CURRENT LITERATURE

TERATOGENICITY

The Teratogenicity of Anticonvulsant Drugs

Holmes LB, Harvey EA, Coull BA, Huntington KB, Khoshbin S, Hayes AM, Ryan LM

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BACKGROUND: The frequency of major malformations, growth retardation, and hypoplasia of the midface and fingers, known as Anticonvulsant embryopathy, is increased in infants exposed to anticonvulsant drugs in utero. However, whether the abnormalities are caused by the maternal epilepsy itself or by exposure to anticonvulsant drugs is not known.

METHODS: We screened 128,049 pregnant women at delivery to identify three groups of infants: those exposed to anticonvulsant drugs, those unexposed to anticonvulsant drugs but with a maternal history of seizures, and those unexposed to anticonvulsant drugs with no maternal history of seizures (control group). The infants were examined systematically for the presence of major malformations, signs of hypoplasia of the midface and fingers, microcephaly, and small body size.

RESULTS: The combined frequency of anticonvulsant embryopathy was higher in 223 infants exposed to one anticonvulsant drug than in 508 control infants (20.6 percent vs. 8.5 percent; odds ratio, 2.8; 95 percent confidence interval, 1.1 to 9.7). The frequency was also higher in 93 infants exposed to two or more anticonvulsant drugs than in the controls (28.0 percent vs. 8.5 percent; odds ratio, 4.2; 95 percent confidence interval, 1.1 to 5.1). The 98 infants whose mothers had a history of epilepsy but took no anticonvulsant drugs during the pregnancy did not have a higher frequency of those abnormalities than the control infants.

CONCLUSIONS: A distinctive pattern of physical abnormalities in infants of mothers with epilepsy is associated with the use of anticonvulsant drugs during pregnancy, rather than with epilepsy itself.

COMMENTARY

The results of Holmes et al. confirm the observations of prior studies and add confidence to the estimates of the magnitude of the risks entailed by in utero antiepileptic drug (AED) exposure. Furthermore, their observations in AED-exposed children, whose mothers did not have epilepsy, are consistent with animal studies that have demonstrated that many AEDs are teratogenic. However, many important questions remain unanswered.

Because most women with epilepsy do not have the choice of avoiding AEDs, the critical question is whether there are AEDs that are less teratogenic. However, prior studies and the Holmes study do not indicate a clear advantage in this regard for the older AEDs. Several newer AEDs have favorable teratogenic profiles in animal studies, but adequate human data are lacking. An ongoing prospective study by the Holmes group seeks to address this issue. The AED pregnancy registry is enrolling pregnant women taking any AED for seizures. The women may enroll by calling the toll free number 1-888-233-2334 (1-888-AED-AED4); the Website is at http://neuro-www2.harvard. Children of women with epilepsy are not only at risk for anatomical defects but are also at risk for neurodevelopmental delay. Although AEDs have been implicated, the magnitude and differential effects of in utero AED exposure on neurodevelopment also remain unresolved. Another ongoing perspective study seeks to determine whether AEDs differ in their effects on cognition and behavior as a result of in utero exposure. Local contact numbers can be found at http://www.neuro.mcg.edu/nead or by calling 1-706-721-2797.

In summary, women with epilepsy and their children are at increased risks. AEDs increase the risk of malformations and likely contribute to developmental delay. The exact mechanisms of these effects remain uncertain. Of even greater clinical concern, it remains unclear whether any of the AEDs have less overall teratogenicity. However, the risks of AEDs and seizures need to be put in perspective. For most women with epilepsy, the risks of seizures outweigh the risks of AEDs. Furthermore, it is important that the message to women with epilepsy be balanced so that they understand that the large majority of children born to them are normal.

by Kimford J. Meador, M.D.