

SSRI use during pregnancy

Do antidepressants' benefits outweigh the risks?

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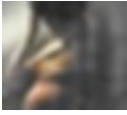
Untreated depression can have serious consequences, but many pregnant women resist taking antidepressants because they overestimate the risk of birth defects.¹ Their fears were reinforced in December 2005, when the FDA changed the pregnancy rating for paroxetine to class D, indicating evidence for risk to the fetus.

Women with recurrent depression show a very high risk of relapse if they discontinue antidepressants during pregnancy, and recent studies indicate that being depressed while pregnant may pose a greater risk than medication would. To help you weigh the FDA advisory's implications and counsel your patients, this article:

continued



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Box

Effects of depression during pregnancy

The hormonal and vascular changes associated with depression during pregnancy may create a poor environment for fetal development.

Maternal depression affects the hypothalamic-pituitary-adrenal axis, adrenocorticotropic hormones (ACTH), and endorphins.⁷ Maternal stress during the third trimester of pregnancy has been associated with increased levels of ACTH and cortisol. These in turn may increase the release of corticotrophin-releasing hormone (CRH) from the placenta.³ Because CRH controls the timing of labor and delivery, disrupting this system may increase the risk of preterm delivery. Endorphins are also affected, and these influence fetal learning, nervous system development, and labor pain.²⁷

Maternal anxiety during pregnancy is associated with increased uterine artery resistance. Animal studies show that increased maternal corticosteroids influence uterine blood flow and placental growth.²⁹ The resulting decrease in placental blood flow may be associated with poor fetal growth and development.

- compares evidence of the risk of untreated depression with that of taking selective serotonin reuptake inhibitors (SSRIs) while pregnant
- recommends how to individualize depression treatment during pregnancy and the postpartum, based on your patient's history and need for medication.

Case: 'Could paroxetine harm my baby?'

Ms. P, age 32, plans to conceive within 6 months and seeks advice about stopping antidepressant use. She has recurrent major depression and was hospitalized once in her mid 20s for suicidal ideation. She has stopped medication before but resumed treatment after relapse. She is euthymic on paroxetine, 40 mg/d, which she has taken for 5 years.

Ms. P has heard about recent FDA warnings about paroxetine, and her friends have warned her against taking medications during pregnancy. She is not depressed now but wonders what will happen without medication. She asks you, "If I get depressed during pregnancy and restart my medication, could that harm my baby?"

RISKS OF UNTREATED DEPRESSION

Major depression occurs in 10% to 25% of pregnant women.² Depression during pregnancy is the strongest predictor of postpartum depression,³ and 15% of women with untreated depression during pregnancy attempt suicide.⁴

A prospective naturalistic study⁵ examined depression relapse during pregnancy among women similar to Ms. P. The 201 women had had major depression before pregnancy and were euthymic at conception. Among the 86 with depressive relapse, the risk was:

- 68% (44 of 65) in those who discontinued medication
- 26% (21 of 82) in those who continued taking medication throughout pregnancy.

Relapse also occurred in 45% (9 of 20) whose medication increased and in 35% (12 of 34) whose medication decreased during pregnancy.

Physiologic (*Box*) and psychological factors—such as role transition to parenthood—may increase relapse risk during pregnancy and postpartum in women with a history of depression.

Case continued: 'It's back'

Because of Ms. P's concerns and the FDA warning, you taper her off paroxetine. She conceives 6 weeks later. Other than some mild nausea and fatigue, she does well at first. Ten weeks into the pregnancy, though, she begins to experience depressed mood, decreased appetite, early morning awakenings, and

difficulty enjoying pleasurable activities. Her fatigue worsens, and she becomes irritable and withdrawn. “I know my depression is back, but I still don’t want to take medication,” she says. Instead, she agrees to brief supportive therapy.

Pregnancy, labor, and delivery.

Maternal anxiety or stress during pregnancy appears to be associated with negative pregnancy outcomes (*Table 1*). Ms. P’s depression may increase risk for her baby, as preterm labor, lower Apgar scores, and significantly lower average birth weight for gestational age have been reported.⁶ Risk appears to increase with depression severity, as measured with the Beck Depression Inventory (BDI). Depression has been associated with a 2- to 3-fold increased risk of pre-eclampsia.⁴

Some studies suggest increased risk for spontaneous abortion in depressed women, although this is controversial. Other studies show delayed habituation of fetal heart rate to vibroacoustic stimulation and higher levels of cortisol, indeterminate sleep, and norepinephrine in neonates of women with depression during pregnancy.⁷

Long-term effects on children. Children whose mothers suffer depression during pregnancy may have long-term emotional problems.

