

## ANOTHER NAIL IN THE COFFIN

**Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs.** Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW, NEAD Study Group. *N Engl J Med* 2009;360(16):1597–1605. **BACKGROUND:** Fetal exposure of animals to antiepileptic drugs at doses lower than those required to produce congenital malformations can produce cognitive and behavioral abnormalities, but cognitive effects of fetal exposure of humans to antiepileptic drugs are uncertain. **METHODS:** Between 1999 and 2004, we enrolled pregnant women with epilepsy who were taking a single antiepileptic agent (carbamazepine, lamotrigine, phenytoin, or valproate) in a prospective, observational, multicenter study in the United States and the United Kingdom. The primary analysis is a comparison of neurodevelopmental outcomes at the age of 6 years after exposure to different antiepileptic drugs in utero. This report focuses on a planned interim analysis of cognitive outcomes in 309 children at 3 years of age. **RESULTS:** At 3 years of age, children who had been exposed to valproate in utero had significantly lower IQ scores than those who had been exposed to other antiepileptic drugs. After adjustment for maternal IQ, maternal age, antiepileptic drug dose, gestational age at birth, and maternal preconception use of folate, the mean IQ was 101 for children exposed to lamotrigine, 99 for those exposed to phenytoin, 98 for those exposed to carbamazepine, and 92 for those exposed to valproate. On average, children exposed to valproate had an IQ score 9 points lower than the score of those exposed to lamotrigine (95% confidence interval [CI], 3.1–14.6;  $p = 0.009$ ), 7 points lower than the score of those exposed to phenytoin (95% CI, 0.2–14.0;  $p = 0.04$ ), and 6 points lower than the score of those exposed to carbamazepine (95% CI, 0.6–12.0;  $p = 0.04$ ). The association between valproate use and IQ was dose dependent. Children's IQs were significantly related to maternal IQs among children exposed to carbamazepine, lamotrigine, or phenytoin but not among those exposed to valproate. **CONCLUSIONS:** In utero exposure to valproate, as compared with other commonly used antiepileptic drugs, is associated with an increased risk of impaired cognitive function at 3 years of age. This finding supports a recommendation that valproate not be used as a first-choice drug in women of childbearing potential.

## COMMENTARY

Thoughtful women who want to bear children face myriad concerns and frequently worry about everything they have done and are doing, as it affects their fetus. They worry about illnesses they have experienced, medications or drugs they have used, environment factors, and certainly about exposure of their fetus to ongoing possible toxins—medications, alcohol, and smoking, to name a few. Women with epilepsy who want to bear children shoulder an even greater burden. They also worry about the impact of seizures and their antiepileptic drugs on the fetus, seeking to minimize risks. The Internet does not help matters: there are lawyers eager to launch suits related to anything attributable to exposure to an antiepileptic drug (AED), particularly “birth injuries,” and have seemingly hurried to add “lower IQ” to their list of injuries. As recently as a decade ago, there was a paucity of information about AEDs to guide women with epilepsy and their physicians in making informed choices (1). At that time, the practice parameters indicated: 1) that medications should be chosen based upon

seizure type, 2) prenatal testing should be offered to patients taking carbamazepine or valproic acid, and 3) further research using registries was recommended. From these registries has come a clearer understanding of the magnitude and nature of the risks, and it has led to the most recent Practice Parameter update from the American Academy of Neurology and American Epilepsy Society (2). The recommendation is that valproic acid and polytherapy be avoided, if possible, throughout pregnancy to prevent both malformations and a negative impact on cognitive development. Publication of this Practice Parameter occurred before the current paper by Meador et al. was available for consideration (3).

The Meador et al. study is an exemplary product of cooperation between a large number of centers, in the United States and the United Kingdom that studied the neurodevelopmental effects of AEDs. The drugs studied (i.e., carbamazepine, lamotrigine, phenytoin, and valproate) reflect the prevalence of use, when the work began in 1999—not necessarily the medications that would be commonly used today. Their planned interim analysis of children between 2 and 3 years of age demonstrated a significantly lower IQ for fetuses exposed to valproate than for fetuses exposed to the other medications, even when adjustments were made for the typical variables

that might explain the different outcomes. However, some important variables that are not well explained are as follows: Why is a child's IQ not related to the maternal IQ when exposed to valproate but is related when exposed to the other medications? How might other variables that were significantly different in the valproate group (especially the type of epilepsy) also be important to IQ outcome? Why are there many factors that are significantly associated with the use of valproate but not the other medications? In this strictly observational study, there is an inability to control for a crucial factor—it is not known why certain women were treated with valproate. Might it be that these women experienced idiopathic generalized epilepsy and had not responded to any other medications, except valproate? Note that 76% of those treated with valproate had no seizures during the pregnancy, while the other groups had a somewhat better control rate (79–88%). Valproate also was used more frequently in the UK group.

Although Meador and colleagues clearly demonstrate that those individuals who were on the higher dose of valproate (i.e., above 1000 mg/day) were most adversely affected, the significance of that effect cannot be fully appreciated unless the data in a Supplementary Appendix are examined. Web Figure 5 of the Appendix shows the maternal IQ was subtracted from the child's IQ and plotted against medication dose. Would the adverse impact of valproate on IQ be eliminated if the data for doses over 1000 mg were excluded? Why were these women on such high doses? The study would require a standardization of doses to make these comparisons meaningful. Furthermore, actual blood levels were not used, and these data do not take into account the fact that the drug load for valproate is higher in the fetus and newborn compared with the other medications, which have a more neutral impact. As a comparable concern, clinicians are keenly aware that pregnancy typically decreases the concentrations of lamotrigine, phenytoin, and to some extent, carbamazepine. Finally, IQ outcomes at 3 years were actually missing for 77 children, almost 25% of the population. Although IQ scores obtained between the ages of 2 and 3 are considered adequately predictive of future IQ scores, it should be noted that these children are in the normal range; thus, it will be important to ascertain functional outcomes as these children become older.

Recognizing the complexity of the biology in this population, this paper demonstrates the difficulties involved in data

analysis for this topic. Fifteen of the 35 references refer to tests used or statistical analyses required to compute the data. Although it is obvious that these methodologies have been carefully vetted by reviewers and statisticians, clinicians are not trained to deal with the complexities of linear regression models adjusted for a variety of factors, Markov-chain Monte Carlo methods for monotone missing data, forest plots, propensity scores, or imputing missing outcomes. Interpretation of articles such as this one can be daunting for those in academic medicine. How can they be read or how are they misread by those in routine practice?

Conscientious physicians and mothers-to-be certainly want the best possible outcome for the fetus. For a variety of reasons, including concerns about weight, polycystic ovary disease, and certainly teratogenicity, most physicians endeavor to minimize the use of valproate for women in the childbearing years. This study appears to put yet another nail in the coffin, further confirming that the use of valproate in this group of women is problematic. However, in some women, valproate is critical to optimal seizure control. Perhaps, guided by the knowledge that lower doses appear to have less risk, appropriate treatment can continue to be provided for these individuals, while minimizing the risk to the fetus and the anxiety that patients must feel.

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## References

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3. Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW, NEAD Study Group. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med* 2009;360:1597–1605.