

## CLINICAL PRACTICE

## Depression during Pregnancy

Donna E. Stewart, M.D.

*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 author's clinical recommendations.*

**A 24-year-old married woman presents with a 1-month history of diminished concentration and interest, insomnia, fatigue, tearfulness, and depressed mood. She is 10 weeks pregnant, stopped working 3 weeks ago, and mostly stays in bed. Two years ago, she was successfully treated briefly with sertraline at a daily dose of 50 mg for depression after a suicide attempt. She reports that she wants to continue the pregnancy and says that she does not feel suicidal. What would you advise?**

## THE CLINICAL PROBLEM

Major depression is a common and treatable mental disorder and a major cause of disability.<sup>1</sup> In population-based surveys, approximately 7% of adults reported depression in the preceding 12 months<sup>1</sup> and 12.7% reported depression during pregnancy.<sup>2,3</sup>

The diagnostic criteria for a major depressive episode are shown in Table 1.<sup>4</sup> Depression that does not meet the full criteria may still cause considerable distress and require treatment.<sup>4,5</sup>

The strongest risk factor for depression during pregnancy is a history of depression.<sup>6</sup> Other risk factors include a family history of depression or bipolar disorder, childhood maltreatment, single motherhood, having more than three children, cigarette smoking, low income, age younger than 20 years, insufficient social support, and domestic violence.<sup>6-8</sup>

The consequences of depression during pregnancy include difficulty performing usual activities and failure to seek prenatal care; inadequate diet; the use of tobacco, alcohol, and other harmful substances; and the risk of self-harm or suicide.<sup>8</sup> Depression may affect fetal growth as well as infant temperament and later behavior in childhood.<sup>9-11</sup> Postpartum depression is more common in women with prenatal depression than in women who do not have prenatal depression, and it may lead to difficulties with infant care, mother-child attachment, care of other children, and the relationship with the woman's partner.<sup>7</sup>

Depression is often recurrent; approximately 90% of affected persons have more than one episode.<sup>12</sup> The natural course of a major depressive episode (whether related or unrelated to pregnancy) is variable. Longitudinal data on patients who are not pregnant indicate that the probability of recovery without treatment is approximately 20% in the first week after diagnostic criteria are met but declines with an increasing duration of depression (e.g., after 6 months, the likelihood of recovery during a subsequent week is <1%).<sup>13</sup> Depression may become more severe or resistant to treatment over time, and the risk of self-harm or suicide is a vital consideration.<sup>7</sup>

From the Women's Health Program and the Toronto General Research Institute, University Health Network, University of Toronto, Toronto. Address reprint requests to Dr. Stewart at the Toronto General Hospital, 200 Elizabeth St., EN-7-229, Toronto, ON M5G 2C4, Canada, or at donna.stewart@uhn.ca.

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## KEY CLINICAL POINTS

## DEPRESSION DURING PREGNANCY

- Major depression is a disabling, treatable disorder that affects more than 12% of pregnant women.
- Untreated depression during pregnancy has been linked to increased risks of suicide, miscarriage or preterm birth, poor fetal growth, and impaired fetal and postnatal development.
- Treatment includes psychotherapy, antidepressant medication, or both; the latter is indicated for severe depression.
- Data from randomized, controlled trials of antidepressants during pregnancy are lacking, but observational data suggest that selective serotonin-reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors are relatively safe.
- Some adverse outcomes appear to be slightly more common in offspring of women who take antidepressants during pregnancy; these include preterm birth, neonatal adaptation difficulties, neonatal persistent pulmonary hypertension, and rare cardiac abnormalities in neonates.
- Women with depression should be informed of the risks associated with antidepressant drugs as well as those associated with untreated depression, and they should be closely monitored throughout pregnancy and the first postpartum year.

## STRATEGIES AND EVIDENCE

## EVALUATION

All women who are pregnant or considering pregnancy should be asked about a personal history and family history of mental disorders and treatment.<sup>7</sup> Routine questions about antenatal depression are encouraged<sup>14</sup> and should include questions recommended by the National Institute for Health and Clinical Excellence<sup>7</sup> (Table 2); the Edinburgh Postnatal Depression Scale,<sup>15</sup> which is validated for use during pregnancy (see the Supplementary Appendix, available with the full text of this article at NEJM.org); or the Patient Health Questionnaire 9 (PHQ-9).<sup>16</sup>

