

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



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Overall risks are low, and fears of lawsuits should not deter appropriate care

Recently there has been an increase in advertising soliciting participants for class-action lawsuits involving birth defects and antidepressants, particularly sertraline. Many psychiatrists are unsure why these ads are running in seemingly every medium because there has been no change in the FDA pregnancy classification for most selective serotonin reuptake inhibitors (SSRIs), except for paroxetine going from a C to a D rating in 2005.¹ Some studies have found SSRIs increase the risk of adverse birth outcomes and others have not, which makes it difficult for clinicians to know what to discuss with patients regarding the risks and benefits of using antidepressants during pregnancy, as well as the risks of untreated major depressive disorder (MDD).

It can be hard to encourage some patients to take necessary medications in the best of circumstances, let alone suggest that a pregnant woman take a medication that has been labeled “dangerous.” This article seeks to alleviate physicians’ fears about being caught in a no-win situation by:

- explaining factors that may have led to this increase in class-action lawsuits
- clarifying the risks of using certain medications and not treating depression
- suggesting ways physicians can protect themselves and their patients.

The FDA’s position

In July 2006, the FDA issued a public health advisory regarding SSRI use during pregnancy and the possibility of persistent pulmonary hypertension (PPHN).² This warning was based on a single study that found the risk of developing PPHN (base-

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FDA statements about antidepressant use during pregnancy

2006: In a warning about the risk of persistent pulmonary hypertension (PPHN) with antidepressant use during pregnancy, the FDA acknowledged “decisions about how to treat depression in pregnant women are increasingly complex.”² The FDA issued the warning based on a study by Chambers et al,³ noting that the study was “too small” to look at individual medications.

This warning also cited a study by Cohen et al⁴ that found “women who stopped their [antidepressant] medicine were five times more likely to have a relapse of depression during their pregnancy than were the women who continued to take their antidepressant medicine while pregnant.”² Although the warning identified a potential “rare” danger, the FDA guidance was that “women who are

pregnant or thinking about becoming pregnant should not stop any antidepressant without first consulting their physician. The decision to continue medication or not should be made only after there has been careful consideration of the potential benefits and risks of the medication for each individual pregnant patient.”

2011: In this communication,¹ the FDA stated “the initial Public Health Advisory in July 2006 on this potential risk was based on a single published study. Since then, there have been conflicting findings from new studies evaluating this potential risk, making it unclear whether use of [selective serotonin reuptake inhibitors (SSRIs)] during pregnancy can cause PPHN.” The FDA also said that the “potential risk with SSRI use during pregnancy remains unknown.”

line rate: 1 to 2 per 1,000 births) was 6 times greater for fetuses exposed to SSRIs in late pregnancy.³ Many legal websites highlight this 2006 warning as proof of SSRIs’ danger. However, because subsequent studies have had conflicting results, the FDA’s current position is that the risks of using SSRIs during pregnancy are “unknown” (*Box*).^{1,4}

Risks of depression

Although most physicians know the risks of untreated MDD, they tend to minimize or forget these risks when a woman becomes pregnant. Pregnant women with MDD face not only the expected risks of their psychiatric illness but additionally face risks of pre-eclampsia, suicide (20% of deaths in the postpartum period are due to suicide), and infanticide.⁵⁻¹⁰ Risks to the fetus include poor prenatal care, increased risk of intrauterine exposure to drugs or alcohol, increased exposure to maternal cortisol with resulting neurodevelopmental changes, preterm delivery, low birth weight, and failure to thrive.⁶⁻⁸ Later difficulties for the child of a mother with untreated depression may include poor stress adaptation, decreased cognitive performance, and behavioral difficulties because of poor mother-child bonding and other factors.⁶

For a *Table* highlighting key statistics regarding pregnancy and depression, see this article at CurrentPsychiatry.com.

Limitations of research

Because of ethical difficulties in studying MDD treatment during pregnancy, most data are retrospective and prone to detection and confounding biases, such as¹¹⁻¹⁵:

- the risks associated with depression
- comorbid conditions such as obesity
- maternal age
- poor prenatal care
- how the baby was delivered (eg, Caesarean sections have higher rates of PPHN)¹³
- illicit substance use
- effects of other medications (80% of pregnant women use medications, including non-steroidal anti-inflammatory drugs [NSAIDs], which are associated with PPHN).^{11,16}

No medication is 100% safe during pregnancy and all pregnancies have risks. In the United States, 2% to 3% of pregnancies produce infants with malformations,¹⁷ which makes it hard to determine if a defect is caused by a medication or occurred spontaneously. This is the baseline risk of all malformations; individual malformations are rare and it is difficult to conduct studies that have adequate power to demonstrate the risk for a specific malformation.

