Antidepressant Use, Nonuse Both Involve Risks for Fetus

BY KATE JOHNSON
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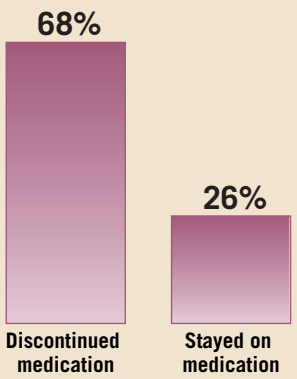
TORONTO — Physicians weighing the risks versus benefits of medicating nonobstetric conditions during pregnancy should consider that their dilemma is not one of fetal exposure versus nonexposure, according to Dr. Zachary N. Stowe, a psychiatrist and director of the Women's Mental Health Program at Emory University, Atlanta.

"You expose the fetus to something, be it illness or the treatment," he said at the annual meeting of the Society for Gynecologic Investigation. And amid the growing evidence of risks associated with prenatal exposure to antidepressants is the danger of losing sight of alternative risks, Dr. Stowe said.

"Of concern to me is that often, the treatment of mental illness is viewed as more 'optional' than, for example, [the treatment of] epilepsy, hypertension, or infection—despite the fact that there are considerably more data demonstrating that maternal depression and anxiety may have more severe sequelae, particularly with respect to child development," Dr. Stowe said in an interview.

Depression Relapse Rates In Pregnant Women



Note: Based on a study of 201 women.
Source: JAMA

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The impact—both short and long term—of prenatal exposure to untreated mental illness should not be underestimated, he warned. Studies show that low birth weight (LBW), small for gestational age (SGA), and preterm delivery are linked with untreated major depression and anxiety disorders. Untreated schizophrenia is also linked with LBW and SGA, as well as stillbirth and increased infant mortality.

And untreated eating disorders are associated with LBW and preterm delivery. In the long term, prenatal exposure to untreated major depression has been linked to motor delays, reactivity, attention problems, and EEG alterations in offspring. And untreated anxiety disorders are associated with conduct disorder and increased anxiety in offspring, said Dr. Stowe, who acknowledges receiving research grants and serving on the speakers' bureaus of "most pharmaceutical companies" that make antidepressants.

Even with medication, depression relapse rates are higher in pregnancy than among nonpregnant women. In a recent prospective study of 201 women with major depression, Dr. Stowe and his colleagues showed a 26% relapse rate among those who maintained their medication until delivery. Women who discontinued their medication had a relapse rate of 68% (JAMA 2006;295:499-507).

Dr. Stowe emphasized that his group's recent review of the literature shows that in almost 17,000 cases of prenatal antidepressant exposure, the highest malformation rate associated with a particular antidepressant is 3.5%. That was the rate found for paroxetine (Paxil).

He stressed that while caution is always imperative when prescribing medication during pregnancy, the Food and Drug Administration's drug categorization system is of little help to prescribers and is more useful for those seeking liability protection.

"I agree with Dr. M. Schou, who wrote in the Journal of Affective Disorders that 'when manufacturers and official agencies warn against drug treatment during pregnancy, their warnings serve to protect themselves and are of little use to clinically responsible physicians,' " he said (J. Affect. Disord. 2001;67:21-32).

While stressing the importance of treating mental illness in pregnancy, Dr. Stowe said it is important that physicians do not underplay fetal exposure to the medication. "The fetus doesn't get exposed to the mother's dose," he noted. "It gets exposed to the mother's serum concentrations." However, his extensive work documenting placental passage of antidepressants and measuring amniotic fluid concentrations of these medications shows that the fetus is exposed to "not a trivial amount. I have heard MDs tell patients that 'the baby really does not get much medication' when they are discussing other medications—which is obviously not true with antidepressants, and mostly unknown for other medications," he said.

His recently published study measured amniotic fluid concentrations of antidepressants at approximately 10% of maternal serum concentrations (Am. J. Psychiatry 2006;163:145-7), and some of his unpublished work suggests that umbilical cord concentrations of antidepressants at delivery are typically more than 50% of maternal concentrations.

