Epilepsy Should Trigger Birth Control Counseling

BY DOUG BRUNK
San Diego Bureau

SAN DIEGO — A survey of women with epilepsy showed that only about half used a highly effective method of birth control, Dr. Alison M. Pack reported in a poster session at the annual meetings of the American Epilepsy Society and the Canadian League Against Epilepsy.

The findings underscore the importance of asking women with epilepsy about their birth control methods, said Dr. Pack of the department of neurology at Columbia University, New York.

"It's not something you ask about once. I think you need to include it in each of your visits with patients," she said in an interview. "You have to ask them what their method of contraception is, and I think you need to counsel them on that."

In what she said is the largest study of its kind, Dr. Pack and her associates asked 180 female patients with epilepsy aged 18-44 years to complete a questionnaire between July 2005 and February 2006 about their reproductive history, sexual behavior, current risk of pregnancy, and contraceptive use. The women were patients at Columbia's epilepsy center and at two other New York–based clinics specializing in treating patients with the disorder.

Of the 180 women, 148 (82%) completed the questionnaire. Their mean age was 32 years; 32% described themselves as Hispanic. The women reported a wide range of educational attainment and income levels. Most (93%) described themselves as heterosexual, three as homosexual, three as bisexual, and four did not answer.

Of the 78 respondents who reported having sexual intercourse in the past 30 days, 58 (74%) used contraception.

Contraceptive methods included male condoms (36%), withdrawal (31%), oral contraception (27%), male or female sterilization (17%), contraceptive patch (5%), rhythm method (5%), intrauterine device (2%), depot medroxyprogesterone (Depo-Provera) (2%), and "other" (19%).

The researchers also found that of the 21 women who reported using a hormonal birth control method, 6 (29%) took an enzyme-inducing antiepileptic drug that is known to increase susceptibility to pregnancy. The respondents reported 181 pregnancies, of which 91 (50%) were unplanned. ■

In Utero Exposure to Valproate Tied to Poor Cognitive Outcomes

BY DOUG BRUNK
San Diego Bureau

SAN DIEGO — In utero exposure to valproate is associated with a greater risk of cognitive impairment in offspring, compared with exposure to other commonly used antiepileptic medications, Dr. Kimford J. Meador reported at the annual meetings of the American Epilepsy Society and the Canadian League Against Epilepsy.

"Further studies are needed to investigate additional [antiepileptic] drugs that have not been studied and determine if the effects we see here continue," said Dr. Meador, a neurologist who directs the epilepsy program in the department of neurology at the University of Florida, Gainesville.

The findings come from a preliminary analysis of cognitive data from the ongoing Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study, a 25-center trial in the United States and England that is funded by the National Institute of Neurological Disorders and Stroke. The long-term goal of NEAD is to examine children born to mothers with epilepsy at 6 years of age to see if differential neuropsychological effects are associated with in utero exposure to the four most commonly prescribed antiepileptic medications.

Dr. Meador and his associates performed neuropsychological testing on 2-year-old children born to mothers with partial or primary generalized epilepsy who were on antiepileptic monotherapy with carbamazepine, lamotrigine, phenytoin, or valproate. Subsequent testing was performed when the children were aged 3.5, 4, and 6 years.

The researchers administered the mental scale of the Bayley Scales of Infant Development and analyzed the children's Mental Developmental Index (MDI) scores while controlling for maternal IQ.

At the meeting, Dr. Meador presented 2-year data on 185 children in the study. During pregnancy, 48 of the children were exposed to carbamazepine, 66 to lamotrigine, 42 to phenytoin, and 29 to valproate.

The mean MDI scores were 93 in children exposed to carbamazepine, 97 in those exposed to lamotrigine, 91 in those exposed to phenytoin, and 86 in those exposed to valproate. An MDI score of 100 represents the mean score in a normal population.

Almost one-quarter of children exposed to valproate (24%) had MDIs of less than 70, compared with 12% of those exposed to carbamazepine, 11% of those exposed to lamotrigine, and 12% of those exposed to phenytoin.