There are several potential adverse outcomes to consider when prescribing psychotropics to a pregnant woman, including miscarriage, malformation, preterm delivery, perinatal toxicity, and behavioral terato-

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Ethical difficulties in studying MDD treatment during pregnancy means most studies have been retrospective and prone to biases

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for key statistics on pregnancy and depression



Antidepressants during pregnancy

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SSRIs have been implicated in adverse birth outcomes but several studies found no increase in birth defects



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Table

Potential concerns when treating pregnant women with psychotropics

Miscarriage (spontaneous abortion)
Malformation (teratogenesis)
Preterm delivery
Perinatal syndrome (toxicity or withdrawal in neonate; usually self-limited and related to serotonin overstimulation or withdrawal; symptoms may include disrupted sleep, irritability, jitteriness, or abnormal breathing)
Behavioral teratogenesis (later behavioral problems in child, eg, lower IQ, developmental delays, or autism)
Lactation compatibility or plans to bottle-feed
Source: References 6,7

genesis (Table).^{6,7} SSRIs have been implicated in adverse outcomes, but there is no strong evidence that they increase the miscarriage rate, and several studies found no increase in birth defects.^{6,13,18-20} Regarding teratogenesis, the FDA switched paroxetine from class C to class D because of a potential 1.5% to 2% risk of fetal cardiac malformation, compared with a 1% baseline rate in the general population.²¹ Drug toxicity or withdrawal in a neonate also is a risk; however, this condition is self-limited and managed supportively by neonatology.²² Behavioral teratogenesis—neurobehavioral problems that develop later in a child's life—remains a hypothetical concern; research has been conflicting, and studies often used flawed methodology.

Evidence linking SSRIs to an increased risk of adverse birth outcomes often has been based on large, retrospective health system database cohort studies looking at SSRI exposure and associations with conditions such as PPHN, cardiac anomalies, attention-deficit/hyperactivity disorder, and autism.^{10,23,24} However, correlation is not the same as causation. It is difficult to prove or disprove the causative factor of adverse outcomes in these studies because:

- these databases were not designed to answer these types of exposure questions (eg, limitations in data collected, such as other potential causes not recorded)
- they have many confounding biases (undocumented illicit substance use, pos-

sible minimization of smoking history, publication basis for positive findings, etc.)

- individuals who provided the data did not follow a standardized method (eg, variability among individual clinicians).

Many of these limitations are evident in a 2009 study by Pedersen et al,²³ who reported the prevalence of septal heart defects was 0.5% (2,315/493,113) among unexposed children and 0.9% (12/1,370) among children exposed to 1 SSRI during early pregnancy (odds ratio [OR] = 1.99 [1.13 to 3.53]). Based on this study's data, the number needed to harm—the number of patients you would need to treat to encounter 1 adverse outcome—was 246, which suggests a relatively low risk. When data for the entire study is reviewed, the ORs for either minor birth defects (control: 7,373/493,113 vs SSRI exposed: 39/1,370; OR = 0.88 [0.54 to 1.41]) or major birth defects (control: 15,518/493,113 vs SSRI exposed: 55/1,370; OR 1.21 [0.91 to 1.62]) were not statistically significant (major and minor malformations were defined using European Surveillance of Congenital Anomalies coding).

Not to case aspersions on this group's work, it should be noted that this study had limitations, including that the researchers:

- did not take into account SSRI dosage
- did not measure depression severity or remittance
- were not able to fully account for potential exposures (eg, over-the-counter NSAIDs)
- were unable to confirm that patients took their medications because the variable measured was prescriptions filled
- did not interview participants about their medication use or symptoms.

