Mrs. D is a 28-year-old married woman who became depressed after her first pregnancy. The depression was treated successfully with paroxetine, 20 mg/d. Before beginning treatment, she reported low mood, spent most of the day in bed, was unable to care for herself, and confessed to thoughts of harming her child.

Mrs. D presents to your clinic asking whether she should continue her selective serotonin reuptake inhibitor (SSRI) because she and her husband are thinking about having a second child. Recently, she tells you, she saw a news article suggesting that antidepressants show little benefit, and she is concerned that her baby might have a heart defect if she continues paroxetine.

Mrs. D wants to discontinue her medication, but her husband thought she should discuss doing so with you first. During this visit she takes a pregnancy test, which is positive. She wants to know what to do.

SSRI use is increasing among women during their childbearing years, a period that also carries the highest risk of depression. An estimated 7% to 23% of pregnant women experience depression; 3.8% of pregnant women receive an SSRI. SSRIs are the most commonly prescribed antidepressants during pregnancy, but their use remains controversial. There is disagreement about the maternal and neonatal risks of untreated depression and SSRI exposure. Media reports of studies demonstrating adverse effects associated with SSRIs may generate fear among women, possibly prompting them to self-discontinue medication.

Evidence of risks and benefits
Clinicians should be aware of possible adverse effects of SSRI use and untreated depression (Table, page 42). The available data precludes definitive associations between untreated depression and poor outcomes (Box, page 42). Studies of SSRI use during pregnancy have shown conflicting results for all potential outcomes. Absolute risk, with the exception of neonatal adaptation syndrome, is estimated to be small. Neonatal adaptation syndrome—which is characterized by jitteriness, poor muscle tone, weak cries, respiratory dis-
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Savvy Psychopharmacology

Stress, hypoglycemia, low Apgar scores, and seizures—occurs in 15% to 30% of infants born to mothers taking SSRIs, but it is transient and resolves during the first weeks of life.

Treatment recommendations
Given the conflicting nature of the evidence, treatment plans should be individualized, weighing the risks and benefits of treatment and the patient’s beliefs and psychiatric history. Consider severity of symptoms and history, including effective therapy and history of relapse. For women with mild or moderate depression, cognitive-behavioral therapy might be an appropriate first-line therapy. However, non-pharmacotherapeutic interventions might not relieve severe depression or be available to all women. When discontinuing an SSRI before pregnancy, counsel the patient to not discontinue the medication abruptly and provide an appropriate taper schedule. See Related Resources (page 44) for detailed recommendations from the American Psychiatric Association and the American College of Obstetricians and Gynecologists.

Reviewing the SSRI literature regarding pregnancy
Sertraline, paroxetine, citalopram, and fluoxetine are the most studied SSRIs during pregnancy; little information is available on escitalopram and fluvoxamine. Prescribing preference generally is given to the medications with the most evidence; paroxetine may be an exception. In 2005, the FDA requested a change in paroxetine’s pregnancy category from C to D, indicating that adequate studies demonstrated a risk of congenital cardiac malformations.

Because of the ethical problems of conducting prospective, randomized, controlled trials of selective serotonin reuptake inhibitors (SSRIs) in pregnant women, evidence often is inconsistent and methodologically flawed. Much of the current literature is based on retrospective reviews of administrative databases, teratology services, or birth registries. This methodology often does not incorporate confounding variables such as dose, timing of exposure, use of other medications, alcohol, tobacco, or illicit drugs, severity of depression, and other medical conditions in the mother. Many of these studies compared women receiving treatment with non-depressed controls, which makes it difficult to separate effects of SSRIs from those of depression. Studies may have small sample sizes, report relative risk over absolute risk, and vary in measured outcomes—making quantitative systematic reviews challenging.

