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North American Antiepileptic Drug Pregnancy Registry

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Background: The North American AED (antiepileptic drug) Pregnancy Registry was established in 1997 for pregnant women in the United States and Canada at the Massachusetts General Hospital in Boston, Massachusetts. The major objective was to obtain, as quickly as possible, information on the frequency of major malformations among infants whose mothers had taken one or more AEDs to prevent seizures or to treat any other medical condition. The highest priority was new information on the many "new" AEDs marketed in the past 10 years.

Methods: The eligible woman calls the toll-free number (1-888-233-2334) to obtain information and, we hope, to enroll. She is sent an informed-consent document to review, sign, and return. She is interviewed 3 times: at enrollment (12 min), 7 months' gestation (5 min), and 8 weeks after delivery (5 min). The findings by the doctor of each exposed infant are obtained with the mother's written permission. The study dysmorphologist uses established inclusion/exclusion criteria to identify major malformations (defined as a structural abnormality with surgical, medical, or cosmetic importance). The Scientific Advisory Committee meets separate from the representatives of the sponsoring companies to review anonymously the major findings. Findings in women who have enrolled before having any prenatal screening, a "pure" prospective group, are used to decide when findings should be released.

The criterion for release of results for a positive association (relative risk, >1) is met when the lower of the 95% confidence interval (CI) is ≥ 2.0. The release criterion for no associated increase in the frequency of all major malformations is met when the upper of the 95% confidence limits does not exceed 2.0. The external comparison group is the findings in the Active Malformations Surveillance Program at Brigham and Women's Hospital. The findings in 69,277 newborns, published previously (1), was a baseline rate of 2.24%, which was reduced to 1.62% after excluding infants with genetic disorders and chromosome abnormalities. The major malformations are identified between birth and age 5 days. The inclusion/exclusion criteria are the same as those used in the AED Pregnancy Registry.

Results: As of July 12, 2004, total enrollment was 3,708 women; 75% of the women were taking one of 20 different monotherapies, and 63% were "pure" prospective enrollees. The lost-to-follow-up rate has been 3%.

The findings have been released for two drugs as monotherapy: phenobarbital (PB) (2) and sodium valproate (VPA) (3), the latter published only as an abstract (an update will be possible after the full results have been published).

As of July 12, 2004, six (6.5%) of 92 pure prospective pregnancies with exposure to PB were associated with major malformations (95% CI, 2.4–13.7%). When compared with the background rate (1.62%), a significantly increased risk (RR, 4.0; 95% CI, 1.9–8.7%) was noted.

Conclusions: A hospital-based pregnancy registry can enroll a significant number of pregnant women who are taking an AED. Many more enrollees are needed to provide the important information needed on many "new" AEDs as monotherapy. Many eligible women do not enroll. We urge all readers to encourage their eligible patients to call 1-888-233-2334 early in pregnancy.

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