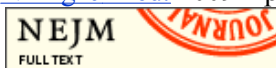




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Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs.

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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 to 14.6; $P=0.009$), 7 points lower than the score of those exposed to phenytoin (95% CI, 0.2 to 14.0; $P=0.04$), and 6 points lower than the score of those exposed to carbamazepine (95% CI, 0.6 to 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. 2009 Massachusetts Medical Society

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