SSRI Use Tied to Slight Risk Of Neonatal Hypertension

BY MELINDA TANZOLA
Contributing Writer

Use of selective serotonin reuptake inhibitors during pregnancy is associated with neonatal abstinence syndrome and a slightly increased risk of persistent pulmonary hypertension of the newborn, according to results of two recently published studies.

In a case-control study, infants of women who took SSRIs in the second half of pregnancy were five to six times more likely to develop persistent pulmonary hypertension of the newborn (PPHN), with an incidence of 1 case for every 100 exposed infants (N. Engl. J. Med. 2006;354:579-87).

In an accompanying editorial, Dr. James L. Mills wrote that "the association is very unlikely to be due to chance. ...The current study was well designed and carefully executed." (N. Engl. J. Med. 2006;354:636-8).

But in an interview, Dr. Gideon Koren of the Motherisk Program in Toronto, who was not involved in the studies, cautioned against placing too much significance on the finding. " These are very small numbers and although this is a large study, [PPHN] is a very rare condition," he said.

PPHN, which affects 1-2 infants per 1,000 live births, causes significant morbidity and mortality. In the case-control study, Dr. Christina D. Chambers of the University of California, San Diego, and her associates investigated the association between SSRI use and PPHN in 377 women whose infants had PPHN and 836 matched controls. Within 6 months after delivery, participants were interviewed by nurses unaware of the study hypothesis.

In women taking SSRIs after the 20th week of gestation, 14 cases of PPHN were noted, compared with 6 cases in control infants. PPHN was three times more likely with antidepressant use after the 20th week of pregnancy, five times more likely if it was an SSRI, and six times more likely after adjustment for confounding variables.

No risk elevation was observed with SSRI use earlier in pregnancy or when non-SSRI antidepressants were used.

The investigators noted that 3% of infants with PPHN died. Dr. Koren said that he spoke with the study investigators, who told him that none of the infants who died were exposed to SSRIs in utero, a fact that is not noted in the published study.

Dr. Koren cautioned that "it would be sad if because of this study, women discontinue SSRIs in late pregnancy, as [depression] can be life threatening for some and a cause of high rates of morbidity."

An unrelated cohort study found that 30% of 60 infants exposed to SSRIs in uteri experienced some degree of neonatal abstinence syndrome; none of 60 control infants showed any symptoms of the syndrome. Among the exposed infants, 10 exhibited mild symptoms and 8 had severe symptoms of neonatal abstinence, according to Dr. Rachel Levinson-Castiel of the Schneider Children's Medical Center of Israel in Petah Tiqwa, and associates (Arch. Pediatr. Adolesc. Med. 2006;160:173-6).

The most common symptoms, measured using the Finnegan score, included tremors (in 37 SSRI-exposed infants vs. 11 control infants), gastrointestinal disturbances (34 vs. 2), sleep disturbance (21 vs. 2), high-pitched cry (18 vs. 0), and hypertonicity or myoclonus (14 vs. 1). Most symptoms peaked within the first 48 hours after delivery, although maximal scores were observed through day 4.

Although the small study size precluded an evaluation of dose effects for most SSRIs, the investigators found a significant association between paroxetine dose and the degree of neonatal abstinence syndrome symptoms. Infants exposed to doses less than 20 mg showed no syndrome signs.

Although the syndrome is indeed a result of withdrawal in most, Dr. Koren added that in some, the symptoms are instead due to a high level of drug in the neonate. "This is important because if it is a lack of drug [causing the symptoms], you may want to give the baby an SSRI whereas if it is poisoning, you cannot give the drug." ■

Herpes Hepatitis Diagnosis Is Crucial During Pregnancy

HONOLULU — The diagnosis of herpes simplex hepatitis during pregnancy is one that simply cannot afford to be missed, Dr. Eileen Hay cautioned at the annual meeting of the American College of Gastroenterology.

That's because treatment with acyclovir or vidarabine is lifesaving—and without it, one-half of affected mothers will die of fulminant hepatitis, stressed Dr. Hay, professor of medicine at the Mayo Medical School, Rochester, Minn.

Herpes hepatitis is a rare disorder. In pregnancy, it occurs in the third trimester. It is usually but not always preceded by a flulike viral prodrome. The typical mucocutaneous herpetic lesions aren't always present.

The characteristic features of this infection are the third-trimester presentation, marked elevation of transaminases (with levels often in the thousands) along with coagulopathy and encephalopathy, but no jaundice.