A woman who has a positive result on a screening test for depression or in whom the clinician suspects depression should undergo a thorough evaluation<sup>5</sup> to determine the duration and intensity of the current symptoms, their effect on the patient's functioning and quality of life, and the patient's thoughts or plans regarding self-harm or suicide, as well as her level of anxiety, any psychotic symptoms, social supports, relationship with her partner, attitude toward her pregnancy, financial security, work history, and safety (e.g., risk of being physically abused). She should also be asked about her previous adjustments to stressful events and her psychiatric history (e.g., depressive episodes and their duration, anxiety, obsessions, compulsions, mania, suicide attempts, or psychotic symptoms and their response to treatment). A history of mania or hypomania indicates bipolar disorder, a major risk factor for severe postpartum depression and postpartum

psychosis.<sup>5,8</sup> Inquiries about family history should specifically include bipolar disorder and other mood disorders (especially those related to pregnancy), other psychiatric diagnoses, and suicide. The history taking should include questions about other medical conditions, medications (including over-the-counter medications), and the use of alcohol, tobacco, and illicit drugs. The examination should include an assessment of the patient's mental status. An evaluation for medical conditions that may cause depression should be performed as clinically indicated.<sup>5</sup>

## MANAGEMENT

Multidisciplinary care is recommended, with the involvement of the patient's obstetrician, internist, or family physician; a psychiatrist or other mental health professional, as appropriate; and a pediatrician (when there is one).<sup>7</sup>

Women should be informed about the risks associated with untreated depression. Treatment options, including psychotherapy (see below) and pharmacotherapy, as well as both the potential benefits and the risks of antidepressant use during pregnancy, should be clearly reviewed, and the discussion documented.<sup>8</sup> Coexisting substance abuse and other psychiatric and medical disorders should be addressed. The use of tobacco, alcohol, and other harmful substances should be discouraged.<sup>5,7</sup> Indications for referral to a psychiatrist are summarized in Table 3.

*Risks Associated with Untreated Depression*

Untreated depression during pregnancy has been associated with increased risks of miscarriage,

low birth weight, and preterm birth.<sup>17</sup> Infants of depressed mothers, as compared with mothers who are not depressed, have been reported to have increased irritability, fewer facial expressions, and higher cortisol levels<sup>11</sup> and to be at risk for developmental delay.<sup>18</sup> However, some of these findings are potentially confounded by other factors associated with both depression and these adverse outcomes, such as alcohol or illicit-drug use and obesity.

#### Antidepressant-Drug Therapy

There are no data from randomized, controlled trials assessing the efficacy or safety of antidepressant drugs during pregnancy. Thus, information regarding the potential effects of antidepressants on the fetus is largely derived from prospective or retrospective cohort or case-control studies, meta-analyses,<sup>19-21</sup> and population-based pregnancy registries,<sup>22-24</sup> in which observed associations between maternal antidepressant use and adverse outcomes may be confounded by co-existing conditions or behaviors in the mother.<sup>25</sup>

Classes of antidepressant drugs for use during pregnancy include the tricyclics, selective serotonin-reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). Although none of these agents have been proved absolutely safe in pregnant women, there are more reassuring data on the SSRIs than on the other two classes of drugs. Women who receive antidepressants typically have more severe depression than women who do not receive medications; thus, risks associated with medication use may be explained by more severe disease or associated coexisting conditions (i.e., confounding by indication). Moreover, since approximately 13% of women take an antidepressant,<sup>26</sup> and more than 80% take at least one dose of medication (other than vitamins) during pregnancy,<sup>27</sup> it can be difficult to assess the separate effect of antidepressants. Finally, newborns exposed to antidepressant medications may be more carefully assessed than other newborns, leading to ascertainment bias.<sup>21</sup>

The risks of several maternal complications, including gestational diabetes, preeclampsia, placental problems, premature rupture of the membranes, bleeding, induced delivery, and having to undergo a cesarean section,<sup>23</sup> have been reported to be slightly increased among women who have received antidepressant drugs during pregnancy. Two meta-analyses<sup>20,28</sup> have shown a slightly increased risk of spontaneous abortion in associa-

**Table 1. Criteria for the Diagnosis of a Major Depressive Episode.\***

Five or more of the following symptoms during the same 2-week period, with the symptoms representing a change from previous functioning and with at least one of the first two symptoms included
Depressed mood most of the day, nearly every day
Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
Insomnia or hypersomnia nearly every day
Psychomotor agitation or retardation nearly every day
Fatigue or loss of energy nearly every day
Feelings of worthlessness or excessive or inappropriate guilt nearly every day
Diminished ability to think or concentrate, or indecisiveness, nearly every day
Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
The symptoms do not meet criteria for a mixed episode (includes hypomanic or manic symptoms)
The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse or other medication) or a general medical condition (e.g., hypothyroidism)
The symptoms are not better accounted for by bereavement

\* Criteria are from the American Psychiatric Association.<sup>4</sup>

**Table 2. Screening Questions for Depression during Pregnancy.**

During the past month, have you been bothered by feeling down, depressed, or hopeless?
During the past month, have you been bothered by having little interest or pleasure in doing things?
If the answer to either question is "yes," ask "Is this something you feel you need or want help with?"