One prospective study found an association between maternal depression during pregnancy and negative affect ratings and increased cortisol levels in 6-month-olds.⁸ Another found increased externalizing behaviors and behavior problems in 27-month-olds whose mothers reported stress during pregnancy.⁹ A follow-up study of prenatal

Table 1

Risks of untreated depression in pregnancy

Risk	Characterized by:
Relapse of maternal depression	Poor self care Substance use Suicide Postpartum depression
Pregnancy, labor, delivery changes	Pre-eclampsia Preterm labor Low infant birth weight (especially if mother experienced stress in first trimester) Maternal HPA axis changes
Long-term outcomes for child	Elevated cortisol levels Poor adaptation to stress Poor performance on cognitive and behavioral measures

HPA: hypothalamic-pituitary-adrenal axis

stress and children’s cortisol reaction on the first day of school further supported the influence of prenatal stress and anxiety on children’s poor adaptability to a stressful situation.⁹

As noted, women who are depressed during pregnancy are at high risk of postpartum depression,³ which has been associated with insecure attachment. Children of mothers with postpartum depression also perform worse on cognitive and behavioral measures than do children of nondepressed mothers.⁴

Case continued: ‘I’ll be a horrible mother’

Ms. P returns 3 weeks later, stating she “just can’t take it anymore.” She is working well with her therapist but struggles to get out of bed and worries she will be “a horrible mother.” She has thought life is not worth living and contemplated overdosing on acetaminophen. She has no intent to act on her suicidal thoughts, however, so you decide to treat her as an outpatient. She agrees to start sertraline, 50 mg/d, but asks how this choice might affect her baby.

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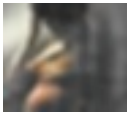


Table 2

FDA categories of risk during pregnancy

A	Well-controlled studies show no risk in humans.
B	No evidence of risk in humans. May be because of: a) no adequate, well-controlled studies in humans, but animal studies have found no adverse effects b) or animal studies have shown an adverse effect but well-controlled studies in humans have not.
C	Risk cannot be ruled out, lacking well-controlled human studies, and animal studies have not been conducted or have shown an adverse effect. Potential benefits may outweigh risk.
D	Well-controlled or observational studies in humans show risk, but potential benefits may outweigh risk.
X	Contraindicated in pregnancy because fetal risk clearly outweighs any possible benefit.

FIRST-TRIMESTER EXPOSURE

All SSRIs cross the placenta because of their low molecular weights. The mean ratio of umbilical cord serum to maternal serum concentrations is lowest for sertraline and paroxetine but detectable for all SSRIs.¹⁰ Fifteen studies totalling 2,600 women have not found an increased risk of major fetal malformations in mothers who used SSRIs at therapeutic dosages during the first trimester. Fluoxetine has been most widely studied, and fluvoxamine the least.²

Swedish birth registry data from 4,291 SSRI-exposed pregnancies show a 2.9% malformation rate, which is similar to the 3% expected among unexposed pregnancies. With paroxetine specifically, the malformation rate was 3.4% among 708 pregnancies, which was not a statistically significant difference.²

Paroxetine was reclassified by the FDA from pregnancy class C to class D (Table 2) primarily because of a study by GlaxoSmithKline of 3,581 expectant women taking 18 different antidepressants. The

retrospective epidemiologic study of insurance databases showed a greater risk of fetal malformations with paroxetine than with other antidepressants.

With paroxetine, the malformation risk was increased in any organ system (odds ratio [OR]; 1.75) but particularly in cardiac defects (OR; 1.79), with ventriculo-septal defect being most common.¹¹ Infants exposed to paroxetine in the first trimester had a 4% risk for major malformation and 2% risk for cardiac malformation. Each of these risk rates is 1% higher than expected in the general population.¹¹

Recommendations. We consider these data a “red flag” warning for

further study but not a reason to become alarmed about SSRIs as a class or paroxetine in particular. The FDA recommends counseling women of child-bearing age about increased risks associated with paroxetine during pregnancy and switching them to another antidepressant if possible. Other studies, however, have shown no increased risk of malformations with SSRIs, including paroxetine.^{12,14} (see “Paroxetine in pregnancy,” page 45). Further study is needed to define the risks of teratogenesis with paroxetine compared with other antidepressants.

