physicians who care for women with psychiatric disorders during pregnancy is to minimize risk to the fetus while limiting morbidity from untreated psychiatric illness in the mother. Because no decision is absolutely free of risk, it is imperative that these clinical decisions be made collaboratively with patients and their partners. It is the physician's responsibility to provide accurate and up-to-date information on the reproductive safety of pharmacologic treatment and to help the patient to select the most appropriate treatment strategy. In this article, we review the available information on antidepressant medication use during pregnancy and provide guidelines for the treatment of depression in pregnant women.

DEPRESSION DURING PREGNANCY

Although pregnancy has previously been described as a time during which women are at lower risk for psychiatric illness, recent studies indicate that about 10% of women suffer from clinically significant depressive symptoms during pregnancy.[5,6] A personal history of affective illness significantly increases risk for depression during pregnancy[6,7]; however, for about one third of the women who become depressed during pregnancy, this represents the first episode of major depression.[6] Other risk factors for antenatal depression include marital discord or dissatisfaction, inadequate psychosocial supports, recent adverse life events, lower socioeconomic status, and unwanted pregnancy.[5–7]

Women with recurrent major depressive disorder who have been maintained on treatment with an antidepressant

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medication prior to conception appear to be at especially high risk for relapse during pregnancy. Although there are data to support the use of certain antidepressants during pregnancy, it is common for women to choose or be advised to discontinue antidepressant treatment during pregnancy. A growing body of literature in nongravid populations indicates that the discontinuation of maintenance pharmacologic treatment is associated with high rates of relapse.[8–12] Preliminary data suggest that pregnancy does not protect against relapse in the setting of medication discontinuation. Among women with recurrent major depression who discontinue antidepressant medication proximate to conception, approximately 70% relapse during pregnancy, typically during the first trimester.[13]

While more severe forms of affective illness may be readily detected, depression that emerges during pregnancy is frequently overlooked. Many of the neurovegetative signs and symptoms characteristic of major depression (e.g., sleep and appetite disturbance, diminished libido, low energy) are also observed in nondepressed women during pregnancy. In addition, certain medical disorders commonly seen during pregnancy such as anemia, gestational diabetes, and thyroid dysfunction may cause depressive symptoms and consequently may complicate the diagnosis of affective illness during pregnancy.[14] Features that may help confirm the diagnosis of major depression include anhedonia, feelings of guilt and hopelessness, and suicidal thoughts. Suicidal ideation is often reported; however, risk of self-injurious or suicidal behaviors appears to be relatively low in this population of women who develop depression during pregnancy.[15,16]

RISKS OF UNTREATED DEPRESSION IN THE MOTHER

Although clinicians have focused primarily on the risks associated with fetal exposure to psychotropic medications, untreated psychiatric illness carries significant risk when it occurs during pregnancy. In fact, current research suggests that maternal depression itself may adversely affect the developing fetus. Although it has been difficult to assess the impact of antenatal depression on fetal development and neonatal well-being, several studies have found an association between maternal depression and factors that predict poor neonatal outcome. Recent studies have found an association between maternal depressive symptoms and preterm birth, lower birth weight, smaller head circumference, and lower Apgar scores.[17–19] The physiologic mechanisms by which symptoms of depression might affect neonatal outcome are not clear. However, increased serum cortisol and catecholamine levels, which are typically observed in patients with depression, may affect placental function by altering uterine blood flow and inducing uterine irritability.[20,21] Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which is associated with depression, may also have a direct effect on fetal development. Animal studies suggest that stress during pregnancy is also associated with neuronal death and abnormal development of neural structures in the fetal brain, as well as sustained dysfunction of the HPA axis in the offspring.[20,22–24]

Psychiatric illness during pregnancy may also contribute to poor self-care and poor compliance with prenatal care. Women with depression often present with decreased appetite and consequently lower-than-expected weight gain in pregnancy, factors that have been associated with negative pregnancy outcomes.[25] In addition, pregnant women with depression are also more likely to smoke and to use either alcohol or illicit drugs,[25] behaviors that further increase risk to the fetus. With more severe depression, there is also the risk of self-injurious behaviors or suicide.

Depression in the mother also places the rest of the family at risk. Depression is typically associated with interpersonal difficulties, and disruptions in mother-child interactions and attachment may have a profound impact on infant development. Recent research indicates that children of depressed mothers are more likely to have behavioral problems and to exhibit disruptions in cognitive and emotional development.[26–28] Furthermore, depression during pregnancy significantly increases a woman's risk for postpartum depression.[5,7] Thus, antenatal depression may have significant negative effects that extend beyond delivery.