\* Questions are from the National Institute for Health and Clinical Excellence.<sup>7</sup>

tion with the use of various antidepressants in women with depression, as compared with women in the general population.

The risk of major fetal congenital malformations in the general population is 2 to 4%.<sup>7,8</sup> Most studies have shown no significant increase in the overall risk of congenital structural malformations with antidepressant use in early pregnancy.<sup>20,29,30</sup> However, an analysis of data from the Swedish Medical Birth Register, which included more than 15,000 fetuses with exposure to antidepressants, showed a significant, albeit modest, increase in the risk of "relatively severe" congenital malformations (odds ratio adjusted for confounders, including body-mass index and smoking status, 1.36; 95% confidence interval [CI], 1.07

**Table 3. Indications for Referral to a Psychiatrist.**

Thoughts, plans, or acts relating to self-harm or suicide
Psychotic symptoms
Bipolar disorder (or history of mania or hypomania)
Current or recent episode of severe depression
No response to pharmacotherapy or psychotherapy
History of schizophrenia or postpartum psychosis
Severe coexisting anxiety, obsessive-compulsive disorder, panic disorder, eating disorder, or substance abuse

to 1.72). Most malformations were cardiac septal defects that were associated with maternal use of tricyclic antidepressants (primarily clomipramine)<sup>23</sup> but not with maternal use of SSRIs or SNRIs. Some studies, including a meta-analysis<sup>21</sup> of seven studies, have shown an association between the use of paroxetine and congenital cardiac defects.<sup>23,24,31</sup> A Danish population-based study did not confirm this finding, but it showed a significant increase in the risk of congenital septal heart defects with exposure in utero to more than one SSRI.<sup>22</sup> Several studies have linked sertraline, citalopram, and fluoxetine to small increases in the risk of cardiac defects among infants,<sup>22-24,32</sup> raising the possibility of a class effect. Some studies, but not others,<sup>33</sup> have shown modest increases in the risk of anencephaly,<sup>30</sup> craniosynostosis,<sup>30</sup> omphalocele,<sup>30</sup> and hypospadias<sup>23</sup> with the use of SSRIs in pregnant women. Citalopram has been associated with a small absolute increase in neural-tube defects.<sup>24</sup> The observation that among infants in a Finnish study,<sup>24</sup> fetal alcohol spectrum disorders were 10 times as common in SSRI-exposed infants as in unexposed infants underscores the potential confounding effects of alcohol, among other factors.

In a meta-analysis of nine studies, antidepressant use during pregnancy was associated with a slightly increased risk of birth before 37 weeks of gestation (odds ratio, 1.85; 95% CI, 0.79 to 4.29) and a birth weight of less than 2500 g (odds ratio, 3.64; 95% CI, 1.01 to 13.08).<sup>19</sup> These associations were stronger for tricyclic antidepressants than for SSRIs or SNRIs.<sup>23</sup> Increased risks of preterm birth and lower birth weight in association with SSRI use have remained significant in studies adjusting for maternal illness,<sup>34-36</sup> including untreated depression, or using propensity-score matching.<sup>35,36</sup>

In the Swedish Medical Birth Register, rates of hypoglycemia, jaundice, respiratory problems, and low Apgar scores were slightly increased

among neonates who had been exposed to antidepressants, with the highest rates associated with exposure to tricyclic antidepressants, SNRIs, and SSRIs.<sup>23</sup> A “neonatal adaptation syndrome” has been described in 15 to 30% of newborns exposed to SSRIs in late pregnancy<sup>25,37,38</sup>; symptoms and signs include irritability, weak crying or none, tachypnea, temperature instability, hypoglycemia, and occasionally seizures; these symptoms and signs typically resolve within 2 weeks after birth. Possible mechanisms may include withdrawal effects, drug toxicity, and changes in brain function.<sup>8</sup> Similar symptoms and signs occur in neonates after exposure to tricyclic antidepressants during pregnancy.<sup>25,30</sup> In a meta-analysis of nine studies, infants exposed to SSRIs were more likely to be admitted to a neonatal intensive care unit than were infants without this exposure.<sup>19</sup> In a large case-control study, fetal exposure to SSRIs after 20 weeks’ gestation (but not before)<sup>39</sup> was associated with an increased risk of persistent pulmonary hypertension of the newborn, a very rare but serious condition; in the Swedish register study, this condition was associated with exposure to SSRIs both early and later in pregnancy, but the absolute risk was low<sup>23</sup> (0.56 cases per 1000 births).

