

INDIVIDUALIZING TREATMENT IS KEY

A talk about, then a plan for, antidepressants in pregnancy

📌 Start? Stop? Sustain? Switch? How should you advise a patient about a serotonin reuptake inhibitor during pregnancy—for her health and the well being of the fetus?

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IN THIS ARTICLE

How depression can harm a pregnancy
page 27

SRIs and neonatal abnormalities
page 28

Breastfeeding concerns
page 30

CASE Depressive disorder, anticipating a pregnancy

Your patient Megan—well-educated, 29 years old, G0P0—has come to you to discuss her antidepressant (paroxetine [Paxil]) because she is planning her first pregnancy.

Megan has a history of recurrent major depressive disorder (MDD), which is in remission (see “What is MDD?,” page 27).

How will you begin the conversation with this patient about keeping MDD in remission during her pregnancy and ensuring the safety of her fetus?

There is a 20% to 25% lifetime prevalence of depression in women; the disorder peaks during childbearing

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years, however.¹ As of 2003, 13% of pregnant women had taken an antidepressant at some time during their pregnancy, a percentage that has doubled since it was assessed in 1999.²

You are faced with several quandaries in deciding whether to recommend that your patient continue, or discontinue, antidepressant therapy during pregnancy:

- As many as 68% of women who terminate antidepressant treatment before or during pregnancy relapse.
- Even 26% of women who continue antidepressant during pregnancy relapse—requiring a dosage adjustment or change in treatment.³
- Yet the elevated cortisol levels of severe, untreated depression may harm the placenta and fetus.^{4,5}

So, what do you need to know to assess the risks and benefits of “Megan” stopping, or continuing, paroxetine during her anticipated pregnancy? And what are the risks to Megan’s fetus of treating, or not treating, her depression with a serotonin reuptake inhibitor (SRI*)?

CONTINUED ON PAGE 27

*Terminology has changed: “Selective” has been dropped from “SSRI” to yield simply “SRI.”

Gauging the risks of depression in pregnancy

In any given patient, her history and family history of depression are key to determining the likelihood that she will suffer ongoing or recurrent depression.

CASE continued Repeated treated episodes plus a family history

In obtaining Megan's history, you learn that she has had three prior episodes of depression, all of which were successfully treated with paroxetine. Megan has been stable on paroxetine for 3 years.

Notably, the second episode of depression was initially treated with a 16-week trial of psychotherapy alone; when depressive symptoms did not remit, paroxetine was added. That episode was considered severe because it included pervasive thoughts of suicide.

You also learn that Megan's mother suffered from postpartum depression and that her father and paternal grandmother were treated for depression.

Known risk factors for depression during pregnancy include: maternal anxiety; prior diagnosis of depression during pregnancy; history of postpartum anxiety or depression; prior diagnosis of either anxiety or depressive disorder; significant life stress (e.g., divorce, death of a loved one); degree of social support—particularly, intimate social support; “intended-ness” of pregnancy; domestic violence; and insurance status.⁶

You review with Megan her risk factors for depression during pregnancy, namely: three prior episodes of MDD and a strong family history of mood disorder. Her MDD is considered “severe” because she has a history of suicidality. You tell Megan that, given these factors, she is at high risk of a recurrence of her depressive illness during pregnancy.

Megan asks: “Would getting depressed during pregnancy hurt the baby?”

Depression during pregnancy affects both infant and maternal well-being, although studies are in conflict about the extent of that

morbidity. Multiple areas of potential risk to mother and infant have been studied, including the effect of depression on:

- maternal well-being
- growth of the infant
- spontaneous abortion
- preterm delivery
- neonatal physiologic and neurobehavioral measures
- long-term considerations for the developing infant and child.

Within these categories of risk, a diagnosis of depression during pregnancy has been associated (in some but not all studies) with a higher risk, or rate, of:

- postpartum depression
- preterm birth
- lower maternal weight gain
- maternal tobacco, alcohol, and other substance use
- lower infant gestational age at birth
- small-for-gestational age infant birth.⁷⁻¹⁰

In terms of long-term impact on offspring, studies differ in their estimation of risk; however, children exposed to untreated, maternal depression at 18 weeks' and 32 weeks' gestation did show a greater degree of developmental delay at 18 months than children who were born to a mother who was not depressed during pregnancy.¹¹

You discuss these risks with Megan. She asks: “What treatment do you recommend for me?” You turn to the 2009 guidelines published jointly by the American Psychiatric Association (APA) and ACOG.

