Depression in pregnancy: When doing nothing is *not* an option

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TARGET AUDIENCE

Obstetrician/gynecologists and women's health practitioners.

EDUCATIONAL OBJECTIVES

After participating in this activity, physicians should be able to:

- Identify the criteria for major depression as well as the differential diagnoses.
- Summarize the prevalence of depression during pregnancy and in the first 3 months postpartum.
- Summarize the treatment options for antenatal depression based on safety and efficacy as well as the management recommendations for postpartum depression.
- Assess the risks associated with antidepressant pharmacotherapy during pregnancy.

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Dr. Lusskin discloses that she is on the Speakers' Bureaus of AstraZeneca, Wyeth, and Forest Pharmaceuticals. She is also Director of Psychopharmacologic Agents, The Reproductive Toxicology Center, a nonprofit foundation that operates Reprotox (www.reprotox.org).

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Treating depression during pregnancy is just as essential as treating epilepsy or hypertension.

Antenatal depression affects the health and well-being of the mother, baby, and family. And although many women, their partners, and even physicians think they can "tough it out" during pregnancy, untreated depression is far from a benign illness.[1] A depressed woman is more likely not to comply with her prenatal care, to self-medicate with tobacco, alcohol, and illicit drugs, and to commit suicide, all of which underscore a pressing need for appropriate treatment. She may also consider terminating her pregnancy—even when it was planned (Table 1).[2]

Which patients are most at risk?

Depression affects between 14% and 23% of pregnant women and from 11% to 32% of women in the first 3 months postpartum, according to the Agency for Healthcare Research and Quality.[3] Moreover, as new ACOG guidelines also reiterate, many postpartum episodes begin in pregnancy.[4,5]

Women with a history of major depression are at high risk for relapse during pregnancy, especially if they discontinue medications.[6] In a study of 201 women who were not depressed at conception,

How do you and your depressed patients walk that fine line between the risks of taking—or *not* taking—antidepressants during pregnancy? Which drugs or alternate therapies seem safest? An expert cautions that maternal and fetal risks of *untreated* mental illness—ranging from spontaneous abortion to suicide—may outweigh the risks of antidepressants.

Jim Shive

68% of those who discontinued their medication during pregnancy relapsed, compared with only 26% of those who continued; the hazard ratio was 5.0 (95% CI, 2.8–9.1). And because even staying on the drugs doesn't completely protect pregnant patients against relapse, these women require close monitoring.[7,8]

Identifying depression in pregnancy

Since there's no separate category for perinatal depression, be aware of the American Psychiatric Association criteria for diagnosing major depression, which requires a patient to have experienced at least five of nine possible symptoms over the previous 2 weeks.[9] To make the diagnosis, one of these five *must* be either:

1. a depressed (or low) mood nearly all-day long, nearly daily, or
2. sharply diminished interest or pleasure in the majority of activities with that same frequency.

The other seven symptoms to look for, which should be occurring nearly daily, are:

3. a decrease or increase in appetite (or a monthly weight change—up or down without dieting—of at least 5% of her body weight);

TABLE 1

Maternal and fetal risks of untreated antenatal depression

Maternal

- Bleeding during pregnancy
- Cesarean delivery
- Noncompliance with prenatal care
- Poor appetite during pregnancy
- Poor weight gain during pregnancy
- Postpartum depression (especially when sleep deprived)
- Preeclampsia
- Reduced sleep during pregnancy
- Self-medication with tobacco, alcohol, and drugs
- Spontaneous abortion
- Suicide

Fetal

- Admission to an NICU
- Behavioral problems in childhood and adolescence
- Lower Apgar scores
- Lower dopamine and serotonin levels
- Preterm delivery
- Small for gestational age
- Smaller head circumference

Source: Lusskin S, et al.[1]

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4. sleeping too much or trouble sleeping;
5. nonsubjective psychomotor agitation or retardation;
6. energy loss or fatigue;
7. lessened ability to concentrate or think, or difficulty with decision-making;
8. feeling worthless, or overly or inappropriately guilty
9. attempting, specifically planning, or thinking about suicide, or having recurring thoughts of death.[9]