Dr. Stowe said physicians who choose to prescribe antidepressants in pregnancy should also keep the pharmacokinetics and pharmacodynamics of pregnancy in mind and be aware that maternal serum concentrations decrease over the course of pregnancy. "It is important to consider increasing the dose, if necessary, to maintain an adequate maternal response." In an accompanying presentation, Dr. Ruth E. Tuomala of Harvard Medical School, Boston, echoed Dr. Stowe's message, but in the context of a very different condition: HIV. The benefits of perinatal prophylactic measures can be lost if antiretroviral therapy is inadequate, she warned. ■

DRUGS, PREGNANCY, AND LACTATION

Weighing New Evidence on SSRI Use

Until fairly recently, studies and reviews of global teratovigilance data have been relatively reassuring that SSRIs were particularly safe, especially with regard to their teratogenicity. In fact, there are more reproductive safety data available for SSRIs than for many medicines women take during pregnancy. However, new reports have raised concerns regarding the teratogenicity of paroxetine, which we have previously discussed (INTERNAL MEDICINE NEWS, Nov. 15, 2005, p. 24), as well as risk for putative neonatal distress syndromes and, most recently, possible increased rates of persistent pulmonary hypertension of the newborn (PPHN) following late-pregnancy exposure to SSRIs.

BY LEE S. COHEN, M.D.

What do the new reports describe and how do the findings inform clinical care? One study supports previous reports of a "neonatal abstinence syndrome" with characteristic symptoms of jitteriness, sleep disturbance, dysregulation, tachypnea, and myoclonus in infants whose mothers used antidepressants during pregnancy. In this prospective cohort study of 120 infants, examiners used a systematic scale to assess full-term SSRI-exposed newborns with respect to presence or absence of a wide range of previously reported symptoms.

Of the 60 infants exposed in utero to various SSRIs for a mean of 35.5 weeks, 8 had severe symptoms and 10 had mild symptoms, compared with none of the 60 infants who had not been exposed in utero to these drugs (Arch. Pediatr. Adolesc. Med. 2006;160:173-6). A particularly noteworthy finding is that no infant with symptoms required treatment intervention; symptoms were transient and of little if any clinical significance.

In the second study, investigators using a case-control design described an elevated risk for PPHN, a far more serious syndrome associated with severe respiratory failure, in newborns with in utero exposure to SSRIs late in pregnancy. In this study, which enrolled almost 400 women whose infants had PPHN, matching them to more than 800 control mothers and infants, the use of SSRIs at any point during pregnancy was not associated with PPHN, but there was a significant association between PPHN and in utero exposure to an SSRI after 20 weeks' gestation (N. Engl. J. Med. 2006;354:579-87).

The study describes a very disturbing and striking finding. But an accompanying editorial points out that the number of cases reported is small (N. Engl. J. Med. 2006;354:636-8). And though not mentioned in the editorial, the vulnerability to reporting bias in such a study is great. One wonders whether women without an adverse outcome may be reluctant to disclose use of an antidepressant during pregnancy, compared with those with an adverse outcome as serious as PPHN. Because the conclusions are based on a small number of PPHN cases, a difference of a small number of cases in either direction can strengthen or attenuate a positive finding.

The authors of the second study suggest that the incidence of PPHN associated with SSRI exposure in late pregnancy approaches 1%. But because hundreds of women have used SSRIs during late pregnancy, it is unlikely that such a dramatic clinical finding would not have been reported prior to this study—the first of such reports. These studies understandably alarmed women who are taking antidepressants. In fact, they were published just weeks after we reported the results of a prospective study of 201 women with a history of major depression who were prospectively followed during pregnancy. Women who discontinued their antidepressant medication proximate to conception were at a fivefold greater risk for depressive relapse during pregnancy, compared with those who continued with an antidepressant (JAMA 2006;295:499-507).

These data certainly suggest that pregnancy is not protective with respect to depression and that many women who stop antidepressants will relapse during pregnancy.

Although some women will still stop antidepressant therapy during pregnancy, patients should be informed that depression during pregnancy can increase the risk for other neonatal complications and can substantially increase their risk for postpartum depression. Other women will choose to continue antidepressant use during pregnancy, regardless of the findings of some of these more recent studies, given what some patients will view as a modest risk for the neonatal outcomes described.

Regardless of individual choices, which will be extremely variable, it is crucial to present all available information to reproductive-age women on antidepressants who plan to conceive or who are pregnant, so that collaborative decisions can be made based on these data and personal wishes. No decision is perfect or risk free. Interestingly, women provided with the same information may make very different decisions.

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