NONPHARMACOLOGIC TREATMENT OF DEPRESSION DURING PREGNANCY

Until recently, there have been no clinical trials of nonpharmacologic treatments for antenatal depression. Interpersonal therapy (IPT) is a short-term, manual-driven psychotherapy that deals primarily with 4 major problem areas: grief, interpersonal disputes, role transitions, and interpersonal deficits.[29] Given the importance of interpersonal relationships in couples expecting a child and the significant role transitions that take place during pregnancy and subsequent to delivery, IPT is ideally suited for the treatment of depressed pregnant women. Spinelli[30] has adapted IPT for the treatment of women with antenatal depression, focusing on the role transitions and interpersonal disputes characteristic of pregnancy and motherhood. In a pilot study of 13 women,[30] IPT significantly reduced the severity of depressive symptoms and induced remission in all patients. None of the women (N = 10) who were followed after delivery developed postpartum depression. Although this study is limited by its small size and lack of a control group, the results are encouraging. Not only does this modality of treatment treat the acute symptoms of depression during pregnancy, but also it appears to decrease risk for depression after delivery.

PHARMACOLOGIC TREATMENT OF DEPRESSION DURING PREGNANCY

When considering the use of a psychiatric medication during pregnancy, the clinician must address 3 types of risk to the developing fetus: (1) risk of organ malformation or teratogenesis, (2) risk of neonatal toxicity or withdrawal syndromes during the acute neonatal period, and (3) risk of long-term neurobehavioral sequelae.[4]

To provide guidance to physicians seeking information on the reproductive safety of various prescription medications, the FDA has established a system that classifies medications into 5 risk categories (A, B, C, D, and X) based on data derived from human and animal studies. Category A medications are designated as safe for use during pregnancy, while category X drugs are contraindicated and are known to have risks to the fetus that outweigh any benefit to the patient. Most psychotropic medications are classified as category C, agents for which human studies are lacking and for which "risk cannot be ruled out." No psychotropic drugs are classified as safe for use during pregnancy (category A).

Unfortunately, this system of classification is frequently ambiguous and may sometimes be misleading. For example, certain tricyclic antidepressants have been labeled as category D, indicating "positive evidence of risk," although the pooled available data do not support this assertion and, in fact, suggest that these drugs are safe for use during pregnancy.[31,32] In contrast, bupropion, for which human studies are lacking, is classified as category B. Therefore, the physician must rely on other sources of information when providing well-informed recommendations on the use of psychotropic medications during pregnancy. For obvious ethical reasons, it is not possible to conduct randomized, placebo-controlled studies on medication safety in pregnant populations. Therefore, much of the data on reproductive safety have been derived from retrospective studies and case reports, although more recent studies have utilized a prospective design.[32–34]

The baseline incidence of major congenital malformations in newborns born in the United States is estimated to be between 3% and 4%.[35] During the earliest stages of pregnancy, formation of major organ systems takes place and is complete within the first 12 weeks after conception. A teratogen is defined as an agent that interferes with this process and produces some type of organ malformation or dysfunction. Exposure to a toxic agent before 2 weeks of gestation is not associated with congenital malformations and is more likely to result in a nonviable blighted ovum.[36] For each organ or organ system, there exists a critical period during which development takes place and may be susceptible to the effects of a teratogen.[37] For example, formation of the heart and great vessels takes place from 4 to 9 weeks after conception. Formation of lip and palate is typically complete by week 10. Neural tube folding and closure, which form the brain and spinal cord, occur within the first 4 weeks of gestation.

Neonatal toxicity, or *perinatal syndromes,* refers to a spectrum of physical and behavioral symptoms observed in the acute neonatal period that are attributed to drug exposure at or near the time of delivery. Although case reports over the last 2 decades describe a wide range of transient neonatal distress syndromes associated with exposure to (or withdrawal from) antidepressants, the incidence of these adverse events appears to be low. Anecdotal reports that attribute these syndromes to drug exposure must be cautiously interpreted, and larger samples must be studied in order to establish a causal link between exposure to a particular medication and a perinatal syndrome.

