Women with Epilepsy Planning Pregnancy: We *Can* Improve Outcomes by Improving Care

Fetal Antiepileptic Drug Exposure and Cognitive Outcomes at Age 6 Years (NEAD Study): A Prospective Observational Study

Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD Study Group. Lancet Neurol 2013;12: 244–252.

BACKGROUND: Many women of childbearing potential take antiepileptic drugs, but the cognitive effects of fetal exposure are uncertain. We aimed to assess effects of commonly used antiepileptic drugs on cognitive outcomes in children up to 6 years of age. METHODS: In this prospective, observational, assessor-masked, multicentre study, we enrolled pregnant women with epilepsy on antiepileptic drug monotherapy (carbamazepine, lamotrigine, phenytoin, or valproate) between October, 1999, and February, 2004, at 25 epilepsy centres in the UK and the USA. Our primary outcome was intelligence quotient (IQ) at 6 years of age (age-6 IQ) in all children, assessed with linear regression adjusted for maternal IQ, antiepileptic drug type, standardised dose, gestational birth age, and use of periconceptional folate. We also assessed multiple cognitive domains and compared findings with outcomes at younger ages. This study is registered with ClinicalTrials.gov, number NCT00021866. FINDINGS: We included 305 mothers and 311 children (six twin pairs) in the primary analysis. 224 children completed 6 years of follow-up (6-year-completer sample). Multivariate analysis of all children showed that age-6 IQ was lower after exposure to valproate (mean 97, 95% CI 94-101) than to carbamazepine (105, 102-108; p=0·0015), lamotrigine (108, 105-110; p=0·0003), or phenytoin (108, 104-112; p=0·0006). Children exposed to valproate did poorly on measures of verbal and memory abilities compared with those exposed to the other antiepileptic drugs and on non-verbal and executive functions compared with lamotrigine (but not carbamazepine or phenytoin). High doses of valproate were negatively associated with IQ (r=-0·56, p<0·0001), verbal ability (r=-0·40, p=0·0045), non-verbal ability (r=-0·42, p=0·0028), memory (r=-0·30, p=0·0434), and executive function (r=-0·42, p=0·0004), but other antiepileptic drugs were not. Age-6 IQ correlated with IQs at younger ages, and IQ improved with age for infants exposed to any antiepileptic drug. Compared with a normative sample (173 [93%] of 187 children), right-handedness was less frequent in children in our study overall (185 [86%] of 215; p=0·0404) and in the lamotrigine (59 [83%] of 71; p=0·0287) and valproate (38 [79%] of 40; p=0·0089) groups. Verbal abilities were worse than non-verbal abilities in children in our study overall and in the lamotrigine and valproate groups. Mean IQs were higher in children exposed to periconceptional folate (108, 95% CI 106-111) than they were in unexposed children (101, 98-104; p=0·0009). INTERPRETATION: Fetal valproate exposure has dose-dependent associations with reduced cognitive abilities across a range of domains at 6 years of age. Reduced right-handedness and verbal (vs non-verbal) abilities might be attributable to changes in cerebral lateralisation induced by exposure to antiepileptic drugs. The positive association of periconceptional folate with IQ is consistent with other recent studies.

Commentary

This article is one of many reporting the outcome of the NEAD (Neurodevelopmental Effects of Antiepileptic Drugs) study, a major and important prospective evaluation of women receiving antiepileptic drugs (AEDs) during pregnancy.

Epilepsy is a chronic condition that occurs throughout the lifespan. It is also a condition that can be life threatening if left untreated; typically, treatment consists of chronic antiepileptic drug (AED) therapy. All these factors contribute to the fact that many women with epilepsy will be receiving AEDs throughout their childbearing years. There has been a keen desire to protect the smallest and most vulnerable population exposed to AEDs; namely, children as yet unborn, whose mothers are receiving these drugs. As early as the 1970s, studies warned of the potential dangers of in utero exposure to AEDs. By the 1980s, physicians were being warned of the dangers of AEDs such as valproate, phenobarbital, carbamazepine and phenytoin (1). Recent pregnancy registries, which are more carefully designed than previous versions, use prospective observation and attention to confounders and have eased some earlier concerns (for

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example, reassuring us of the safety of carbamazepine) while confirming the danger of valproic acid (2, 3). The focus of most of these efforts was squarely on risk for congenital malformations. Recently, largely as a result of the efforts of the NEAD investigators, the focus has changed to cognitive outcomes. A number of children exposed to four common AEDs have now been followed throughout their childhood. The newest report presents the outcomes of the children at 6 years of age. Compared to the prior report when the children were 4 1/2, there is good news and bad news (4). The bad news: Children exposed to VPA in utero continue to have lower IQs at age 6 years. More detailed testing at age 6 also revealed poorer language, memory, and executive function than would have been expected based on their mother's IQ and in comparison to children exposed to the other 3 AEDs (lamotrigine, phenytoin and carbamazepine). The good news: The IQs actually improved slightly compared to prior assessments. The authors hypothesize that this might have resulted from practice effects, repeated testing, or to early intervention since all the parents had access to their children's test results from as early as 2 years old. The other potentially good news is that women could improve their chances of having a child with a better IQ with a simple intervention: taking periconceptual folic acid (usually defined as 4 weeks before and up to 8 weeks after conception), although improvement was less for the children exposed to VPA. This is consistent with recent data that periconceptual folate reduces autism risk (5). Of course, confounding explanations could account for this finding; for example, receiving folic acid could have been a marker for better overall care during pregnancy, including nutrition, perinatal vitamins, prenatal counseling, and so on. However, since the intervention is so easy and otherwise harmless, it makes sense to use it until or unless studies suggest otherwise. Another piece of good news, confirmed from previous reports, is that there was no association between increasing the dose of the other 3 AEDs and lower IQ. This is particularly important for lamotrigine, since doses may need to be increased markedly during pregnancy due to higher clearance, and at least one pregnancy registry has found an association between increasing lamotrigine dose during pregnancy and higher risk of fetal malformations (6, 7).

So, where does this new information lead us in regard to optimal care of women with epilepsy?

1. There should be greater attention to folate use and the need to start prior to conception, as some data suggests that initiation later in pregnancy may not be of benefit. Here, there is clearly room for improvement. A recent study indicated that many women do not receive folate during childbearing years, even at major medical centers and when receiving valproate (8). This is not always the fault of the treating doctors. Many pregnancies are not planned, and it is sometimes difficult to impart the importance of folic acid when women are not considering pregnancy. Even when they are, it is not so easy: An ongoing study of women with epilepsy who were actively planning pregnancy surprisingly indicated that the women were more likely to be noncompliant with folate and perinatal vitamins than with AEDs. Data from the NEAD study will be very useful in emphasizing the importance of folate intervention.

2. If VPA is needed, it should be given at the lowest dose possible, ideally below 1000 mg. In this study, the investigators could not show a clear difference in outcomes between children exposed to VPA doses below 1000 and the other AEDs, although the numbers were low and the confidence intervals wide.

3. If a woman delivers a child after exposure to valproic acid, AED polytherapy, or other risk factors for cognitive dysfunction, serious consideration should be given to early cognitive screening.

This type of research is critically important because it produces information that can actually change outcomes for the better. There is a great need for more of the same. Fortunately, many of the same investigators are now embarking on a new study, MONEAD, looking at epilepsy and AED-associated complications of pregnancy. They—and we—will no doubt learn a great deal.

by Jacqueline A. French, MD

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