In addition, researchers noted that mothers who filled their antidepressant prescription at least twice also were likely to have other factors that put them at higher risk for having a child with birth defects—such as older age or smoking. The biggest problem with the study was a lack of a control group, such as depressed women who did not receive medication (eg, the risk of depression itself could explain the rise, or those with more severe depression could be prescribed antidepressants).¹⁵



Antidepressants during pregnancy

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The U.S. Supreme Court has prohibited state lawsuits against manufacturers of generic agents

continued from page 12

In a more recent study,²⁴ 33 of 11,014 infants exposed to SSRIs after gestational week 20 developed PPHN (absolute risk: 3 per 1,000 births, compared with an incidence of 1.2 per 1,000 births in the general population), with an adjusted OR of 2.1 (95% CI 1.5 to 3.0). Although the authors warned that the results suggest a “class effect,” the rate of PPHN also was higher for mothers with a history of a psychiatric hospitalization within the last 10 years who were not taking medication (OR = 1.3, 95% CI 1.0 to 1.6) and the OR for escitalopram (1.5, CI 0.2 to 10.5) was not statistically significant. This study did include a control group, but the 10-year window may have been too wide to represent a group with similar comorbid risks. Similar to the previously discussed study, mothers prescribed SSRIs were older, 1.7 times more likely to be smokers, and twice as likely to be prescribed NSAIDs. The study did not analyze the risk factors of smoking and body mass index because of an initial subset analysis (which was not reported) finding that these known risk factors for PPHN “did not confound the results.”²⁴

The basis of class-action lawsuits

Interest in class-action lawsuits involving birth defects and antidepressants, particularly sertraline, appears to be increasing. Many websites advertising these lawsuits quote unnamed articles from reputable medical journals to support the claim that the medications are dangerous and cause a wide range of birth defects. Although some of the birth defects mentioned are specific, others (eg, “breathing problems” or “gastrointestinal side effects”) are so broad that any problem or complication could conceivably be attributed to the antidepressant. The degree of causation—if any at all—for many of these conditions has not been determined. A national advertising campaign looking for any problem may be occurring because the exact risks are “unknown.”¹

The 2009 U.S. Supreme Court ruling in *Wyeth v Levine*²⁵ allows individuals to sue manufacturers of branded medications in state and federal court for lack of proper labeling. However, the 2011 U.S. Supreme Court case of *PLIVA, Inc. v Mensing*²⁶ prohib-

its state lawsuits against manufacturers of generic medications over labeling because by federal (superseding) law, generic manufacturers must use the same warnings as the branded medication. This may in part explain why many medications targeted in commercials and websites for class-action lawsuits are branded products, even though generics are available.

The focus of these types of lawsuits has been on drug manufacturers, in part because of the success of past litigation. Past class- and single-action lawsuits involving birth defects against pharmaceutical companies, such as Richardson-Merrell Inc.—the manufacturer of thalidomide and Bendectin, the branded version of a combination of pyridoxine and doxylamine used to treat nausea and vomiting during pregnancy—were successful. Although limb defects with thalidomide were scientifically proven, Bendectin was never conclusively shown to cause birth defects even though it had been prescribed to 40% of pregnant women at one point. The legal theory behind the lawsuits is that the manufacturers should have done more research to determine the potential for birth defects.²⁷ In a case against SmithKline Beecham Corporation,²⁸ which makes Paxil, the branded version of the SSRI paroxetine, a jury found the manufacturer negligent for failing to warn about Paxil’s association with cardiac defects. The result was a \$2.5 million jury verdict. Since that case, the manufacturer has settled >800 additional suits for >\$1 billion. Because this risk of using paroxetine has been established, physicians should discuss this risk with their patients as part of an informed consent because they could be liable if they don’t.²¹ This legal concept is known as the “learned intermediary doctrine,” which states that once the risk is known, the intermediary (eg, the physician) is responsible to ensure that a product (eg, medication) is used appropriately. The 2011 FDA statement saying the risk for SSRIs during pregnancy is unknown¹ is important because it removes physicians as “learned intermediaries.”

Protect your patient and yourself

An estimated 13% of pregnant women take antidepressants; SSRIs are the most com-

monly used antidepressant during and after pregnancy.⁹ Although not every depressed pregnant woman requires medication, those with moderate to severe depression often do. Rational medication decisions, informed consent, and good documentation are important when treating these women. Discuss the risks of untreated illness as well as the risks of medications to ensure that the patient understands that avoiding medication does not guarantee a safe pregnancy. Suggest psychotherapy and electroconvulsive therapy as options when appropriate. When possible, include the patient's partner and family in the discussion to help improve compliance and potentially reduce strife.²⁹ The psychiatrist or patient should discuss the medication plan with the patient's obstetrician or family physician.