Because neuronal migration and differentiation occur throughout pregnancy and into the early years of life, the central nervous system (CNS) remains particularly vulnerable to toxic agents throughout pregnancy. However, insults that occur after neural tube closure produce changes in behavior and function, as opposed to gross structural abnormalities. *Behavioral teratogenesis* refers to the potential of a prenatally administered psychotropic drug to cause long-term neurobehavioral sequelae. For example, are children who have been exposed to an antidepressant in utero at risk for cognitive or behavioral problems at a later point during development? Animal studies demonstrate changes in behavior and neurotransmitter function after prenatal exposure to a variety of psychotropic agents.[38–40] The extent to which these findings are of consequence to humans has yet to be demonstrated. Thus far, human studies that have assessed the impact of fetal exposure to psychotropic medications on behavior have been reassuring and have demonstrated no negative effects.[34]

Tricyclic Antidepressants

Although early case reports suggested a possible association between first trimester exposure to tricyclic antidepressants (TCAs) and limb malformation, 3 prospective and more than 10 retrospective studies have examined the risk of organ dysgenesis in over 400 cases of first trimester exposure to TCAs.[4,31,32,41–43] When evaluated on an individual basis and when pooled, these studies fail to indicate a significant association between fetal exposure to TCAs and risk for any major congenital anomaly. Among the TCAs, desipramine and nortriptyline are preferred since they are less anticholinergic and the least likely to exacerbate orthostatic hypotension, which occurs during pregnancy.

Various case reports have described perinatal syndromes in infants exposed to TCAs in utero. A TCA withdrawal syndrome with characteristic symptoms of jitteriness, irritability, and, less commonly, seizure[44–48] has been observed. Withdrawal seizures have been reported only with clomipramine.[44,45] In addition, neonatal toxicity

attributed to the anticholinergic effect of TCAs, including symptoms of functional bowel obstruction and urinary retention, have also been reported.[49,50] In all cases, these symptoms have been transient.

Selective Serotonin Reuptake Inhibitors

Except for fluoxetine, information on the reproductive safety of the selective serotonin reuptake inhibitors (SSRIs) is limited. Four prospective studies have evaluated rates of congenital malformation in approximately 1100 fluoxetine-exposed infants.[32,33,51,52] The postmarketing surveillance registry established by the manufacturer of fluoxetine and one other retrospective study[42] complement these findings. These data, collected from over 2500 cases, indicate no increase in risk of major congenital malformation in fluoxetine-exposed infants.

While no study observed an increase in risk for major congenital anomaly, Chambers and colleagues[33] noted an increase in risk for multiple minor malformations in fluoxetine-exposed infants. In this study, minor anomalies were defined as structural defects that had no cosmetic or functional importance. In addition, this report suggested that late exposure to fluoxetine was associated with premature labor and poor neonatal adaptation. Interpretation of the findings in this study is limited by several methodological difficulties.[53,54] For example, the fluoxetine-exposed women and control groups differed significantly in terms of important variables, such as age, presence of psychiatric illness, and exposure to other medications. In addition, nonblinded raters were utilized, and only half of the fluoxetine-exposed infants were evaluated, which raises the question of selection bias. While further data are needed to ensure clinical confidence, the data collected thus far on fluoxetine suggest that it is unlikely to be a significant human teratogen.

Information regarding the reproductive safety of sertraline, paroxetine, fluvoxamine, and citalopram use during pregnancy is gradually accumulating but is limited in terms of sample size.[42,55–57] One prospective study of 531 infants with first trimester exposure to SSRIs (mostly citalopram, N = 375) did not demonstrate an increased risk of organ malformation.[55] In a retrospective study of 63 infants with first trimester exposure to paroxetine, no increase in teratogenic risk was observed.[56]

In a prospective, controlled cohort study, Kulin and colleagues[57] reported on outcomes in neonates exposed in utero to fluvoxamine (N = 26), paroxetine (N = 97), and sertraline (N = 147). Pregnancy outcomes did not differ between the exposed and nonexposed groups in terms of risk for congenital malformation or complications during pregnancy (e.g., miscarriage, stillbirth, or prematurity). Birth weights and gestational age were similar in both groups. While this information on SSRIs is reassuring, one of the major limitations of this study is that the analysis grouped the 3 antidepressants together versus analyzing each antidepressant separately for teratogenic risk. Larger samples are required to establish the reproductive safety of these newer antidepressants. It is estimated that at least 500 to 600 exposures must be collected to demonstrate a 2-fold increase in risk for a particular malformation over what is observed in the general population.[58]

