

WHEN SHOULD WE PAY ATTENTION TO UNFAVORABLE NEWS FROM PREGNANCY REGISTRIES?

In Utero Antiepileptic Drug Exposure: Fetal Death and Malformations. Meador KJ, Baker GA, Finnell RH, Kalayjian LA, Liporace JD, Loring DW, Mawer G, Pennell PB, Smith JC, Wolff MC; NEAD Study Group. *Neurology* 2006;67:407–412.

BACKGROUND: Pregnancy outcomes following in utero exposure to antiepileptic drugs (AEDs) are uncertain, limiting an evidenced-based approach. **OBJECTIVE:** To determine if fetal outcomes vary as a function of different in utero AED exposures. **METHODS:** This ongoing prospective observational study across 25 epilepsy centers in the United States and United Kingdom enrolled pregnant women with epilepsy from October 1999 to February 2004 to determine if differential long-term cognitive and behavioral neurodevelopmental effects exist across the four most commonly used AEDs. This initial report focuses on the incidence of serious adverse outcomes including major congenital malformations (which could be attributable to AEDs) or fetal death. A total of 333 mother/child pairs were analyzed for monotherapy exposures: carbamazepine (n = 110), lamotrigine (n = 98), phenytoin (n = 56), and valproate (n = 69). **RESULTS:** Response frequencies of pregnancies resulting in serious adverse outcomes for each AED were as follows: carbamazepine 8.2%, lamotrigine 1.0%, phenytoin 10.7%, and valproate 20.3%. Distribution of serious adverse outcomes differed significantly across AEDs and was not explained by factors other than in utero AED exposure. Valproate exhibited a dose-dependent effect. **CONCLUSIONS:** More adverse outcomes were observed in pregnancies with in utero valproate exposure versus the other antiepileptic drugs (AEDs). These results combined with several recent studies provide strong evidence that valproate poses the highest risk to the fetus. For women who fail other AEDs and require valproate, the dose should be limited if possible.

COMMENTARY

The study by Meador and colleagues, who form the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study group, is one of a number of recently published studies that addresses the impact of AEDs on infants born to women receiving them during pregnancy (1–5). Of interest, the study was funded by the National Institutes of Health for a completely different purpose, namely to address the impact of in utero AED exposure on the cognitive development of children born to mothers with epilepsy. The study is ongoing, and the cognitive outcome will be reported at a future date. Reported here are the important pregnancy outcomes, major fetal malformation or fetal death, associated with specific AEDs. This study confirms the finding of several other registries that the incidence of these adverse pregnancy outcomes is increased in the offspring of mothers receiving valproate (1–5).

How should physicians respond to information coming at an ever-increasing rate from a number of registries? When an adverse outcome is reported to be at a greater frequency for a particular AED, should the response be to stop prescribing that drug to women of childbearing age? The answer to this question is not so simple. One problem is that the stud-

ies and registries have provided conflicting information. For example, the North American pregnancy registry recently reported an increased incidence of cleft lip/cleft palate associated with the use of lamotrigine, with an incidence of approximately 8.9/1,000 cases, as compared with 0.5 to 2.16/1,000 in nonepileptic mothers not receiving AEDs (6). Yet, an increased incidence of this malformation was not seen in any of the other registries or in a large prospective lamotrigine pregnancy registry (2). Confusing the matter further, the British pregnancy registry found a correlation between the likelihood of major fetal malformations and higher lamotrigine dose (1). This correlation was not found in other registries, not even in those that had enrolled a large enough number of women with lamotrigine exposure to provide the power to detect a dose-response relationship.

How, then, do we account for these differences? As with every other type of investigation, details matter. If the studies are carefully reviewed, subtle differences in design begin to emerge that might explain the differing results. For example, there are disparities in how patients are identified for inclusion. In some registries, patients can only be included if they either have had no perinatal testing at the time of enrollment or have had negative testing up to that point. Since patients often do not enroll until their 5th or 6th month of pregnancy, this protocol would exclude patients who had early evidence of fetal malformation, thereby potentially lowering the incidence of malformations

identified in the study. Other registries require that women self-identify for enrollment, after being provided a phone number from their physician. It is the experience of many physicians that only a fraction of women who are told about a registry will actually call to enroll. This fact might increase the representation of motivated women, who might differ in important ways from women who do not enroll. In other registries, women are enrolled by their physician, possibly providing a broader sampling of the population.

Differences in the timing of malformation ascertainment also might factor into the contradictory results seen across registries. Some registries only assessed at birth, while others followed children for months to years after delivery. Control groups also may differ and often are not representative of the type of patients enrolled in the registry. For example, the lamotrigine pregnancy registry compared outcomes of women enrolled throughout the United States with outcomes of patients seen at the Center for Disease Control's Metropolitan Atlanta Congenital Defects Program—even though the Metropolitan Atlanta population probably was not equivalent to the United States as a whole in terms of race, socioeconomic status, or exposure to other potential teratogens, such as cigarettes and alcohol (2). If the control population had a relatively high rate of major malformations compared to the expected rate of the women enrolling in the registry, malformations in the women exposed to AEDs might be missed. In this respect, comparisons between two groups of women in the same registry who have been exposed to different drugs (e.g., women exposed to carbamazepine versus valproic acid) might have greater validity than comparisons to the external control group. Even within the same registry, it is impossible to exclude population bias related to nonrandomized selection of AEDs. For example, if the genetic abnormality that confers risk for juvenile myoclonic epilepsy also confers a higher risk of major malformations in offspring, there might be a bias against valproic acid, a drug of choice for that condition.

The NEAD study was an ideal study from the perspective of several of the issues reviewed here. Infants were followed for several years after birth, which would clearly increase the likelihood of discovering abnormalities that are not immediately apparent postpartum. In contrast to some of the other registries, the association of malformations with important potential confounders, such as socioeconomic status, age of the mother, epilepsy syndrome, AED dose, and compliance, was explored and eliminated in the NEAD study. Drugs were compared to each other, obviating the need for an external comparison group. In addition, rather than being given a national registry phone number to call, patients were asked by their own

physicians to provide consent, which may have increased the likelihood of a representative sample of women. The weakness of the study lies in the relatively low number of patients enrolled. This factor might reduce the importance of the study's finding that there were no differences in rates of fetal death or major malformation among three of the AEDs studied, namely carbamazepine, phenytoin, and lamotrigine. However, the fact that valproic acid was found to convey a higher risk, despite the relatively small sample size, only highlights the importance of the effect. Therefore, the results of this study should be given careful consideration.

In summary, because of differences among pregnancy registries described here and because, for obvious reasons, a randomized trial is impossible, it would be reasonable to wait until a finding has been confirmed in several studies before altering drug selection in women contemplating pregnancy. The fact that valproic acid has been associated with a significantly higher risk of malformations in six studies means that the signal is strong enough to warrant consideration of selecting an alternative AED, when a choice exists. A more thorny issue arises when valproic acid has conveyed seizure control, and conversion to alternative therapy may be associated with a risk of seizure breakthrough. In this case, discussion of the risk/benefit relationship is essential, at the very least.

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References

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