



## **Maternal Valproate Use Tied to Major Birth Defects**

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ROCKVILLE, MD. — In utero exposure to the antiepileptic drug valproate is associated with major malformations, Dr. Lewis Holmes said at a meeting of the Food and Drug Administration's Center for Drug Evaluation and Research.

Among 140 pregnancies during which women took valproate as monotherapy, nine infants had major malformations, including heart defects, spina bifida, multicystic dysplastic kidney, postaxial polydactyly type B, inguinal hernia, and penile hypospadias. One infant had multiple major malformations. This rate of major malformations is approximately four to five times that seen in unexposed control children.

The study was based on data culled from the Anti-Epileptic Drug Pregnancy Registry (AED), which was developed by Dr. Holmes and his colleagues in 1997 and sponsored by six pharmaceutical companies. Dr. Holmes stressed that the registry does not allow for determining whether a major malformation was due to prenatal exposure to antiepileptic drugs or to epilepsy itself.

As of March 2003 approximately 3,000 women had been enrolled, but only data from those enrolled before undergoing prenatal screening were used in the study.

The registry is important, because the range of antiepileptics' teratogenic effects has not been studied systematically, said Dr. Holmes, professor of pediatrics at Harvard Medical School and director of genetics in the perinatal diagnostic unit of Massachusetts General Hospital, both in Boston.

Data from the registry published in 2001 suggested that phenobarbital is also linked to a four- to fivefold increased risk of major malformations in exposed pregnancies. The data focused on 65 pregnancies during which women took phenobarbital as monotherapy; all of the women had registered before their first prenatal screening.

Major malformations in exposed infants included one cleft lip and palate and four heart defects, for an incidence of 7.8%, compared with 1.62% in a comparison group of children whose mothers did not take antiepileptic medications in pregnancy.

More than 200 antiepileptic drug regimens and 29 monotherapies have been identified among the women who've enrolled in the AED pregnancy registry. Most of the women are pregnant for the first time and enroll before their 16-week prenatal testing. They are interviewed three times—when they first call to register, at 7 months' gestation, and 6-8 weeks after childbirth.

Only major malformations are included in the registry. Minor anomalies, birthmarks, prematurity-related findings, positional deformities, and genetic disorders are not included.

“Most women report findings that don't count as major malformations,” Dr. Holmes said.

The registry is sponsored by Abbott, Elan, GlaxoSmithKline, Novartis, Ortho-McNeil, and Pfizer.

For more information, visit the AED Pregnancy Registry Web site at [www.mgh.harvard.edu/aed/index.htm](http://www.mgh.harvard.edu/aed/index.htm). To register patients, call 888-233-2334.