CONTINUED ON PAGE 28

What is MDD?

- Major depressive disorder (MDD) is defined by criteria in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)
- The disorder varies in severity, 1) across an affected person's lifetime and 2) within a depressive episode
- A current or prior episode of depression that includes 1) a significant impact on an individual's functioning, 2) active suicidality, or 3) hospitalization signals severe MDD
- In women, average age at first episode of depression is 24 years



These guidelines recommend that you consider **1)** the severity of her current depression, **2)** her history of depression severity, and **3)** her preference for treatment.¹² For mild depression during pregnancy, when there is no history of severe depression, or for a history of depression that responded well to psychotherapy in the past, a trial of psychotherapy without medications is recommended.

But Megan's history of depression falls into the "severe" category, and a prior episode of depression did not respond well to psychotherapy. Your recommendation to her, therefore, is that she should continue taking an antidepressant—unless she feels strongly that she should discontinue it.

Risks of SRIs in pregnancy

Megan considers what you've discussed about her high risk of developing recurrent depression during pregnancy. She decides that she wants to continue taking her antidepressant during pregnancy, but she has concerns—based on what she has been reading on the Internet.

Megan hands you a detailed printout downloaded from a Web site unfamiliar to you and asks about risks to the baby of such medications as paroxetine.

What should you tell Megan about SRIs in pregnancy—paroxetine, specifically?

You preface your remarks to her by noting that the data physicians work with are imperfect—because randomized, controlled clinical trials pose an ethical dilemma as a method of study in pregnant women. You then discuss with her current scientific understanding of potential risks to her fetus.

The difference in the rates of structural malformation among SRI-exposed and SRI-unexposed groups has been studied; most studies have found no increased rate of major or specific cardiac malformations.¹² However, first-trimester paroxetine appeared, in some studies, to be associated with an increased rate of cardiac malformations. That led to a category-"D" pregnancy classification in 2005 and an FDA "Public Health Advisory."

Other large cohort studies have not uncovered such an association. It has been hypothesized that the methodology of data collection may have influenced this finding.¹³

Other malformations have been implicated in some studies but not others, and have included associations between specific SRIs and cardiac ventricular outflow defects, craniosynostosis, and omphalocele. The absolute risk of these defects remains extremely low, however, and close to the background rate seen in the general population.¹⁴

Megan asks: "With that risk-category 'D' for paroxetine, do you recommend I continue taking it or should I switch to another medication while I'm pregnant?"

You review again with Megan that, although some studies have linked first-trimester paroxetine to an increased risk of cardiac malformation, that finding has not been replicated in several large cohort studies. You explain that, if she had a history of recurrent depression that had failed to respond to many antidepressants and only paroxetine worked, an attempt at switching the SRI would not be recommended because of the potential for relapse.

Megan tells you that she would feel safer not taking a category-"D" drug. You agree and propose a judicious approach: Because she has come to see you before she became pregnant, with enough time to complete a slow crossover to an alternative SRI, and because she has not had any earlier trials of other SRIs, a slow taper of paroxetine, coupled with a crossover to an alternative SRI, is a reasonable option—with the caution that substitution always carries a risk of relapse.

Problems in newborns

Megan considers the risks you've discussed so far. She remembers a recent article in a magazine for pregnant women that described severe "respiratory" and "withdrawal" symptoms in infants who were born to mothers taking an SRI antidepressant. She wonders if she should consider discontinuing her SRI in the third trimester to try to mitigate those risks.

CONTINUED ON PAGE 30

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Megan is asking you about an SRI exposure risk that has been fairly consistent across studies, called **neonatal abstinence syndrome (NAS)** or poor neonatal adaptation.

NAS is a cluster of symptoms that occurs in 15% to 30% of newborns who have been exposed to an SRI during the third trimester of pregnancy.¹⁵ Signs include irritability, weak cry, tachypnea, temperature instability, and hypoglycemia—all of which are transient, peak during the first 48 hours after delivery, and resolve in less than 2 weeks.