THIRD-TRIMESTER EXPOSURE

In a recent meta-analysis, infants exposed to SSRIs in utero showed an increased risk for prematurity (OR; 2.03) and low birth weight (OR; 2.37).¹⁵ Other studies, however, showed no differences in these risks in SSRI-exposed infants or attributed the results to untreated maternal depression or smoking.¹⁶

A Medline search across the last 20 years¹⁷

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found 26 case reports, three prospective controlled cohort studies, and other records of >400 women who received fluoxetine, sertraline, or paroxetine in the third trimester. The authors found the evidence “ambiguous” as to the cause of adverse events and concluded that the risk of not treating major depression with adequate SSRI therapy at that stage of pregnancy “most likely” outweighs the risk of harm to infants.

Transient neonatal complications.

Thirty percent of neonates exposed to SSRIs in the third trimester experience transient adaptation problems, which peak 48 hours after birth¹⁸ (Table 3). Symptoms may include initial lack of crying, increased muscle tonus, flush, irritability, jitteriness, hypothermia, abnormal breathing, and disrupted sleep and motor activity.^{2,19,20}

Transient neonatal symptoms from SSRI exposure are thought to be a serotonin withdrawal syndrome or serotonin overstimulation.²¹ The syndrome is usually mild, self-limited, and requires only supportive treatments. All antidepressants’ labels warn of these effects.

Pulmonary hypertension. An increased risk of persistent pulmonary hypertension of the newborn (PPHN) has been shown in infants exposed to SSRIs after 20 weeks’ gestation. A retrospective case-control study concluded that the absolute risk of PPHN with SSRIs is relatively low (6 to 12 cases per 1,000 pregnancies).²²

Recommendation. Some authors have recommended tapering antidepressants in the third trimester, but the risk of postpartum depression appears to outweigh any potential benefit from discontinuation. Because birth timing is unpredictable, some women whose antidepressants are tapered off could be without medication for a long time.

Table 3

**Neonatal SSRI withdrawal:
Symptoms, causes, and treatment**

Symptoms	Initial lack of crying Increased muscle tonus Irritability, jitteriness Abnormal breathing pattern Disrupted sleep and motor activity
Hypotheses of cause	Serotonin overstimulation or withdrawal
Treatment	Close observation Supportive measures

Thus, we recommend:

- continuing SSRIs during late pregnancy
- monitoring the newborn for 48 hours for transient neonatal adaptation symptoms or PPHN.^{2,17,18}

LONG-TERM EFFECTS OF SSRI EXPOSURE

Do SSRIs during pregnancy have long-term effects on infants’ neurodevelopment? Study results are mixed. For example:

- A prospective, controlled, cohort trial found no adverse effects on IQ, language, or behavioral development in children ages 15 months to 6 years whose mothers took tricyclic antidepressants (N = 46) or fluoxetine (N = 40) during pregnancy, compared with 36 unexposed controls.²³

- Another prospective study showed lower Bayley Psychomotor Developmental Index scores in 31 SSRI-exposed infants compared with 13 infants born to depressed mothers not on antidepressants. Reduced body control, coordination, and fine motor skills might suggest possible subtle effects of SSRIs on motor development in exposed infants, the authors concluded.²⁴

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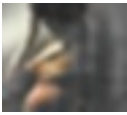


Table 4

Recommendations for managing paroxetine risk during pregnancy

Patient status

Recommendation

Taking paroxetine and planning pregnancy

Advise of possible 1% increase in risk of fetal malformation
Switch to another SSRI unless paroxetine has been the only successful therapy for depression
If stopping paroxetine, slowly taper to avoid withdrawal symptoms

Taking paroxetine and is pregnant

Advise of possible 1% increase in risk of fetal malformation
Continue paroxetine; a slow taper probably could not be completed before the first-trimester period associated with increased risk of fetal cardiac defects
If any paroxetine exposure in first trimester, order ultrasound to monitor for fetal malformations

Case continued: A healthy delivery

Ms. P's depression improves a few weeks after she restarts an SSRI. She delivers a healthy term baby with Apgar score of 7. The baby initially does not cry, awakens easily, and shows mild irritability. His mother's SSRI use, her severe depression during part of the pregnancy, or some other factor may have caused his mild neonatal complications.

