Pregnancy as ‘Stress Test’ Could Predict Future CV Health Risks

BY KATE JOHNSON
Montreal Bureau

TORONTO — Physicians weighing the risks versus benefits of medicating non-obstetric 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, he said.

“Of concern to me is that often, the treatment of mental illness is viewed as more ‘optimal’ 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.

The impact of 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.

Moreover, 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 alternations 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 relaparization rate associated with a particular anti- depressant 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 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” of 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 concentration decreases 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 echoed Dr. Stowe’s message, but in the context of a very different condition: HIV. Compared with depression, the consequences of fetal and neonatal exposure to HIV are perhaps more widely appreciated within both medical and lay circles. However, the benefits of perinatal prophylactic measures can be lost if antiretroviral therapy (ART) is inadequate, she warned.

Where physicians often try to minimize certain medications during pregnancy, they should be thinking about maximizing ART in pregnant HIV-positive patients with the goal of reducing the risk of perinatal transmission, said Dr. Tuomala of Harvard Medical School, Boston.

The indications for ART in nonpregnant patients are a CD4+ count of 350 or less and a detectable viral load, however, these requirements are relaxed in pregnancy. “Thus antiretrovirals are given to many pregnant women with HIV who would not otherwise receive them,” she said. Aggressive treatment with potent combination therapies has been shown to reduce the perinatal transmission rate to 1%, compared with a 21% transmission rate when no ART is used (J. Acquir. Immune Defic. Syndr. 2002;29:484-94), she said.

But to maximize its effectiveness, this aggressive therapy must be maintained throughout the pregnancy and the delivery. “The goal should be to minimize the maternal viral load at delivery and maximize fetal viral load,” she said. “This is the cause, not the consequence, of these medications—and so there is no need to stop these drugs, she said. In fact, if any medication needs to be stopped because of hyperemesis, she recommends all medications be eliminated to avoid the risk of development resistance.

The only exception is the antiretroviral fosamprenavir (Sustiva, Bristol-Myers Squibb), which is the only HIV medication now classified as category D because it has been linked to an increase in neural tube defects, she said. This drug should ideally be stopped before conception. “Acknowledge that HIV-infected women are choosing to get pregnant; give them preconception counseling, and get them off this drug before they conceive,” she advised. In addition, there is some suggestion of an association between nucleoside reverse transcriptase inhibitors (NRTIs) and neonatal mitochondrial toxicity syndrome.

Maternal toxicities associated with ART can include gastrointestinal problems, anemia, and/or hepatic steatohepatitis of acute onset (NRTIs); hyperglycemia (protease inhibitors); and hepatitis (nevirapine and others).

Depression Relapse Rates
In Pregnant Women

<table>
<thead>
<tr>
<th>Depression Relapse Rates</th>
<th>26%</th>
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<tbody>
<tr>
<td>Continued medication</td>
<td></td>
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<tr>
<td>Stopped on medication</td>
<td>68%</td>
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Discontinued medication: Note: Based on a study of 201 women.
Source: JAMA

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