Evidence on SSRI use in pregnancy is necessarily limited

Because of the ethical problems of conducting prospective, randomized, controlled trials of selective serotonin reuptake inhibitors (SSRIs) in pregnant women, evidence often is inconsistent and methodologically flawed. Much of the current literature is based on retrospective reviews of administrative databases, teratology services, or birth registries. This methodology often does not incorporate confounding variables such as dose, timing of exposure, use of other medications, alcohol, tobacco, or illicit drugs, severity of depression, and other medical conditions in the mother. Many of these studies compared women receiving treatment with non-depressed controls, which makes it difficult to separate effects of SSRIs from those of depression. Studies may have small sample sizes, report relative risk over absolute risk, and vary in measured outcomes—making quantitative systematic reviews challenging.

Past Research

The possible teratogenic effects of SSRIs have not been assessed in prospective, controlled trials in pregnant women. The majority of the evidence has been derived from retrospective studies of SSRI use during pregnancy, which have limitations. These limitations include nonrandomized comparisons, potential confounding factors, and large sample sizes.

Current Practice

Treatment plans should be individualized, weighing the risks and benefits of treatment and the patient’s beliefs and psychiatric history. Consider severity of symptoms and history, including effective therapy and history of relapse. For women with mild or moderate depression, cognitive-behavioral therapy might be an appropriate first-line therapy. However, non-pharmacotherapeutic interventions might not relieve severe depression or be available to all women. When discontinuing an SSRI before pregnancy, counsel the patient to not discontinue the medication abruptly and provide an appropriate taper schedule. See Related Resources (page 44) for detailed recommendations from the American Psychiatric Association and the American College of Obstetricians and Gynecologists.

Clinical Point

For pregnant women with mild or moderate depression, CBT might be an appropriate first-line therapy.

Table

Potential adverse outcomes during pregnancy

When depression is untreated
- Spontaneous abortion
- Preterm delivery, low birth weight, small for gestational age
- Preeclampsia
- Reduced fetal responsiveness in utero
- Lack of maternal health maintenance (poor weight gain; use of tobacco, alcohol, or cocaine; less likely to regularly attend appointments)

When depression is treated with a selective serotonin reuptake inhibitor
- Spontaneous abortion
- Preterm delivery, low birth weight, small for gestational age
- Preeclampsia
- Congenital cardiac septal defects
- Persistent pulmonary hypertension of the newborn
- Neonatal adaptation syndrome
- Poor neurodevelopmental outcomes
- Respiratory distress syndrome in newborn
- Endocrine and metabolic disturbance in newborn

Source: References 2-10

Box

Because of the ethical problems of conducting prospective, randomized, controlled trials of selective serotonin reuptake inhibitors (SSRIs) in pregnant women, evidence often is inconsistent and methodologically flawed. Much of the current literature is based on retrospective reviews of administrative databases, teratology services, or birth registries. This methodology often does not incorporate confounding variables such as dose, timing of exposure, use of other medications, alcohol, tobacco, or illicit drugs, severity of depression, and other medical conditions in the mother. Many of these studies compared women receiving treatment with non-depressed controls, which makes it difficult to separate effects of SSRIs from those of depression. Studies may have small sample sizes, report relative risk over absolute risk, and vary in measured outcomes—making quantitative systematic reviews challenging.

Evidence on SSRI use in pregnancy is necessarily limited
Additional studies have been conducted, and the teratogenicity of paroxetine is debatable. A recent review reports 8 studies that suggest a malformation risk, compared with 15 studies that show no risk. The American Academy of Pediatrics considers SSRIs to be compatible with breast-feeding. The best-studied drugs include sertraline and paroxetine. Fluoxetine should be avoided when possible because a long elimination half-life can cause the drug to accumulate in the newborn, increasing the risk of irritability, hypertonia, sedation, and poor suckle.

There is no best SSRI for all pregnant women. Risks and benefits, including previous treatment success and failure, should be taken into account before starting or switching therapy. Whenever possible, consider monotherapy to avoid compounding the risk of harm.

References

Antidepressant use during pregnancy: How to avoid clinical and legal pitfalls

Authors Susan Hatters Friedman, MD, and Ryan C. W. Hall, MD, report that:

“Drug toxicity or withdrawal in a neonate … is a risk; however, this condition is self-limited and managed supportively by neonatology.”