Weigh Fetal Exposure Risks Against Undertreating

The impact of prenatal exposure to untreated mental illness should not be underestimated.

BY KATE JOHNSON
Montreal Bureau

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, he 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.

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.

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.

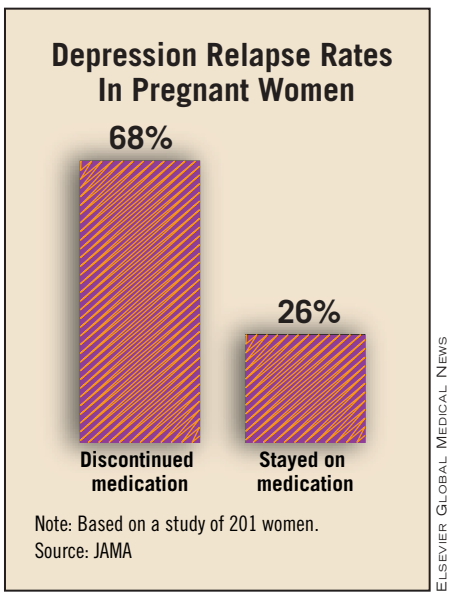
Even with medication, depression relapse rates are higher in pregnancy than among nonpregnant women. In a recent prospective study of 201 women with major depression, Dr. Stowe and his colleagues showed a 26% relapse rate among those who maintained their medication until delivery. Women who discontinued 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 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."



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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 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 medication exposures 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 [if they were not pregnant]," 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 intracellular antiretroviral levels, as well as to provide postexposure prophylaxis to infants," she said.

On the safety of ART, pregnancy outcome studies do not suggest an increase in spontaneous abortion, stillbirth, LBW, or low Apgar scores in association with 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 together to avoid the risk of developing resistance.

The only exception to this is efavirenz (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 steatosis/lactic acidosis (NRTIs); hyperglycemia (protease inhibitors); and hepatitis (nevirapine and others). ■

Pregnancy as 'Stress Test' Could Predict Future CV Health Risks

BY KATE JOHNSON
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TORONTO — Pregnancy could be viewed as a type of cardiovascular "stress test" that could uncover previously silent risk factors for future cardiovascular problems, according to Carl H. Hubel, Ph.D.

"Studying women during pregnancy may facilitate the identification of cardiovascular risk and offer an opportunity for early intervention to decrease their likelihood of developing problems later in life," said Dr. Hubel of Magee Women's Research Institute in Pittsburgh.

Speaking at the annual meeting of the Society for Gynecologic Investigation, Dr. Hubel outlined his own work and that of other researchers that both show that preeclampsia and other complications relating to placental insufficiency such as low birth weight and preterm delivery are associated with an increased risk of cardiovascular events up to 30 years later.

"Metabolic factors predisposing to endothelial dysfunction such as insulin resistance, dyslipidemia, and inflammation may also predispose to preeclampsia and may later manifest as cardiovascular disease," he said, suggesting that endothelial repair is a potential target on the horizon. "Surveillance of cardiovascular risk factors during pregnancy per se may help to identify additional subsets of women who would benefit from early and aggressive risk factor modification post partum."

In a study of 30 women with a previous eclamptic pregnancy, Dr. Hubel and his colleagues found that 33% were taking blood pressure medications 30 years after the index pregnancy, compared with only 7% of controls (BJOG 2000;107:776-84). More recently, the same group of women also showed increased levels of C-reactive protein (CRP), an inflammatory marker of cardiovascular disease risk—and a higher prevalence of dyslipidemia, and insulin resistance compared with controls.

"We cannot rule out that preeclampsia is the cause, not the consequence, of these risk factors," he said in an interview. "Preeclampsia has a prevalence rate of 3%-5% of pregnancies—so one would have to follow large numbers of women from preconception, through their pregnancies, and into later life just to capture enough women who develop preeclampsia to determine the answer."

But regardless of this, he suggests women who have had preeclampsia, preterm birth, or a low-birth-weight baby should be monitored more closely for risk factors that might contribute to future cardiovascular risk.

"Perhaps this is a group of women that shouldn't wait until after age 45 to have their CRP and lipids measured," Dr. Hubel said. ■