Multiple hypotheses have been put forward to account for NAS, including the possibilities that it reflects a withdrawal syndrome, pharmacotoxicity, or an underlying gene-SRI interaction. The physiology behind NAS remains unknown, however.¹²

Megan next asks you about persistent pulmonary hypertension of the newborn (PPHN). You explain that PPHN is of recent concern in women who have been taking an SRI in the latter half of their pregnancy.

The rate of PPHN in the general population is 0.5 to 2 newborns for every 1,000. Associated mortality is approximately 10% to 20%.¹⁶⁻¹⁸ This rate is thought to rise to approximately 6 of every 1,000 newborns among those who have been exposed to an SRI in utero—with some evidence of increased risk conferred through SRI exposure during later pregnancy (studies define this as the second half of the pregnancy).¹⁵ Although the relative risk of PPHN is increased threefold to sixfold when an SRI is used in pregnancy, **absolute risk remains extremely low.**

Concerns have been raised over research methodology in the few studies that have looked into SRI exposure and PPHN. Not all such studies found a change in relative risk or absolute risk of PPHN in SRI-exposed infants, compared to what was found in non-SRI-exposed infants.^{15,19,20}

Megan presses you, however, with the understandable question of whether she should taper her SRI during the last trimester (which the Web site she has found recommends).

With the above information in mind, you explain that, given current understanding of the low absolute risk of PPHN, and given her illness history and severity of prior depression, you would not recommend that she taper the antidepressant in the third trimester.

Furthermore, the same counsel applies in regard to NAS: Given the risk of psychiatric morbidity caused by discontinuing an SRI during the third trimester, you do not recommend that she taper an SRI during that period to avoid NAS.

You explain that, instead, physicians now counsel women who take an SRI about the signs of NAS so that they can be prepared if they observe any of them in their infant.

Megan has one more question: “Will I be able to breastfeed while I’m taking an antidepressant?”

Postpartum issues to consider

Given the inherent difficulties and risks of relapse associated with a crossover to an alternative antidepressant postpartum, it makes sense, when possible, for a woman to take an antidepressant during pregnancy that can safely be continued while she is breastfeeding.

You tell Megan that, even though the quality of the data in this area is also thin, SRIs that have a low maternal serum profile are considered safest in breastfeeding.

To date, two SRIs—sertraline and paroxetine—have not been detectable in the breast milk of women taking either of them.²¹

CASE Appointment concluded, overflowing with information, advice, and optimism

Megan says that, taking into account all that you and she have talked about, and even though she wants to return with her husband, she would like to switch to sertraline before she becomes pregnant—while she gauges its effectiveness at keeping her disorder in remission.

A good outcome requires you to prevail over obstacles

Because a diagnosis of depression spans a

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Treatment algorithms for depression meant to simplify our decisions must always be individualized and extended into the postpartum period

continuum of severity and, often, is not perceived as an acutely life-threatening illness, **evaluating the risks and benefits of treatment is a murky undertaking.**

Our role as physicians is to, first, educate ourselves and our patients about these variables and, second, support our patients in the decisions that they make. Physicians who care for pregnant women must be aware of the **benefits and limitations of treatments** as reported in the most current literature if they are going to assist women with decisions about treatment in the best possible way.

Social stigma. There remains the impact of stigma. Depressive and anxiety disorders are often perceived to be either under the control of an affected person's "free will" or not as serious as other forms of "medical" disease. Consequently, the role that cultural and social pressures play in the risk-benefit analysis conducted by pregnant women and their physicians can't be discounted.

Customized decision-making. As more data emerge about the treatment of depression in pregnancy, it has become clear: Treatment algorithms meant to simplify our decisions must always be **individualized and extended into the postpartum period.**

Treatment selection. Management of **mild depression during pregnancy does not always require medication.** Multiple variables—the list is long, and includes a patient's psychiatric history, family psychiatric history, response to prior treatment, severity of depression, severity of prior depression, degree of social support, and personal desires—must be considered in determining what treatment is appropriate before, during, and after a pregnancy.

For a woman who suffers mild or moderate depression, with few antenatal depression risk factors, a trial of psychotherapy is recommended as first-line treatment. For a woman suffering from severe depression, or one who has a history of severe depression that has not responded well to psychotherapy alone, continuation or initiation of an SRI antidepressant is the current recommendation. 🚫

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