Insufficient research has been conducted on longer-term effects in children of maternal antenatal depression and fetal exposure to antidepressants; such research is complicated by the effects of ongoing maternal depression on outcomes in children. One population-based, case-control study showed a modest increase in the risk of autism spectrum disorders after first-trimester fetal exposure to any antidepressant,<sup>40</sup> but this finding requires further study. Most studies have shown no significant difference between the developmental outcomes of children with exposure to antidepressants in utero and those of children without this exposure, but available data are limited.<sup>25</sup>

#### *Psychotherapies*

Cognitive behavioral therapy aims to change attitudes and behaviors that contribute to depression. Interpersonal psychotherapy aims to improve interpersonal factors, such as a lack of social skills, that contribute to depression.<sup>5</sup> Both cognitive behavioral therapy and interpersonal psychotherapy, administered in 6 to 12 weekly 1-hour sessions, have been shown to be effective in the treatment of depression.<sup>5</sup> Although data from randomized trials involving pregnant women are

limited,<sup>41</sup> professional guidelines recommend these therapies for depression during pregnancy.<sup>5,7,8</sup>

#### TREATMENT RECOMMENDATIONS

Treatment should involve a stepped-care approach. The clinical response should be monitored, preferably with a validated scale such as the PHQ-9.<sup>16</sup>

Women with mild depression of recent onset ( $\leq 2$  weeks) can be cared for initially with watchful waiting, nondirective counseling, or encouragement to exercise.<sup>7</sup> If no improvement occurs within 2 weeks, the clinician should recommend cognitive behavioral therapy or interpersonal psychotherapy.<sup>7</sup> Although the use of antidepressants for mild or moderate depression is controversial,<sup>7,42</sup> they may be appropriate in some women who prefer this treatment, women for whom cognitive behavioral therapy or interpersonal psychotherapy is not accessible or who have had a poor response to these therapies, and women with an inability to perform usual activities, a history of severe depression, or a response to previous antidepressant therapy.<sup>5,7,8</sup>

Individual, group, or computer-assisted cognitive behavioral therapy or interpersonal psychotherapy should initially be recommended for pregnant women with moderate depression.<sup>7</sup> If no improvement occurs over 8 weeks (or earlier in women with impairment of function, a history of severe depression, or a previous response to antidepressants), or if there is concern about suicide risk, antidepressants should be strongly considered.<sup>8</sup>

For severe depression, an antidepressant, cognitive behavioral therapy, and interpersonal psychotherapy are all valid choices.<sup>5,7,8</sup> The patient's choice, difficulty in accessing or having a response to cognitive behavioral therapy or interpersonal psychotherapy, and the need for a more rapid response all argue in favor of the use of an antidepressant.<sup>5,8</sup> Although it was not studied specifically in pregnant women, a combination of antidepressant therapy and psychotherapy was shown in a meta-analysis of three studies to result in modestly higher remission rates and lower relapse rates than either treatment alone.<sup>5</sup>

For women with preexisting depression who are planning a pregnancy or are already pregnant, the severity of past and current episodes of depression, response to treatment, and patient preferences should guide treatment decisions.<sup>8</sup> If the current or past depression is mild to moderate, consideration can be given, if the woman prefers,

to gradual tapering of the antidepressant during a switch to interpersonal psychotherapy or cognitive behavioral therapy.<sup>7,8</sup> However, careful monitoring is recommended to detect deterioration or relapse, which appear to be common during pregnancy and the postpartum period, particularly if the antidepressant is discontinued abruptly.<sup>43</sup>