Nursing staff carefully observe the infant for 2 days in the newborn nursery, and his irritability fades away. Ms. P decides to continue taking antidepressants to care for herself and the baby.

WEIGHING TREATMENT OPTIONS

For each woman with a history of depression who is pregnant or intends to conceive, we recommend a risk-benefit analysis of her depression severity and need for an antidepressant:

Mild depression (BDI <20 and no history of recurrent depressive episodes, hospitalization, suicidality, weight loss, or inability to function). Consider treating depression without medication. Interpersonal psychotherapy and morning

light therapy have improved antepartum depression in small trials.^{25,26}

Moderate to severe depression (history of recurrent depressive episodes, hospitalization, or suicidality). Strongly consider medication. If your patient is taking an SSRI, counsel her about:

- the 70% risk of depression relapse if she stops the medication, even for the first trimester
- risks of untreated depression during pregnancy (poor self-care, preterm labor, birth complications, and increased risk for poor stress adaptations in children).

If she refuses antidepressant treatment, monitor her for suicidal tendencies, deteriorating social function, psychosis, and inability to comply with prenatal care during the pregnancy and postpartum.

Choosing an SSRI. No one SSRI is the safest choice for all women, especially when data on breastfeeding come into play.

- Fluoxetine has been studied more than other SSRIs during pregnancy; most evidence is

reassuring, except for transient neonatal complications. With its long half-life, fluoxetine is not recommended during breastfeeding because it may accumulate in infant sera.

- Sertraline has shown low umbilical cord to maternal serum ratios in small samples and has reassuring breast-feeding data.

- Citalopram, compared with sertraline, has been studied more in pregnancy but has a higher fetal-to-maternal serum ratio (as does escitalopram). These SSRIs are usually second-line for starting a new antidepressant during pregnancy but could be first-line if they have worked well for a patient or she has had adverse effects with fluoxetine or sertraline.

You may need to increase SSRI dosages as pregnancy progresses. Increased metabolism and weight gain during pregnancy can lower SSRI serum levels, allowing depressive symptoms to re-emerge in the third trimester. Counsel the patient to continue taking the antidepressant for at least 12 months postpartum, then re-evaluate the need for medication based on her history.

Paroxetine precautions. If your patient is taking paroxetine and wishes to become pregnant, consider switching to another SSRI (using a slow cross-taper) unless paroxetine has been the only effective medication (*Table 4*). When discussing risks of any SSRI, explain that the baseline risk for congenital malformations is 3%. Paroxetine might increase this risk by 1% and other SSRIs by less.

If a woman becomes pregnant while taking paroxetine, often the time when cardiac defects occur is passed or will be before you slowly taper the medication to avoid withdrawal. If the patient's depression has been severe, the risk of shifting her to an untested SSRI is probably higher than the possible 1% increased risk of fetal malformation. If she has taken paroxetine during the first-trimester, refer for ultrasound to monitor for cardiac anomalies.

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KNOW THE FACTS



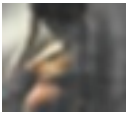
**13% of patients
had diabetes in the
landmark CATIE
schizophrenia study
at baseline—4 times
more common than in
the general population.¹**

Be aware.
Screen and monitor
your patients.
Make a difference.



Reference: 1. Goff DC, Sullivan LM, McEvoy JP, et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. *Schizophr Res.* 2005;80:45-53.

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Related resources

- ▶ California Teratogen Information Service (CTIS). Pediatric department, University of California San Diego Medical Center. www.otispregnancy.org/ctis.html
- ▶ Psychiatric disorders during pregnancy and postpartum. MGH Center for Women's Mental Health, Massachusetts General Hospital. www.womensmentalhealth.com
- ▶ MOTHERISK Web site. Teratogen information and updates on reproductive risk research. The Hospital for Sick Children, University of Toronto. www.motherisk.org

DRUG BRAND NAMES

Citalopram • Celexa
Escitalopram • Lexapro
Fluoxetine • Prozac

Paroxetine • Paxil
Sertraline • Zoloft

DISCLOSURES

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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Inadequately treated depression during pregnancy can harm mother and child, whereas SSRIs are relatively safe to use. Evaluate history, severity of depression, and need for medication. For patients planning pregnancy, consider switching from paroxetine to another SSRI. For those who conceive on paroxetine, the risk of switching may outweigh the 1% increased risk of birth defects.

BottomLine