Anticonvulsants May Not Affect Child's IQ

BY DOUG BRUNK
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TUCSON, ARIZ. — The use of carbamazepine, phenytoin, or phenobarbital as monotherapy by pregnant women was not associated with significant deficits in full-scale IQ in their offspring, a small study showed.

However, these data counter previous reports of lowered intellectual ability in children born to mothers who took anticonvulsant medications during pregnancy, Dr. Kenneth Lyons Jones said at the annual meeting of the Teratology Society.

One in every 200 pregnant women requires antiepileptic medication during her pregnancy.

DR. JONES

"The results, then, should be considered in conjunction with previous studies when evaluating the risks associated with use of these medications during pregnancy," cautioned Dr. Jones, chief of the division of dysmorphology and teratology in the department of pediatrics at the University of California, San Diego.

Despite the documented increased risk for certain major malformations following prenatal exposure to anticonvulsants, he said that "substantial controversy" exists regarding their impact on neurobehavioral outcomes.

"Compounding these concerns is the fact that in the United States, between 7.6 million and 12.7 million women have epilepsy, and 95% of them are being treated with anticonvulsant drugs," Dr. Jones said. "In addition, 1 in every 200 pregnant women in the general population requires antiepileptic medication during her pregnancy."

He and his associates studied 82 children aged 4-14 years whose mothers were on anticonvulsant monotherapy and contacted the California Teratogen Information Service (CTIS) during their pregnancy. Of the 82 children, 30 were exposed to carbamazepine, 23 were exposed to phenytoin, and 29 were exposed to phenobarbital.

The researchers randomly selected 50 matched controls born to women who contacted CTIS due to an exposure not deemed to be teratogenic.

All children underwent neuropsychiatric testing that included a measure of full-scale IQ (FSIQ). Testing was conducted at the Center for Behavioral Teratology at San Diego State University or in a location near the child's home.

Dr. Jones reported that 26% of children exposed to phenytoin were rated as affected with features of the anticonvulsant facies based on ratings of minor malformations, compared with 24% of those exposed to phenobarbital and only 3% of those exposed to carbamazepine. No one in the control group was considered affected.

In terms of the FSIQ, there were no statistically significant differences in scores between exposed children and controls, nor did any of the exposed children differ from each other, even after controlling for age and socioeconomic status.

Dr. Jones acknowledged certain limitations of the study, including the fact that the population studied was homogeneous, the sample size was small, and there was potential for selection bias. ■

Catheter Use in Hyperemetic Patients Tied to Complications

WASHINGTON — Complications were significantly more likely among pregnant women when their hyperemesis was managed with a peripherally inserted central catheter line than with either a Dobhoff tube or medication, Dr. Calla M. Holmgren reported in a poster presented at the annual meeting of the American College of Obstetricians and Gynecologists.

Dr. Holmgren and her colleagues at the University of Utah, Salt Lake City, compared the three interventions in a prospective cohort study of 70 hyperemetic patients. Two of 24 patients whose mother's hyperemesis was managed with a PICC line developed sepsis and were admitted to the neonatal intensive care unit, and one fetus died as a direct result of PICC line use. Also, 7 of the 24 patients had thrombosis, 3 had skin infections, and 2 had bacteremia. One patient with bacteremia was admitted to the NICU.

By comparison, 1 of 13 women managed with a Dobhoff tube had tube displacement, and 2 of the 33 women managed with medication had adverse reactions.

—Heidi Splete

DRUGS, PREGNANCY, AND LACTATION

First- and Second-Generation Anticonvulsants

Although it has been known for years that some first-generation antiepileptic drugs (AEDs) cause birth defects, intrauterine growth retardation (IUGR), and, possibly, developmental delay, these toxicities were not thought to apply to the second-generation AEDs. New information has challenged that belief.

The first-generation AEDs known to cause birth defects and other developmental toxicities include the hydantoins (ethotoin [Peganone], fosphenytoin [Cerebyx], mephenytoin [Mesantoin], and phenytoin [Dilantin]), phenobarbital, primidone (Mysoline), carbamazepine (Tegretol), and valproic acid derivatives (Depakene, Depakote). In a 2001 study, the incidence of embryopathy (major and minor anomalies, microcephaly, and IUGR) after first-trimester monotherapy was 21% (phenytoin), 27% (phenobarbital), 14% (carbamazepine), 21% (any monotherapy), and 28% (polytherapy) (N. Engl. J. Med. 2001; 344:1132-8).

