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***FAST** TRACK*

Add persistent pulmonary hypertension of the newborn to the reported risks of SSRIs during pregnancy

Q Is it reasonable to continue SSRIs during pregnancy?

A Yes. However, there is a small risk of persistent pulmonary hypertension of the newborn (PPHN) when the drugs are taken in late pregnancy. On the other hand, if the drugs are discontinued, there is a serious likelihood depression will recur, which poses other fetal and maternal risks.

About 10% to 20% of infants with PPHN do not survive, even with treatment. In the general population, PPHN typically occurs in 1 or 2 infants per 1,000 live births, but in women taking selective serotonin reuptake inhibitors (SSRIs), it occurs in 6 to 12 infants per 1,000 births.

EXPERT COMMENTARY

These 2 studies add a lot to what we have learned[1,2] about the risks and benefits of treating depression during pregnancy. *The New England Journal of Medicine* investigation was a sophisticated case-control study that identified an increased risk of PPHN associated with the use of SSRIs after 20 weeks' gestation. The study in *The Journal of the American Medical Association* was a prospective naturalistic investigation in which longitudinal psychiatric assessments were conducted in pregnant women who elected to maintain or discontinue antidepressant therapy near the time of conception. No randomization occurred because of ethical concerns.

In the case-control study, no increased risk of PPHN was found for maternal SSRI use before 20 weeks' gestation or for non-serotonergic antidepressants at any point during pregnancy. However, the relative risk of PPHN with late-pregnancy SSRI exposure, compared with early or no exposure, was 6.1 (95% confidence interval, 2.2–16.8).

In the *JAMA* study, significantly more women who stopped taking antidepressants had recurrence of major depression than did women who continued taking antidepressants: relapse occurred in 44 of 65 women (68%) after discontinuing the drugs, versus 21 of 82 women (26%) who continued treatment. Most recurrences emerged rapidly: 50% in the first trimester and 90% by the end of the second trimester.

Interestingly, women older than 32 had a 60% reduction in the rate of relapse, compared with women younger than 32. A history of depressive illness (>5 years) and/or multiple recurrences (>4 episodes) significantly increased the risk of relapse.

Women are most vulnerable to depression during childbearing years

Major depressive disorder affects about 12% of women per year, with greatest prevalence during the childbearing years.[3] Maintenance antidepressant therapy is recommended for women with recurrent major depressive disorder (3 or more lifetime episodes) because another episode is essentially certain without prophylaxis.

For many years, pregnancy was thought to be protective against psychiatric illness, but new data have refuted this theory.

Link between SSRIs and pulmonary hypertension not necessarily causal

In the general population, PPHN typically

CONTINUED

occurs in 1 or 2 infants per 1,000 live births and involves substantial morbidity and even mortality.

One possible mechanism for a causal relationship between PPHN and maternal SSRI use is that the lungs serve as a "reservoir" for antidepressant agents, and accumulation of SSRIs in the lungs has been reported. According to Chambers and colleagues, "Serotonin not only has vasoconstrictive properties that increase pulmonary vascular resistance, but also has mitogenic and comitogenic effects on pulmonary smooth-muscle cells. Thus, higher circulating levels of serotonin in the fetus and accumulation of serotonin in the fetal lung might result in the proliferation of smooth-muscle cells that is characteristic of PPHN."

The study by Chambers and colleagues was a case-control investigation, however, which although useful for evaluating associations between exposures and adverse outcomes (especially for rare diseases such as PPHN), cannot establish causality.

What to tell patients

A clearer way to discuss the finding about PPHN is to focus on the absolute risk, which was 6 to 12 cases of PPHN per 1,000 births (0.6%–1.2%). In other words, 99% of women treated with an SSRI delivered infants without pulmonary hypertension.

What about nonserotonergic antidepressants?

Although no association was found between nonserotonergic antidepressants and PPHN, these drugs have their own set of risks and benefits. Bupropion or nonserotonergic tricyclic antidepressants (such as nortriptyline) are reasonable choices to treat depression during pregnancy. Unlike other types of antidepressants, therapeutic serum levels have been established for tricyclic antidepressants. Serum level monitoring during pregnancy can be a useful, if burdensome, component of follow-up.[3]

However, the potential for fetal cardiac toxicity (particularly with overdose) poses a risk not shared by SSRIs. Similar to SSRIs,[2] tricyclic use is associated with neonatal signs (irritability, restlessness, tremor) when taken near term.[1] Venlafaxine is a serotonin-norepinephrine reuptake inhibitor that has not been associated with major congenital malformations[4]; however, neonatal signs also occur with this serotonergic agent.

We have fewer data on reproductive outcomes with bupropion and venlafaxine use than with SSRIs or tricyclic antidepressants, but this lack of data does not necessarily mean there is a lack of adverse outcomes.

Weighing the risks

Add PPHN to the list of other reported risks of SSRIs during pregnancy, such as minor physical anomalies (no functional or cosmetic significance), preterm birth, decreased birth weight, neurobehavioral effects, and neonatal syndrome.[2,5] These risks have not included major malformations or long-term developmental deficits in childhood.[1,5]

Untreated depression itself poses risks: preterm birth, growth restriction, preeclampsia, neonatal neurobehavioral effects, and impaired maternal function.[6]

After weighing these risks with her physician, a woman could reasonably decide that the benefits of drug treatment outweigh the risks, or she could decide the opposite. Certainly evidence-based nondrug therapies such as psychotherapy (cognitive behavioral or interpersonal psychotherapy), electroconvulsive therapy, and bright light therapy should be considered.[7] However, not all women elect, respond to, or have access to such treatments.

Bottom line: No absolutes

Although our ability to quantitatively weight treatment choices improves with the publication of studies such as these, the path to the most favorable outcome remains a highly individualized decision

***FAST** TRACK*

Tell patients 99% of gravidas treated with an SSRI delivered infants without pulmonary hypertension

with no absolutes. Continuing use of antidepressants does not guarantee that remission will be sustained. Careful monitoring and dose adjustment are necessary in order to maintain adequate serum levels in women who take tricyclics,[8] particularly during the third trimester. Higher dose requirements also have been described for SSRIs because of increased drug metabolism during pregnancy.[9]

If the gravida decides to continue antidepressant therapy, she should choose the drug (an SSRI, tricyclic, or bupropion) that is most effective for her. ■

Katherine L. Wisner, MD, MS, Professor of Psychiatry, Obstetrics and Gynecology and Reproductive Sciences, Epidemiology, and Women's Studies, Women's Behavioral HealthCare Program, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pittsburgh

Barbara H. Hanusa, PhD, Assistant Professor of Psychiatry and Research Director, Women's Behavioral HealthCare Program, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pittsburgh

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