The extent to which prenatal exposure to fluoxetine or other SSRIs is associated with neonatal toxicity is still unclear. Case reports and one prospective study have described perinatal complications in fluoxetine-exposed infants, including poor neonatal adaptation, respiratory distress, feeding problems, and jitteriness.[33,59] Other prospective studies have not observed perinatal distress in infants exposed to fluoxetine or other SSRIs.[57,60,61]

Other Antidepressants

To date, prospective data on the use of mirtazapine, venlafaxine, nefazodone, trazodone, and bupropion are not available. Scant information is available regarding the reproductive safety of monoamine oxidase inhibitors (MAOIs). One study in humans described an increase in congenital malformations after prenatal exposure to tranylcypromine and phenelzine, although the sample size was extremely small.[62] Moreover, during labor and delivery, MAOIs may produce a hypertensive crisis should tocolytic medications, such as terbutaline, be used to forestall delivery. Given this lack of data, and the cumbersome restrictions associated with their use, MAOIs are typically avoided during pregnancy.

Risk of Behavioral Teratogenesis

With regard to long-term neurobehavioral sequelae in children exposed to either fluoxetine or TCAs, the data are limited but reassuring. In a landmark study, Nulman and colleagues[34] followed a cohort of children up to preschool age who had been exposed to either TCAs (N = 80) or fluoxetine (N = 55) in utero and compared these subjects with a cohort of nonexposed controls (N = 84). Results indicated no significant differences in IQ, temperament, behavior, reactivity, mood, distractibility, or activity level between exposed and nonexposed children. The authors concluded that their findings support the hypothesis that fluoxetine and tricyclic antidepressants are not behavioral teratogens. However, these data are preliminary, and further investigation into the long-term neurobehavioral effects of prenatal exposure to antidepressants, as well as other psychotropic medications, is clearly warranted.

GUIDELINES FOR THE TREATMENT OF DEPRESSION DURING PREGNANCY

Only recently has attention focused on the treatment of depression during pregnancy[4,31]; however, the management of antenatal depression is largely guided by practical experience, with few definitive data and no controlled treatment studies to inform treatment. The most appropriate

treatment algorithm depends on the severity of the disorder. Clinicians must work collaboratively with the patient to arrive at the safest decision based on the available information. A patient's past psychiatric history and current symptoms, as well as her attitude toward the use of psychiatric medications during pregnancy, must be carefully assessed.

Women with histories of major depression frequently present for consultation regarding the use of psychotropic medications during pregnancy, or they may seek treatment after recurrence of illness following conception. Not infrequently, women present with the first onset of psychiatric illness during pregnancy. All decisions regarding the continuation or initiation of treatment during pregnancy must reflect an assessment of the following risks: (1) risk of fetal exposure to medication, (2) risk of untreated psychiatric illness in the mother, and (3) risk of relapse associated with discontinuation of maintenance treatment. A discussion of each of these risks should be documented in the patient's medical record.

With the advent of newer and better-tolerated antidepressants, a growing number of women are prescribed antidepressant medications during the childbearing years. For those women with recurrent major depression who are on maintenance treatment and plan to conceive, the clinician and patient must decide whether to maintain or discontinue antidepressant treatment during pregnancy. Ideally, decisions regarding the use of psychotropic medications during pregnancy should be made prior to conception. In this setting, the clinician must provide information regarding the patient's risk for relapse in the setting of medication discontinuation. One must also take into account the risk of chronic, recurrent depression and treatment resistance in patients who experience depressive relapse after medication discontinuation.[63–65]

In patients with milder forms of illness, it is appropriate to consider discontinuation of pharmacologic therapy during pregnancy. Adjunctive interpersonal or cognitive-behavioral therapy may also be used prior to conception to facilitate the gradual tapering and discontinuation of an antidepressant medication in women planning to become pregnant. Furthermore, these modalities of treatment may also reduce the risk of recurrent depressive symptoms during pregnancy. Close monitoring during pregnancy is essential, even if all medications are discontinued and there is no need for medication management. Psychiatrically ill women are at high risk for relapse during pregnancy, and early detection of recurrent illness may significantly reduce morbidity and facilitate treatment.

Many women are not able to discontinue antidepressant treatment because they experience recurrent depressive symptoms on discontinuation. For those women with more severe or refractory illness, the patient and clinician may instead decide that the safest option is to continue pharmacologic treatment during pregnancy. In this setting, the clinician should attempt to select medications for use during pregnancy that have a well-characterized reproductive safety profile. Often, doing so may necessitate switching from one psychotropic agent to another with a better reproductive safety profile, for example, switching from an MAOI to fluoxetine. In certain cases, one may decide to use a medication for which information regarding reproductive safety is sparse. For instance, a woman with refractory depressive illness who has responded only to one antidepressant for which data on reproductive safety are limited (i.e., venlafaxine) may choose to continue this medication during pregnancy rather than risk relapse by discontinuing this agent or switching to another antidepressant.