Liver biopsy shows hepatocytes with the classic viral inclusion bodies of herpes simplex virus.

It's necessary to consider delivery only in the very rare instance in which the patient shows no response to treatment with antiviral therapy, Dr. Hay said.

—Bruce Jancin

DRUGS, PREGNANCY, AND LACTATION

FDA Advisory on Paroxetine

Multiple studies over the past decade have been supportive of the reproductive safety of the selective serotonin reuptake inhibitors (SSRIs) when used during the first trimester; these studies include one recent metaanalysis and other extensive reviews. Particularly reassuring have been the prospective data on fluoxetine (Prozac) and citalopram (Celexa). As a result, clinicians have been relatively reassured about the absence of teratogenic risk associated with the SSRIs.

BY LEE COHEN, M.D.

New concerns were recently raised about the reproductive safety of paroxetine by a presentation at the Teratology Society annual meeting that reported an increased risk of omphalocele associated with first-trimester exposure. This report was based on preliminary, unpublished data from the National Birth Defects Center, which I reviewed in a recent column (INTERNAL MEDICINE NEWS, Nov. 15, 2005, page 24). A weaker association was also found between omphalocele and other SSRIs.

A Food and Drug Administration public health advisory about paroxetine followed in December, describing preliminary results of two other unpublished studies indicating that paroxetine exposure in the first trimester may increase the risk of congenital malformations, particularly cardiac malformations. At the FDA's request, paroxetine manufacturer GlaxoSmithKline has changed the pregnancy category label for paroxetine from C to D.

It is surprising that the FDA's recommendation and advisory are based on preliminary analyses from several recent, unpublished, non–peer-reviewed epidemiologic studies, as these are data that should be considered, at least at this point, inconclusive.

Using data from the Swedish National Registry, one study found a 2% rate of cardiac defects among infants exposed during the first trimester to paroxetine vs. 1% among all registry infants. But a previous study using registry data that was based on a slightly smaller number of children exposed to paroxetine did not report this association (J. Clin. Psychopharmacol. 2005;25:59-73).

Another study, using data from a U.S. insurance claims database, found the rate of cardiovascular malformations was 1.5% among infants exposed to paroxetine during the first trimester vs. 1% among infants exposed to other antidepressants. The majority were atrial or ventricular septal defects, which are common congenital malformations.

The modest increases in relative risk of a common anomaly, when derived from a claims database with inherent methodologic limitations, make interpretation of these data problematic. Unfortunately, the language in the FDA advisory, suggesting that "the benefits of continuing paroxetine may outweigh the potential risk to the fetus," may get lost in the information patients receive.

Although there are not as many published studies on the teratogenic risk of paroxetine as for other SSRIs, it is noteworthy that prospective studies have not identified a higher rate of congenital or cardiac malformations associated with prenatal exposure to paroxetine.

How does one counsel women of reproductive age who have major depression? And what is the best option for patients being treated with paroxetine who want to get pregnant or who have an unplanned pregnancy? Until the issue is clarified with more rigorously obtained and conclusive data, it is reasonable to avoid paroxetine in women who are actively trying to get pregnant or plan to in the future.

For those with major depression who are antidepressant-naive, it may be most prudent to prescribe an SSRI or an SNRI for which there are no unfavorable data to date, such as fluoxetine or citalopram/escitalopram, or an older tricyclic antidepressant such as nortriptyline.

What makes sense for those who have failed to respond to one of those medications previously, as in the all-too-common scenario of nonresponse to multiple SSRIs and response only to paroxetine? In this situation, the use of paroxetine in women who are planning to conceive or who are already pregnant should not be considered absolutely contraindicated.

If the medication is discontinued before or during pregnancy, it should be done gradually, as is consistent with standard clinical practice.

Until the data are peer-reviewed and published, decisions about use of this medicine in women who are planning a pregnancy or are pregnant will have to be made on a case-by-case basis. But we need to keep in mind that nothing is more critical than sustaining euthymia during pregnancy. Untreated depression in pregnancy is associated with compromised fetal well-being as well as increased risk for postpartum depression.

The FDA advisory is available online at www.fda.gov/cder/drug/advisory/paroxetine200512.htm.

DR. COHEN *directs the Perinatal and Reproductive Psychiatry Program at Massachusetts General Hospital, Boston, which offers information about pregnancy and women's mental health at www.womensmentalhealth.org. He is a consultant to manufacturers of several antidepressant drugs, including paroxetine and other SSRIs.*