Migraine Drugs Not Tied to Birth Defects

BY MICHELE G. SULLIVAN

PHILADELPHIA — Sumatriptan and naratriptan do not appear to significantly raise the risk of major congenital malformations in fetuses that are exposed to the drugs in utero, according to the latest analysis of an international pregnancy registry.

Established in 1996, the GlaxoSmithKline registry has accumulated data on 849 pregnancies exposed to the drugs. Birth defects occurred in 4.5% of infants exposed in the first trimester or during all of their gestation, which was not significantly higher than that previously identified for women with migraines.

'While its use in pregnancy cannot be encouraged,' there is evidence that 'sumatriptan is not associated with a substantial increase in the risk of major congenital malformations.'

Major congenital malformations are known to occur in the offspring of women with migraines at a slightly higher rate than in the general population (3.4% vs. 2%-3%, respectively), Marianne C. Cunnington, Ph.D, of GlaxoSmithKline in Harlow, England, reported in a poster at the International Headache Congress.

The registry relies on a voluntary reporting strategy that encourages health care providers to submit information on exposed pregnancies as early as possible. Retrospective case reporting also is accepted. Pregnancy outcome is ascertained by medical records that the provider forwards after birth, or by medical records confirming other outcomes, including fetal demise or abortion.

At the outset, the registry collects data on the timing, dosage, duration, indication, and administration of the drugs; maternal demographics; expected date of delivery; and any prenatal testing. At follow-up, there is a review of the pregnancy outcome, drug exposure during pregnancy, and the women's headache history during pregnancy.

So far, the registry has amassed information on 761 pregnancies exposed to sumatriptan and 88 exposed to naratriptan. Outcomes are known for 570 of the sumatriptan-exposed pregnancies and 57 of the naratriptan-exposed pregnancies. Twenty-one sumatriptan-exposed pregnancies and 31 naratriptan-exposed pregnancies are pending delivery. The rest have been lost to follow-up, Dr. Cunnington noted in the poster at the congress, which was sponsored by the International Headache Society and the American Headache Society.

Among the sumatriptan-exposed pregnancies, there were 23 birth defects, 4 fetal deaths, 32 spontaneous fetal losses, and 11 induced abortions.

The malformations that occurred in infants who were exposed to sumatriptan in the first trimester included abnormal head circumference, single palmar crease and systolic murmur; moderate craniosynostosis; cerebral abnormality with developmental delay; partial cleft lip; ventricular septal defects; biliary atresia; diaphragmatic hernia; pyloric stenosis; anterior displacement of anus; hip dysplasia; polydactyly; malformation of left hand; and Down syndrome.

No data were available for the three birth defects that occurred in infants who were exposed to sumatriptan after the first trimester.

Among fetuses exposed to naratriptan, there were five spontaneous losses, one induced abortion, and one live infant with a 2.5-mm ventricular septal defect that was expected to close spontaneously.

Dr. Cunnington noted that five additional independent studies, including a Swedish study of more than 2,000 sumatriptan recipients, have failed to find an increase in birth defects associated with in utero exposure. "While its use in pregnancy cannot be encouraged," she and her colleague Sara A. Ephross, Ph.D., wrote, "there is consistent evidence that sumatriptan is not associated with a substantial increase in the risk of major congenital malformations following exposure."

To report pregnancies exposed to sumatriptan, naratriptan, or the sumatriptan/naproxen combination, North American physicians can call 800-336-2176, and international physicians can call 910-256-0549.

The report was published online in Headache (doi: 10.1111/j.1526-4610.2009.01529.x). ■

DRUGS, PREGNANCY, AND LACTATION

Perinatal Depression: APA and ACOG Weigh In

BY LEE COHEN, M.D.

Questions about the management of depression during pregnancy continue to elicit discussion in clinical and academic venues. In the last decade, there have been numerous studies and reports evaluating the impact of antidepressant use and maternal depression during pregnancy on fetal and neonatal well-being and on long-term neurobehavioral outcomes.

