DRUGS, PREGNANCY, AND LACTATION

Anticonvulsant Use in Pregnancy

It is estimated that approximately 500,000 women in the United States who have a diagnosed seizure disorder are of reproductive age. Anticonvulsant medications used to prevent seizures, such as phenytoin, were among the first medications identified as human teratogens more than 30 years ago. Since that time, it has been generally accepted that women with a seizure disorder have an increased risk of having a child with developmental disabilities, and that this risk is higher among women who are treated with polytherapy as opposed to monotherapy. It is also generally accepted that this risk is not due entirely to the mother's underlying seizure disorder, but rather is associated with the medication exposure itself.

BY CHRISTINA CHAMBERS, PH.D., M.P.H.

However, there are several important questions that have not yet been definitively answered: What are the comparative risks of specific anticonvulsants, does lowering the dose decrease the risk, does periconceptional folic acid supplementation modify anticonvulsant-attributable risk, does the same risk apply to anticonvulsant medications when used to treat psychiatric disorders, and what are the long-term consequences such as cognitive deficits in children with prenatal exposure?

In recent years, some of these questions have been addressed by several ongoing population-based or registry-type studies being conducted in multiple countries throughout the world. Although sample sizes for specific medications tend to remain relatively small, and careful long-term follow-up for neurodevelopmental deficits is rare, new information is emerging. Most studies have confirmed a relative excess of congenital malformations with first-trimester exposure to valproate mono- or polytherapy, compared with other anticonvulsants or no anticonvulsant exposure. As expected with human teratogens, the malformations associated with valproate exposure represent a specific pattern including neural tube defects, facial clefts, and hypospadias. Similarly, as expected for human teratogens, in many studies the risk appears to be dose related, and not all exposed fetuses are affected.

Most recently, investigators from a multicenter study based at Emory University and in the United Kingdom have completed 3-year follow-up on the neurodevelopmental effects of anticonvulsant drugs, and report a significant dose-related effect of valproate across several domains of cognitive development. Other commonly used medications, such as carbamazepine, phenobarbital, lamotrigine, and phenytoin are currently being evaluated in the same study.

Recently, an expert panel assembled by the American Academy of Neurology conducted an evidence-based review of the safety of anticonvulsant medications in pregnant women with epilepsy. The panel's summary, published last May (Epilepsia 2009;50:1237-46), concluded that there is a high probability of comparative teratogenicity of first-trimester valproate exposure relative to carbamazepine, and possibly compared with phenytoin or lamotrigine.

The panel also concluded that intrauterine exposure to anticonvulsant polytherapy or to valproate monotherapy probably results in poor cognitive outcomes, but panel members were less confident regarding the current weight of evidence for phenytoin or phenobarbital. The risk for impaired cognitive development may be related to the use of anticonvulsants throughout pregnancy or at least into the third trimester.

As ongoing anticonvulsant studies continue to accrue sample size, the panel's recommendations at present are as follows:

- Clinicians should consider avoiding first-trimester treatment of patients with valproate and/or with polytherapy in order to decrease the risk for major congenital anomalies.
- Clinicians should avoid if possible valproate and/or polytherapy treatment throughout pregnancy in order to reduce the risk for cognitive deficits. Avoidance of phenytoin and phenobarbital throughout pregnancy might also be considered.

The panel concluded that periconceptional folic acid supplementation (at a range of doses) was possibly effective in reducing the risk of major congenital malformations in women with epilepsy, but recommended that clinicians consider supplementation at or above the 0.4 mg/day currently recommended for all women of reproductive age (Epilepsia 2009; 50:1247-55).

As with many other chronic maternal conditions, these recommendations must be evaluated in the context of appropriate treatment for the mother with a seizure disorder, in consideration of any treatment changes before pregnancy occurs, and in consideration of the safety of alternative medications.

To date, there are insufficient data on the absolute risks for most specific anticonvulsants in pregnancy, and especially for the newest medications. Well-conducted long-term neurodevelopmental studies with sufficient sample size are also lacking for most anticonvulsants. While specific mechanisms of teratogenesis have been suggested, susceptibility factors that might help identify individual pregnancies at higher or lower risk have not been clarified. International efforts to address many of these questions are underway.