The apparent adverse effect of valproate was related to anticonvulsant blood level. "This is true whether we analyzed it for blood levels across the entire pregnancy or for just the third trimester," Dr. Meador noted. The pattern also held true after the researchers controlled for confounding factors, including seizure frequency, maternal age, history of alcohol use during pregnancy, and gestational age. ■

DRUGS, PREGNANCY, AND LACTATION

Glyburide for Gestational Diabetes

When treatment for gestational diabetes is indicated, the drug of choice, insulin, can be problematic for some women because of the need for daily injections, which can affect compliance. The cost of therapy may also be an issue for women in lower socioeconomic groups.

BY GIDEON KOREN, M.D.

The use of oral hypoglycemic agents for treating women with gestational diabetes has not been recommended in the past because many of these drugs cross the placenta, increasing the risk of neonatal hypoglycemia. But there are now several studies that provide encouraging data suggesting that the second-generation sulfonylurea glyburide is a safe option for both the woman and baby.

The first study indicating that glyburide might be a safe option for treating gestational diabetes was conducted in 1994, using the human placental perfusion model, which entails taking the term placenta after birth and reconstructing the blood vessels of the mother and newborn to determine whether a drug crosses the placenta. The investigators showed that while most of the oral hypoglycemic drugs tested crossed the placenta, a minimal amount of glyburide passed the placenta (Am. J. Obstet. Gynecol. 1994;171:653-60).

One of the investigators, Dr. Oded Langer, and associates conducted a randomized, controlled trial comparing insulin with glyburide in 404 women with singleton pregnancies and gestational diabetes who started treatment between 11 and 33 weeks' gestation.

The study was published in 2000. Both treatments were equally effective in achieving the target level of glycemic control in the women, with 4% of women on glyburide requiring treatment with insulin. Importantly, there were no significant differences in neonatal complications between the two groups: The percentages of babies who were large for gestational age, had macrosomia, had lung complications, were hypoglycemic, were admitted to neonatal intensive care units, or had fetal anomalies were similar in both groups. Serum insulin levels in the cord were similar in both groups, and no glyburide was detected in the cord serum of babies in the glyburide group, confirming the 1993 study (N. Engl. J. Med. 2000;343:1134-8).

A recently completed meta-analysis by Motherisk of all studies on this topic also found no evidence of an increased risk to the newborn associated with glyburide treatment, corroborating the 2000 study.

Why glyburide does not cross the placenta is an interesting question, one that several research groups are investigating. The placenta is not just a passive barrier, and it has different carrier systems that can selectively efflux different drugs from the baby back to the mother. We also know that the opposite occurs. For example, the placenta carries iron from the mother to the baby; even when the mother is anemic, the placenta ensures that the baby receives iron.

We published a paper earlier this year using the same placental perfusion model used in the 1993 study, but put glyburide on both sides of the placenta and found that it is actively pumped from the baby to the mother (Am. J. Obstet. Gynecol. 2006;195:270-4). The central thinking now is that the most likely placental transporter for glyburide is the breast cancer–resistant protein abundantly available in the placenta.

Glyburide provides an example of a drug that has not been given to women with gestational diabetes because of the false impression that it does cross the placenta, but the available data indicate that despite being a small molecule, it does not.

These novel findings may have major implications for women with gestational diabetes who require treatment because many would be happy not to have to use insulin daily. In many parts of the world, glyburide is already widely used for treating gestational diabetes. And although some women will require insulin, or a combination of glyburide with insulin, there are many women with gestational diabetes who will do well with glyburide. Glyburide is available as a generic, which is a significant cost advantage.

Finally, this may be one of the first examples of a medication that is considered safe to use in pregnancy because it has been found not to cross the placenta. In the future, drug therapy in pregnancy may involve the development of drugs that are pumped by the placenta back to the mother, using placental transporters to control fetal exposure (Placenta 2006;27:861-8).

DR. KOREN is professor of pediatrics, pharmacology, pharmacy, medicine, and medical genetics at the University of Toronto. He heads the Research Leadership in Better Pharmacotherapy During Pregnancy and Lactation at the Hospital for Sick Children, Toronto, where he is director of the Motherisk Program, a teratogen information service (www.motherisk.org). He is also the Ivey Chair in Molecular Toxicology at the University of Western Ontario.