It is noteworthy that we have more data regarding the effects of prenatal exposure to psychiatric medications than perhaps to any other types of medication women use during pregnancy.

A recent addition to the literature is a joint report from the American Psychiatric Association (APA) and the American College of Obstetricians and Gynecologists (ACOG) on the management of depression during pregnancy. The working group, convened by the APA and ACOG and including a developmental pediatrician, provided a critical review of the available English language literature on fetal and neonatal outcomes associated with exposure to mood disorder and antidepressant treatment during childbearing (Gen. Hosp. Psychiatry 2009;31:403-13; Obstet. Gynecol. 2009;114:703-13).

The working group's copious review suggests that the impact of maternal mood disorder on reproductive outcomes is extremely variable. For example, data on the effects of depression on outcomes such as fetal growth, preterm delivery, and various neonatal effects are highly inconsistent, with some studies suggesting depression during pregnancy is associated with low birth weight or small-for-gestational-age infants and an almost equal number suggesting no such effects.

Similarly, the substantial literature that has emerged over the last decade regarding the impact of antidepressants on birth outcomes has produced variable findings. One would hope that more data would provide the clinician with a more precise quantification of the risks associated with fetal exposure to antidepressants. But the findings in much of the literature have been variable with respect to outcomes, such as the impact of fetal exposure to selective serotonin reuptake inhibitors (SSRIs) on birth weight; some studies have suggested that birth weight is lower with exposure, but others do not show this.

The authors of the joint report highlight the greatest methodological flaw in virtually all of the literature evaluating fetal exposure to antidepressants: the potential confounding factor of maternal mood disorder. We have yet to see a study that compares outcomes among babies born to euthymic women on antidepressants, compared with outcomes among babies born to women who do not have a mood disorder and are not taking these medications during pregnancy.

A concern among both patients and clinicians is the impact of SSRIs on the risk for congenital malformations. The APA/ACOG report, consistent with other reports, states that the cumulative data from prospective studies and administrative databases suggest that the absolute risk of major congenital malformations associated with fetal exposure to SSRIs is inconsistent, and that if there is a risk, it is exceedingly small (OB.GYN. NEWS, June 2009, p. 14).

The most consistent finding across the literature over the last decade regarding fetal exposure to SSRIs is the finding of transient neonatal adaptation symptoms that include irritability, tachypnea, and hypoglycemia among newborns of 15%-30% of women who use SSRIs in the latter part of pregnancy. Few would disagree that this is a syndrome that has been frequently documented in association with SSRI exposure, but the authors of the APA/ACOG report underscore that the syndrome is transient and does not appear to have particular clinical relevance, at least acutely.

Lastly, concerns regarding an increased risk of persistent pulmonary hypertension of the newborn (PPHN) have also been called into question, because of multiple studies with varying results, including one recent study not cited by the working group in which no increase in risk was noted and two earlier studies cited by the working group where a heightened risk for PPHN was described compared with a baseline rate of 0.5-2/1,000 (OB.GYN. NEWS, March 2009, p. 22).

The working group provides the clinician with several schemata regarding the actual management of perinatal depression, with suggestions that vary based on whether a patient is pregnant already and whether she is being treated with an antidepressant. They suggest that women with milder cases of depression be treated with psychotherapy, with more serious consideration given to continuing pharmacologic treatment of perinatal depression in those with recurrent disease. They recommend that these approaches be considered in the context of a carefully tailored discussion that includes the risks and benefits of deferring treatment versus using the antidepressants.

Reading this report by seasoned investigators in both psychiatry and obstetrics and gynecology, one is left with the following conclusions: When it comes to managing perinatal depression, there are no perfect answers and no decision is risk free. Even with this exhaustive review, we don't have studies that direct the clinician in an absolute fashion to a particular treatment. Still, the clinician should be reassured by the numerous studies that have been conducted with antidepressants compared with other medicines that women take during pregnancy.

With these data, clinicians can make thoughtful risk-benefit decisions as they collaborate with their patients, matching patient wishes and clinical histories with a given treatment decision that feels appropriate for that particular patient.

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