Women may also experience new onset of depressive symptoms during pregnancy. For women who present with minor depressive symptoms, nonpharmacologic treatment strategies should be explored first. Interpersonal psychotherapy or cognitive-behavioral therapy may be beneficial for reducing the severity of depressive symptoms and may either limit or obviate the need for medications.[29,30,66] In general, pharmacologic treatment is pursued when nonpharmacologic strategies have failed or when it is felt that the risks associated with psychiatric illness during pregnancy outweigh the risks of fetal exposure to a particular medication.

In situations in which pharmacologic treatment is indicated, the clinician should attempt to select the safest medication regimen, using, if possible, medications with the safest reproductive profile. Among the TCAs, desipramine and nortriptyline are preferred since they are less anticholinergic and the least likely to exacerbate orthostatic hypotension during pregnancy. Fluoxetine, with the most extensive literature supporting its reproductive safety, is a first-line choice. Data are limited regarding the teratogenic risk of the newer SSRIs, including sertraline, paroxetine, fluvoxamine, and citalopram. However, there is a growing literature on the reproductive safety of these newer SSRIs,[55,57] and these agents may be useful in certain settings. In patients with depression who have not responded to either fluoxetine or a TCA, these newer agents may be considered, acknowledging that information on their reproductive safety is limited. When prescribing medications during pregnancy, every attempt should be made to simplify the medication regimen. For instance, one may select a more sedating tricyclic antidepressant for a woman who presents with depression and sleep disturbance, rather than using an SSRI in combination with trazodone or a benzodiazepine.

In addition, the clinician must use an adequate dosage of medication. Frequently, the dosage of a medication is reduced during pregnancy in an attempt to limit risk to the fetus; however, this type of modification in treatment may instead place the woman at greater risk for recurrent illness. During pregnancy, changes in plasma volume, as well as increases in hepatic metabolism and renal clearance, may significantly affect drug levels.[67,68] Several groups have described a significant reduction (up to 65%) in

serum levels of tricyclic antidepressants during pregnancy.[2,3] Sub-therapeutic levels were associated with depressive relapse[31]; therefore, the daily TCA dosage was increased during pregnancy to induce remission. Similarly, many women taking SSRIs during pregnancy require an increase in SSRI dosage to sustain euthymia.[69]

On the basis of a number of anecdotal reports of toxicity in infants born to mothers treated with antidepressants, some authors have recommended discontinuation of antidepressant medication several days or weeks prior to delivery to minimize the risk of neonatal toxicity.[45–48] Given the low incidence of neonatal toxicity, this practice carries significant risk since it withdraws treatment from patients precisely as they are about to enter the postpartum period, a time of heightened risk for affective illness.

Severely depressed patients with acute suicidality or psychosis require hospitalization, and electroconvulsive therapy (ECT) is frequently the treatment of choice. Two recent reviews of ECT use during pregnancy note the efficacy and safety of this procedure.[70,71] In a review of the 300 case reports of ECT during pregnancy published over the past 50 years, there have been 4 reports of premature labor. There have been no reports of premature rupture of membranes caused by ECT. Given its relative safety, ECT may also be considered as an alternative to conventional pharmacotherapy for women who wish to avoid extended exposure to psychotropic medications during pregnancy or for those women who fail to respond to standard antidepressant therapy.

CONCLUSION

Depression occurs commonly during pregnancy, and women with recurrent depression are at particularly high risk for depressive illness in this setting. While the use of psychotropic medications during pregnancy raises concerns, there are data to support the use of certain antidepressants, including fluoxetine and the tricyclic antidepressants. Data on the newer SSRI antidepressants are gradually accumulating and are encouraging. None of the SSRIs or TCAs has been associated with an increased risk of congenital malformation. However, our information on the long-term neurobehavioral effects of these medications remains limited. As depression during pregnancy carries risk for both the mother and the child, it is crucial to recognize depression in this setting and to provide appropriate treatment strategies. Further data on nonpharmacologic and pharmacologic strategies are clearly needed to aid in the treatment of this challenging clinical population.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), terbutaline (Brethine), tranylcypromine (Parnate), venlafaxine (Effexor).

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