Whenever possible, consider using monotherapy, continuing a previously "successful" medication, and using the lowest effective dose.⁵ Clinicians may "underdose" medications because they believe this will lessen the risk from exposure, but this is risky because the fetus is still being exposed to the medication as well as the negative effects of undertreated MDD. If SSRIs are used throughout the pregnancy, the newborn may require additional observation to monitor for potential perinatal syndromes or PPHN.^{6,22}

Many women become pregnant while being treated for depression. Approximately one-half of all pregnancies are unplanned, so women using antidepressants may unknowingly expose their fetus to medication.³⁰ For this reason, it is important to discuss potential pregnancy and birth control concerns with all women of childbearing age before initiating pharmacotherapy.³¹ If an unintended pregnancy occurs, tell your patient to contact you before stopping any medications. Lawsuits also can occur because of

Related Resources

- Motherisk. www.motherisk.org.
- Organization of Teratology Information Specialists. www.otispregnancy.org.
- Massachusetts General Hospital Center for Women's Mental Health. www.womensmentalhealth.org.

Drug Brand Names

Escitalopram • Lexapro Sertraline • Zoloft
Paroxetine • Paxil

Disclosure

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wrongful death by suicide or infanticide because of lack of treatment; risk of untreated illness should not be treated lightly.

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Clinical Point

Ensure that pregnant patients understand the risks of untreated depression as well as the risks of medication

Bottom Line

The risks of untreated mental illness during pregnancy are as important as the risks of fetal exposure to antidepressants. Overall risks of antidepressant use during pregnancy are low and lawsuit concerns should not deter adequate care. Discuss the risks of untreated illness as well as the risks of medications to ensure that your patient understands that avoiding medication does not guarantee a safe pregnancy.

continued

This month's instant poll %

Mrs. F, age 29, is 20 weeks pregnant when she develops moderate depressive symptoms—lack of interest in pleasurable activities, inability to concentrate, and insomnia. Five years ago, she was successfully treated for a depressive episode with fluoxetine, 20 mg/d, for 1 year. **How would you care for her?**

- Refer her for cognitive-behavioral therapy
- Prescribe fluoxetine, 20 mg/d
- Prescribe fluoxetine, 10 mg/d
- Prescribe bupropion, 100 mg/d
- Wait 1 month and see if her symptoms resolve spontaneously

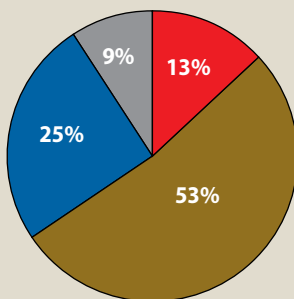
See **"Antidepressant use during pregnancy: How to avoid clinical and legal pitfalls"** page 10-16

Visit **CurrentPsychiatry.com** to answer the **Instant Poll** and see how your colleagues responded. Click on **"Have more to say?"** to comment.

DECEMBER POLL RESULTS

Mr. J, age 25, arrives in the emergency room (ER) disheveled, restless, and irritable. He refuses to provide a medical or psychiatric history and threatens ER staff because he believes they are trying to harm him. A review of his records shows a gradual functional decline starting 3 years ago and no significant medical history. A urine drug screen is negative. **How would you treat Mr. J?**

- 13%** Place Mr. J in a locked, open area for observation
- 53%** Offer oral haloperidol, 0.5 mg to 5 mg, and diphenhydramine, 25 mg to 50 mg, or risperidone, 0.5 mg to 2 mg, plus lorazepam, 0.25 mg to 2 mg
- 25%** Administer IM haloperidol, 0.5 mg to 5 mg, and lorazepam 0.25 mg to 2 mg
- 9%** Administer IM ziprasidone, 20 mg



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Statistics on pregnancy and depression

There are approximately 6 million pregnancies each year in the United States ^a
There are approximately 4 million live births each year in the United States ^a
Two percent to 3% of healthy pregnancies result in a birth defect or miscarriage ^{b-d}
Sixty percent to 70% of birth complications occur due to an unknown cause ^d
Rates of depression during pregnancy are 7% to 25% ^{b,e,f}
Approximately 13% of pregnant women take an antidepressant during pregnancy ^e
Fifteen percent of women with untreated depression in pregnancy attempt suicide ^b
Twenty percent of deaths in the postpartum period are due to suicide ^e
Women who discontinue antidepressants are 5 times more likely than women who continue medications in pregnancy to have a relapse of depression ^{g,h}
SSRIs are the antidepressant class most frequently prescribed to pregnant women ⁱ
Sertraline is one of the most frequently prescribed antidepressants perinatally and has low concentration in breast milk and infant serum ^{i,k}

SSRIs: selective serotonin reuptake inhibitors

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