Depression identified within the first postpartum year is considered postpartum depression.[1] Clinicians and patients often misattribute the symptoms of depression such as insomnia, lack of energy, and changes in appetite and weight, to the expected changes of pregnancy. Sad, blue, hopeless, or helpless mood are symptoms of a possible mood disorder, and thinking about suicide is never normal. Women feel guilty about being depressed during pregnancy, so many suffer in silence. When a woman does complain, she should be evaluated.[1]

You can evaluate many patients' depression, but refer severe cases to a psychiatrist as soon as possible. . .

Hidden symptoms. Depressed pregnant women may not feel bonded to the fetus and may have obsessional (illogical intrusive) thoughts about harming the fetus, which they rarely reveal. Asking a patient about "scary thoughts" may enable the patient to reveal them.

Depressed women can also have other obsessive compulsive symptoms or panic attacks.[2,10] Both anxiety and depressive symptoms need diagnosis and treatment during pregnancy. The differential diagnosis also includes bipolar depression, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, and eating disorders.[10-13]

Screening tools such as the Edinburgh Postnatal Depression Scale (EPDS), the Postpartum Depression Screening Scale, and the Beck Depression Inventory can help detect antenatal depression.[14,15]

Evaluation. A complete psychiatric evaluation includes a urine toxicology screen and baseline labs (thyroid-stimulating hormone, comprehensive metabolic profile, complete blood count). (**Note: ob/gyns should refer *severe* cases to a psychiatrist as soon as possible.**) Also ask the patient if she takes nutriceuticals, herbal medications, or over-the-counter and other medications; these may produce mood changes or interfere with psychotherapeutic drugs.

Treatment: SSRIs, psychotherapy, or both?

Two treatment options have been studied for antenatal depression: drugs and interpersonal psychotherapy.[16] Although cognitive behavioral therapy is effective in postpartum depression, it hasn't been studied in antenatal depression.[17] Combining psychotherapy and medications is often most helpful, although pregnant women haven't been studied.[18] The best time to decide whether to give a pregnant woman antidepressants is before she gets pregnant, given that 49% of all pregnancies are unplanned. Drugs are usually first-line treatment for a woman with a history of medication-responsive depression or for one who has moderate-to-severe depression.[19]

Patients fall into three groups:

1. Women with a history of depression who are not currently depressed on medications. The severity and frequency of relapses, the degree of difficulty in achieving remission, and patient preference are the major factors to consider when deciding whether to continue drugs. If a decision is made to stop antidepressants, the medication should be tapered slowly prior to conception (over 1–3 months) so you can catch a relapse early and treat it promptly.
2. Women with a history of depression who are symptom-free off medications. Hold a discussion

early on to alert your patient about the risks of relapse during pregnancy and postpartum.

3 Women who have symptoms of depression. Careful evaluation and treatment will lead to prompt recovery.

Do you choose an SSRI, an SNRI, or other antidepressant?

Drug choice is guided by a woman's history of response, the family history of response (especially in the drug-naïve patient), the safety data in pregnancy and lactation, and side effects. *In general,* it's better to avoid recently released drugs until safety data have accumulated.

SSRIs and venlafaxine. The leading choices for antenatal depression are the selective serotonin reuptake inhibitors (fluoxetine, sertraline, citalopram, escitalopram, and fluvoxamine) and venlafaxine, a serotonin/norepinephrine reuptake inhibitor (SNRI), in that they have the most safety data in pregnancy and lactation.[20] Although ACOG does not currently recommend paroxetine in pregnancy, its use is justified in some situations: for example, in the already pregnant patient who is doing well on it and in a woman with a relapse who has responded very well to paroxetine in the past.

