Weigh Fetal Exposure Risks Against Undertreatment

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, 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.

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 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).

In his group's recent review of the literature, 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.

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," 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.

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.

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," said Dr. Tuomala of Harvard Medical School, Boston..

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. ■

DRUGS, PREGNANCY, AND LACTATION

Prenatal Vitamins and Reducing Pediatric Cancer Risk

There is some evidence that the use of vitamins in general and folic acid in particular may inhibit the development of some types of cancer in adults, although the data are not from randomized trials and are debated. There are also several studies suggesting folic acid may protect against certain pediatric cancers, and a recently reported metaanalysis conducted by Motherisk found that prenatal vitamin use during pregnancy was associated with a reduced risk of some pediatric cancers.


BY GIDEON KOREN, M.D.

Several years ago, we reported the results of a study in Ontario that found an association between folic acid fortification of flour and a 50% decrease in the prevalence of pediatric neuroblastoma, an apparent protective effect. We conducted this study after the Pediatric Oncology Group in Ontario asked us if we could identify an environmental explanation for the fewer cases of neuroblastoma in children in Ontario, a trend they first noticed in the late 1990s.

The only factor we could identify was that in 1997 and 1998, folic acid fortification of flour became compulsory in Canada, as in the United States. We were able to show that indeed, year by year, with the introduction of folic acid fortification of flour, there was a parallel decrease in the number of neuroblastomas diagnosed in young children in Ontario (Clin. Pharmacol. Ther. 2003;74:288-94).

Intrigued by these results, we looked into whether other investigators had arrived at similar observations about multivitamin supplementation and pediatric cancers. We conducted a metaanalysis of all eight case-control studies published between 1994 and 2005 of prenatal multivitamin supplementation and pediatric cancer rates, comparing the rates of cancer in their children with matched controls whose mothers did not use supplements. The studies were conducted between 1976 and 2002; all were either conducted in the United States, or included U.S. sites. These results were presented by Ingrid Goh, a graduate student in Motherisk, at the American Society of Clinical Pharmacology and Therapeutics meeting in March 2006.

We found that for several prominent pediatric cancers—brain tumors, early-age leukemias (in the first year of life), and neuroblastomas, tumors that are believed to start in utero—the rates were substantially lower among the children of women who took prenatal vitamins containing folic acid during pregnancy. The risk of leukemia was reduced by 36%, the risk of pediatric brain tumors reduced by 35%, and the risk of neuroblastoma by 57%; all statistically significant reductions.

The metaanalysis has limitations, including the retrospective design of the studies, and likely variations in the composition of multivitamins; it is possible that another characteristic of women who are motivated enough to take multivitamins could contribute to the lower cancer rates. Therefore, at present, these studies show a trend and an association, but are not necessarily proof of causation.

Still, as far as we know, this is the first systematic review that has investigated such a protective effect for the use of multivitamins by pregnant women, and provides the first evidence suggesting that prenatal vitamins may have a protective effect in reducing the risk of pediatric cancer and that it may be possible to reduce the risk of certain childhood cancers in utero. This is important because for the most part, not much is known about how to prevent pediatric cancers.

These findings may also contribute to the understanding of the etiology of cancer. Folic acid, for example, is involved in many intracellular processes, and it has been hypothesized that folate deficiencies and cancers in children may be related to partially altered DNA methylation and impaired DNA synthesis and repair.

Presently, we can't separate what constituents in the multivitamin are responsible for the protective effect; this will be much more difficult to sort out. Despite the limitations of the studies in the metaanalysis, they represent another level of evidence for physicians and women that highlight the importance of prenatal supplementation with a multivitamin containing folic acid.

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