The choice of antidepressant should be based on the side-effect profile, the patient's past response, and the agent with the lowest risk profile for the mother and fetus on the basis of available data. In general, SSRIs are similar to one another in efficacy, have fewer maternal and fetal side effects than tricyclic antidepressants, and are safer in overdoses than tricyclic antidepressants.<sup>5</sup> Most studies have suggested similar risk profiles for SNRIs and SSRIs,<sup>8</sup> although data from the Swedish Medical Birth Register indicated that SNRIs were intermediate in risk between the tricyclic antidepressants and SSRIs.<sup>23</sup> Paroxetine should be avoided if possible,<sup>21,23-25,31</sup> since among all antidepressants, it has the strongest association with cardiac malformations. Antidepressants should be started at the lowest effective dose and gradually increased as needed to achieve remission.<sup>5</sup> Physiological alterations during pregnancy may result in higher dose requirements in pregnant women than in women who are not pregnant.<sup>5</sup>

Monotherapy is generally preferable to a combination of antidepressants<sup>22</sup> or an antidepressant combined with a benzodiazepine,<sup>36</sup> since the latter approaches have been associated with higher rates of cardiac malformations in the fetus, after adjustment for the severity of depression in pregnant women.<sup>36</sup> Data on the use of duloxetine, desvenlafaxine, bupropion, and mirtazapine in pregnant women are sparse. Antidepressants for which there are more data on use during pregnancy are a safer choice.

Electroconvulsive therapy is reserved for severe treatment-resistant depression or depression associated with psychotic symptoms or a high risk of suicide.<sup>5,7,8,44</sup> Case reports suggest that the risks associated with the use of electroconvulsive therapy during pregnancy are low with careful monitoring.<sup>44</sup>

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#### AREAS OF UNCERTAINTY

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Large studies comparing cognitive behavioral therapy, interpersonal therapy,<sup>41</sup> and antidepressant drugs in pregnant women are needed to better

guide treatment decisions. Data from randomized, controlled trials of antidepressants in pregnant women are lacking. Additional data are needed from large prospective studies assessing fetal and postnatal outcomes with the use of antidepressant therapy during pregnancy, with attention to the timing, duration, type, and dosage of these drugs and to coexisting conditions in the pregnant woman.<sup>45</sup> Evidence is insufficient to inform recommendations for acupuncture,<sup>46</sup> hormone therapy, bright-light therapy, n-3 fatty acids,<sup>47</sup> or St. John's wort<sup>48</sup> for antenatal depression. The effects of genetic polymorphisms on neonatal outcomes after in utero exposure to antidepressants require further study.<sup>49</sup>

#### GUIDELINES

Guidelines on the treatment of depression during pregnancy are available from the American Psychiatric Association<sup>5</sup> and the National Institute for Health and Clinical Excellence in the United Kingdom.<sup>7</sup> A combined report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists has provided algorithms for management.<sup>8</sup> The recommendations in this article are generally consistent with these guidelines.

#### CONCLUSIONS AND RECOMMENDATIONS

Untreated depression during pregnancy may adversely affect a woman, her fetus, her other children, and her partner. Nonpharmacologic interventions such as cognitive behavioral therapy or interpersonal therapy are often useful in women with mild or moderate depression.<sup>5,7,8</sup> Antidepressant therapy is indicated for more severe depression, but it may also be used for less severe depression if the woman prefers it or if other treat-

ments are inaccessible or unsuccessful.<sup>5,8</sup> Although data from randomized trials of antidepressant therapy in pregnant women are lacking, observational data suggest that SSRIs and SNRIs are relatively safe during pregnancy, although increased risks of some maternal and fetal conditions have been reported, including miscarriage, preterm birth, neonatal adaptation difficulties, neonatal persistent pulmonary hypertension, and cardiac (particularly with paroxetine) and other malformations in neonates; the risks appear to be somewhat higher with tricyclic antidepressants than with SSRIs or SNRIs.<sup>23</sup> Patients should be educated about the risks, but they should be informed that the absolute risks appear to be low and that there are also risks associated with untreated depression.

The woman described in the vignette has a history of depression with a suicide attempt and is currently unable to perform her usual activities. Given her prior response to sertraline, I would initiate treatment with sertraline at a dose of 50 mg daily and see her in 1 week to monitor her response to treatment and assess her for suicidality, as well as any side effects. The dose can be increased by 50 mg every 2 weeks, if needed, to a maximum of 200 mg. With her permission, her partner should also be educated about depression and its treatment. She can be offered interpersonal therapy or cognitive behavioral therapy as adjunctive treatment, given the potentially greater benefit of combination therapy than of pharmacotherapy alone. She should be monitored regularly throughout her pregnancy and the first postpartum year, since she is at increased risk for postpartum depression.<sup>50</sup>

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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