However, a woman shouldn't necessarily be started on or switched to an SSRI or SNRI just because she is planning to become pregnant or is already pregnant. If a patient is uniquely responsive to an older drug (such as nortriptyline) or a less-studied drug (and has failed trials of SSRIs), then the benefits of that drug to the mother may outweigh the less well-characterized risks to the fetus.

What do studies say about drugs' teratogenicity?

We believe the FDA category system is not an adequate guideline,[21] so it's best to review the literature when deciding which antidepressant to use.

Based on animal studies, none of the SSRIs or the SNRIs (venlafaxine and duloxetine) will likely increase the risk for congenital anomalies. Most human studies have not shown an increase in birth defects above the US background rate of about 3%.[20,22-26] Fluoxetine is the best studied drug, but there are also much data on sertraline, paroxetine, and citalopram. The teratogenicity data on citalopram apply to escitalopram.[24] There's only one specific case report of first-trimester exposure to escitalopram, and no published human data on duloxetine (for that reason, duloxetine is not recommended in pregnancy, unless the patient is already pregnant on it).[27]

However, several studies have shown that exposure to SSRIs around the time of conception (chiefly fluoxetine, sertraline, and paroxetine) may slightly increase the risk of birth defects, based on mothers who reported using SSRIs or presumed use based on prescription and events monitoring studies.[28-31]

The FDA has changed paroxetine from category C to D.[32] In a case–control study, SSRI exposure (combined for fluoxetine, sertraline, paroxetine, and citalopram) increased the risk for omphalocele (OR 2.8; 95% CI, 1.3–5.7), craniosynostosis (OR 2.5; 95% CI, 1.5–4.0), and anencephaly (OR 2.4; 95% CI, 1.1–5.1).[31] Paroxetine was associated with omphalocele (N=6, OR 8.1; 95% CI, 3.1–20.8); anencephaly (N=5 exposed, OR 5.1; 95% CI, 1.7–15.3); gastroschisis (N=5, OR 2.9; 95% CI, 1.0–8.4), and right-ventricular outflow tract obstruction (N=7, OR 2.5; 95% CI, 1.0–6.0).

In contrast, a second case–control study found no link between SSRIs (combined for fluoxetine, sertraline, and paroxetine) and omphalocele, craniosynostosis, or anenephaly.[33] However, when each drug was analyzed separately, sertraline was associated with omphalocele (N=3, OR 5.7; 95% CI, 1.6–20.7) and septal defects (N=13, OR 2.0; 95% CI, 1.2–4.0) and paroxetine was linked with right ventricular outflow

Asking your patients about **'scary thoughts'** may help elicit thoughts about **harming** her **baby**. . .

tract obstruction defects (N=6, OR 3.3; 95% CI, 1.3–8.8).

Investigators for both studies said the associations were possibly due to chance, given the small number of cases and use of multiple comparisons. Neither study controlled for illicit substance abuse, severity of alcohol use, or degree of maternal mental illness. It is not clear, then, whether these medications raise the risk for malformations by a minute amount or not at all.[34]

Miscarriage. A meta-analysis has linked antidepressants to miscarriage. However, none of the studies analyzed adequately controlled for history of miscarriage or severity of maternal mental illness, among other factors.[35]

Neonatal complications. Reports on the risks of low birthweight, preterm birth, and fetal demise have been conflicting.[36-39] Many studies have noted an increased risk of transient neonatal complications, often termed "poor neonatal adaptation" associated with SSRIs and the older tricyclic antidepressants.[24,37,40-43] As a result, the FDA issued a safety alert in 2004.[44]

Some **68%** of women in one study who **stopped** their **medications** during pregnancy **relapsed**. . .

The most common complications are transient respiratory distress, jitteriness, feeding difficulties, and temperature instability; seizures have been reported infrequently. Treatment is supportive, and symptoms usually resolve within 48 hours, infrequently lasting up to 2 weeks. No deaths have been reported.