DR. CHAMBERS *is associate professor of pediatrics and family and preventive medicine at the University of California, San Diego. She is director of the California Teratogen Information Service and Clinical Research Program. Dr. Chambers is a past president of the Organization of Teratology Information Specialists (www.otispregnancy.org) and past president of the Teratology Society. She receives grant funding from several pharmaceutical companies that manufacture or distribute anticonvulsants, but the grants are not for anticonvulsant studies. To comment, e-mail her at obnews@elsevier.com.*

Misoprostol vs. Oxytocin For Postpartum Bleeding

BY HEIDI SPLETE

Oral misoprostol may be as effective as intravenous oxytocin for controlling postpartum hemorrhage, based on data from two studies. Both studies involved an off-label use of misoprostol, and each study included more than 800 women.

Oxytocin is the drug of choice for postpartum bleeding, but misoprostol may be more feasible in areas with limited resources, said Dr. Beverly Winikoff of Gynuity Health Projects in New York City and her colleagues.

VITALS

Major Finding: Oral misoprostol may be an alternative to intravenous oxytocin for controlling postpartum hemorrhage.

Data Source: Efficacy of oral misoprostol as an alternative to intravenous oxytocin was studied in 978 women in four hospitals in one trial, and in another 809 women who had received prophylactic oxytocin during the third stage of labor in five hospitals in a second trial.

Disclosures: Both studies were funded by the Bill and Melinda Gates Foundation. Dr. Winikoff and Ms. Blum said they had no financial conflicts to disclose.

The first study, conducted by Dr. Winikoff and her colleagues, assessed the effectiveness of oral misoprostol as an alternative to oxytocin at four hospitals: one in Ecuador, one in Egypt, and two in Vietnam. The researchers randomized 488 women to receive four 200-mcg tablets of misoprostol and an intravenous saline placebo, while 490 women received 40 IU of intravenous oxytocin and placebo tablets. The average age of the patients was 25 years, and the median blood loss at the time of treatment was 700 mL (Lancet 2010 Jan. 7 [doi:10.1016/S0140-6736(09)61924-3]).

Within 20 minutes of administration, active bleeding was controlled in 440 (90%) of the women in the misoprostol group and 468 (96%) of the women in the oxytocin group. This difference was statistically significant. In addition, significantly more women in the misoprostol group bled at least 300 mL after treatment, compared with the oxytocin group (30% vs. 17%).

Oxytocin stopped active bleeding 2 minutes faster, on average, than did misoprostol, and women in the oxytocin group lost approximately 50 mL less blood than did women in the misoprostol group, the researchers noted. Women in the misoprostol group were significantly more likely than those in the oxytocin group to report shivering (47% vs. 17%) and fever (44% vs. 6%). No women in this study had hysterectomies and no deaths were reported.

Although the difference in treatments was statistically significant, misoprostol could substitute for oxytocin in certain settings, Dr. Winikoff and her colleagues said. "Since many women in developing countries deliver at home or at low-level facilities, misoprostol provides a potential for immediate treatment of postpartum hemorrhage."

In a second study conducted by Gynuity Health Projects, lead author Jennifer Blum and her colleagues compared 800 mcg of oral misoprostol to 40 IU of intravenous oxytocin for primary postpartum hemorrhage in women who had received prophylactic oxytocin during the third stage of labor. This study included 407 women in the misoprostol group and 402 women in the oxytocin group. As in the first study, the average age of the patients was 25 years, and the median blood loss at the time of treatment was 700 mL. The study was conducted at five hospitals: one in Egypt, one in Turkey, one in Burkina Faso, and two in Vietnam (Lancet 2010 Jan. 7 [doi:10.1016/S0140-6736(09)61923-1]).

Within 20 minutes of administration, active bleeding was controlled in 363 (89%) of the misoprostol group and 360 (90%) of the oxytocin group. Additional blood loss of at least 300 mL occurred in 139 women (34%) in the misoprostol group and 123 women (31%) in the oxytocin group. The differences in bleeding between the two groups were not significant. But women in the misoprostol group were significantly more likely than those in the oxytocin group to report shivering (37% vs. 15%) and fever (22% vs. 15%). In this study, six women had hysterectomies (four with misoprostol and two with oxytonin), and two of these women died because of uncontrolled postpartum bleeding (both with misoprostol). ■