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Phenytoin also causes a pattern of defects collectively called the fetal hydantoin syndrome (FHS), characterized by variable degrees of hypoplasia and ossification of the distal phalanges and craniofacial abnormalities.

Other defects, such as those involving the heart and growth, are commonly observed. A syndrome with carbamazepine consisting of minor craniofacial defects, fingernail hypoplasia, and developmental delay has been observed; this drug may also cause neural-tube defects (NTDs).

The defects observed with primidone are similar to those in FHS. Phenobarbital has been associated with an increase in congenital defects when used for epilepsy, but not when used for other indications. The use of valproic acid derivatives between the 17th and 30th day after fertilization is associated with a 1%-2% risk of NTDs. Other defects are those of the head and face, digits, urogenital tract, and mental and physical growth. Carbamazepine, phenytoin, primidone, and phenobarbital affect folate metabolism or absorption, and this may increase the risk of birth defects, including NTDs. Women taking these agents should take folic acid 4-5 mg/day, preferably starting before conception. Moreover, anticonvulsants, particularly the hydantoins and barbiturates, are related to hemorrhagic disease of the newborn, so adequate doses of vitamin K should be administered to newborns exposed to AEDs in utero.

In contrast, first-generation AEDs that do not appear to be associated with a significant risk of birth defects include the benzodiazepines (clonazepam [Klonopin], clorazepate [Tranxene], diazepam [Valium], and lorazepam [Ativan]) and succinimides (ethosuximide [Zarontin] and methsuximide [Celontin]). However, some of these drugs have very little human data, and the benzodiazepines are known to cause toxicity in the newborn, most notably, floppy infant syndrome and withdrawal syndrome. In addition, the risk for birth defects from seizures alone is at least two to three times greater than the background risk of 2%-3%.

Until recently, the second-generation AEDs had not been associated with congenital defects. However, new data from the North American AED Pregnancy Registry and five other pregnancy registries have shown a very significant risk of isolated, nonsyndromic oral clefts after first-trimester exposure to lamotrigine (Lamictal) monotherapy (Birth Defects Res. A Clin. Mol. Teratol. 2006;76:313-428). The prevalence of oral clefts in the North American registry was 8.9/1,000, even though all of the mothers had been supplemented with folic acid before conception. This was significantly higher than the prevalence of 0.37/1,000 in a comparison group.

The human pregnancy experience is too limited to assess the embryo/fetal risk for the other second-generation agents: felbamate (Felbatol), gabapentin (Neurontin), pregabalin (Lyrica), levetiracetam (Keppra), tiagabine (Gabitril), and topiramate (Topamax). Although the data also are limited for zonisamide (Zonegran), the drug is teratogenic in three animal species and embryo lethal in a fourth and therefore is best avoided in the first trimester. Oxcarbazepine (Trileptal), a drug closely related to carbamazepine, has been associated with minor facial defects, but the data are too limited to assess the risk in humans.

To summarize, women with epilepsy should not be denied treatment with the most effective agents for their condition because of pregnancy or nursing. They should be treated with the lowest dose and the fewest drugs possible to control their seizures. Periodic serum levels are needed throughout pregnancy to ensure that therapeutic levels are maintained. They should take folic acid (4-5 mg/day), and vitamin K should be given to the newborns.

It is also important to counsel that seizures are a risk to both the mother and the embryo/fetus, as is the drug therapy. AEDs that appear to have the lowest risk for major birth defects are the benzodiazepines, the succinimides, and the second-generation agents. However, the human pregnancy data are very limited for many of these agents.

Carbamazepine and phenytoin are considered compatible with breast-feeding, and gabapentin, levetiracetam, oxcarbazepine, and tiagabine are probably compatible. Two AEDs (primidone and phenobarbital) are known to cause toxicity in the nursing infant and should not be given during breast-feeding. There are no data for the remaining AEDs, but they have the potential to cause toxicity and, if used during breast-feeding, the infants should be closely monitored.

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