None of these earlier studies controlled for the severity of maternal depression, which can affect fetal development *directly* through the neurochemical changes of depression, and *indirectly* through negative maternal health behaviors (such as smoking or illicit drug use). One group that did try to control for severity of maternal depression using linked Canadian health databases concluded that maternal depression was associated with a slight increase in low birthweight (<10%).[45] A half-day increase in neonatal hospital stay was associated with SSRIs, as were small increases in feeding difficulties, jaundice, and convulsions. When factoring in estimated severity of maternal illness, SSRIs accounted for roughly a 3% increase in low birthweight and a 5% increase in respiratory distress.

A retrospective case–control study led to another FDA warning in 2006. Investigators concluded that exposure to fluoxetine, sertraline, or paroxetine in the second half of pregnancy (relative to the first) increased the risk of persistent pulmonary hypertension of the newborn (PPHN) (OR 6.1; 95% CI, 2.2–16.8).[46,47] This study awaits replication.

Although some researchers suggest avoiding SSRIs in the third trimester or tapering off, no published study has shown the safety or efficacy of such a strategy.[41] The third trimester is a more vulnerable time for many women, and SSRI doses often have to be *increased* to maintain a normal mood.[6,8]

Long-term childhood neurodevelopment. Animal studies haven't shown developmental delays following prenatal exposure to SSRIs.[47] But human studies, although relatively small, have consistently found that maternal depression, but not SSRI exposure, adversely affects development in children followed between ages 4 and 7 years.[43,45,49-52]

Breastfeeding. The literature contains very few reports of toxicity and generally low or undetectable SSRI levels in infant serum.[53] There are more data on maternal-infant serum levels for sertraline and paroxetine than for the other SSRIs, and for both drugs, levels were lower than for fluoxetine. Sertraline may be the best choice in lactating women.

In its new guidelines, ACOG reiterates its recommendations to individualize treatment with SNRIs during pregnancy (but to avoid paroxetine, *if possible*) because the risks of maternal mental illness may outweigh the risks of medication.[5]

Management recommendations

Begin treatment planning when a patient enters your practice and. . .

Seek consults. Consultation with a psychiatrist is helpful during pre-pregnancy planning and for managing the complicated patient (one who fails to respond to an initial trial or who has significant suicidal thoughts or psychotic symptoms). *Always* initiate consultation if the patient or family requests it.

Involve the family and others. The partner may provide insights into your patient's illness and can monitor her response to treatment. And it gives you a chance to assess the need to refer them for individual or family therapy or both or for domestic violence services. In addition, the partner's participation in the informed consent discussion will help if the patient forgets any details discussed. Meeting with the partner may also destigmatize the illness for the couple.

Coordinate care with other providers. Work with psychiatrists, psychiatric nurse-practitioners, social workers, nurse midwives, and pediatricians to minimize the chances of sending mixed messages to the patient, which would interfere with her treatment compliance, and to help the prescribing physician monitor the patient more closely.

Make drug decisions prior to pregnancy. Some patients may choose to stop antidepressants prior to or during pregnancy, but they are at risk for relapse. While psychotherapy can help prevent relapse for some, for many it is *not* equally effective. If the decision is made to stop medication, discontinue it *before* pregnancy. Then, if the patient relapses, she can be treated to remission again before becoming pregnant. Relapses during pregnancy are much harder to treat.

Also make any *switch* in medications (from an SSRI to a tricyclic or an atypical antidepressant such as bupropion) prior to pregnancy, for exactly the same reasons. Similarly, to switch in the middle (after 20 weeks) only increases the risk for relapse at a time of already increased vulnerability.

Avoid suboptimal dosing to minimize the chance of relapse and maximize the benefit to the patient. We routinely treat hypertension, asthma, and epilepsy in pregnancy. Depression is no less serious than these illnesses and merits adequate treatment. While psychotherapy alone may be effective for some women, many will require antidepressants to achieve remission. There is no such thing as nonexposure: the fetus will be exposed either to illness or to the medication. ◀

SSRI doses may often need to be increased in the third trimester to maintain a normal mood. . .

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