

Lower IQ Is Linked to Prenatal Valproate Use

BY MICHELE G. SULLIVAN

Children exposed to valproate in utero have significantly lower IQs at age 3 than do children exposed to other antiepileptics during gestation, according to findings from the interim analysis of a large international study.

The drug previously had been associated with a higher rate of birth defects in children exposed prenatally. The combination of findings strengthens a recommendation to avoid valproate as a first-line antiepileptic in women who may bear children, Dr. Kimford J. Meador said in an interview.

"Valproate poses a special risk for both congenital malformations and for cognitive impairment," said Dr. Meador, principal investigator in the Neurodevelopmental Effects of Antiepileptics Drugs (NEAD) study. "Since there are other therapeutic options, it would seem prudent to try those first. At a minimum, it is critical that physicians inform women of this risk when prescribing valproate so that they may make an informed choice."

NEAD is an ongoing study of 309 children, including three sets of twins, born in either the United States or the United Kingdom from 1999 to 2004, whose mothers were taking a single antiepileptic drug (AED): carbamazepine, lamotrigine, phenytoin, or valproate. The children are being followed to age 6. Dr. Meador, professor of neurology at Emory University, Atlanta, and his associates reported the results of a planned 3-year interim analysis in the *New England Journal of Medicine* (2009;360:1597-605).

All of the 303 women in the study were taking the drugs for a seizure disorder. Their mean age at delivery was 30 years. Most women were well controlled on their AED, with about 80% having no seizures during their pregnancy.

Most of the children in the study (258) underwent cognitive assessment at either 2 or 3 years of age, or at both ages. Of these, 73 (28%) had been exposed to carbamazepine, 84 (32%) to lamotrigine, 48 (19%) to phenytoin, and 53 (21%) to valproate. Cognitive testing consisted of the Bayley Scales of Infant Development and the Differential Ability Scales.

IQ scores were adjusted for factors that could significantly affect cognitive development, some of which were maternal IQ; age at delivery; education; type of epilepsy; seizure frequency; socioeconomic status; the use of folate, alcohol, tobacco, and drugs; obstetrical complications; gestational age; birth weight; and breastfeeding.

Children exposed to valproate had

the lowest mean IQs of any of the exposure groups (92)—significantly lower than those of any other treatment group. The mean IQ in those exposed to carbamazepine was 98; to lamotrigine, 101; and to phenytoin, 99. These did not vary significantly from one another.

The association of valproate with reduced IQ held after adjustment for the confounders in both a linear regression and subgroup analysis, the investigators said. They also examined whether the IQ scores were related to AED dosage. In this analysis, only valproate maintained a significant dose-response relationship.

Additionally, higher maternal IQs were associated with higher child IQs in all of the treatment groups except valproate.

The results are consistent with several European studies that have found poor cognitive outcomes in children exposed to the drug prenatally, the investigators said. The drug also has been

found to increase the rate of congenital malformations, compared with other AEDs. A recent meta-analysis found the rate to be as many as 11% of births.

Unfortunately, Dr. Meador and his colleagues wrote, women whose seizures are well controlled on valproate may be placed on the horns of a dilemma when trying to balance gestational safety with seizure control.

"For some patients, valproate is the only medication that adequately controls seizures. Such women should be informed of the potential risks associated with the use of this medication in pregnancy. If a woman taking valproate is already pregnant, it's critical that she not stop valproate without consultation with her physician, since stopping an antiepileptic drug could lead to seizures and serious consequences for both the woman and her fetus."

"One other important point is that less than half of the prescriptions for valproate are for seizures or epilepsy. The majority are for pain or psychiatric indications. I believe that the women taking valproate for other indications are at the same risk as our women with epilepsy," he said in the interview.

The study was supported by grants from the United Kingdom Epilepsy Research Foundation and the National Institute of Neurological Disorders and Stroke. Dr. Meador reported receiving research support from Glaxo-SmithKline, Myriad Pharmaceuticals, Marinus Pharmaceuticals, UCB Pharmaceuticals, and several other companies and foundations. ■

'Valproate poses a special risk for both congenital malformations and for cognitive impairment [at age 3]. ... It is critical that physicians inform women of this risk.'

DRUGS, PREGNANCY, AND LACTATION

Depression and SSRI Exposure

Studies conducted over the last decade have consistently supported the conclusion that pregnancy is not protective with respect to risk for new onset or recurrence of major depression. The last decade also has produced numerous studies evaluating the reproductive safety of selective serotonin reuptake inhibitors (SSRIs) with respect to the risk for major malformations, with most data supporting safety or suggesting a small absolute risk of malformations. Therefore, despite some earlier concerns about a possible increased risk for cardiovascular malformations associated with first trimester exposure to paroxetine (Paxil), data suggest that the absolute risk of major congenital malformations associated with first-trimester exposure to SSRIs is small.

There remain, however, residual concerns regarding the risk for preterm labor and neonatal withdrawal syndromes associated with SSRI use during pregnancy, particularly during the latter stages of gestation. The absolute risks for these types of obstetrical and neonatal difficulties remain unclear.

On the flip side of the risk-benefit decision, data on the impact of depression alone on the risk for major malformations and other obstetrical and neonatal outcomes also are inconclusive.

Some studies have used large administrative databases to examine the effects of antidepressants and depression on various obstetric and neonatal outcomes, but these studies have obvious methodologic limitations with respect to being able to confirm either exposure.

Separating out the effects of exposure to depression versus SSRI use during pregnancy is critical because these two factors must be weighed against each other and balanced in one direction or the other when patients and clinicians make decisions about the relative risks and benefits of taking a medication during pregnancy or assuming the risk of an untreated psychiatric disorder.

One recent study represents an important effort to delineate the differential effects of depression and SSRI exposure during pregnancy on obstetric and neonatal outcomes (*Am. J. Psychiatry* 2009;166:557-66). The prospective, multicenter study evaluated the relative impact of depression and SSRIs on minor physical anomalies, maternal weight gain, infant birthweight, pregnancy duration, and neonatal characteristics in 238 pregnant women who were divided into three groups: those with no SSRI, no depression; those with continuous or partial exposure to an SSRI during pregnancy; and those

with major depressive disorder (continuous or partial). As noted previously, while this question has been addressed in previous studies using large administrative databases, this is the first prospective study to do so.

Although limited by small sample sizes in the different groups, the study found no association between partial or continuous exposure to SSRIs and an increased risk in minor anomalies, or between depression and an increased risk of minor anomalies. No major malformations were observed in any group. These results are at variance with the landmark 1996 study reporting an increased risk for minor anomalies associated with first-trimester SSRI exposure (*N. Engl. J. Med.* 1996;335:1010-5). In this new study, there was also no association between depression or SSRI exposure and reduced maternal weight gain. Mean infant birth weights were

similar in the groups (doi:10.1176/appi.ajp.2008.08081170).

What was particularly noteworthy in this study was that, among women with continuous depression without exposure to an SSRI and those with continuous SSRI exposure, more than 20% of the infants were delivered preterm, compared with 4%-9% of the infants in the other groups. Hence, these results don't provide compelling data driving the risk-benefit decision with respect to the differential effects of either exposure to SSRI or depression, at least with respect to certain outcomes.

Finally, there were no differences associated with exposure to either continuous SSRI treatment or continuous depression with no SSRI and neonatal adaptation, including respiratory signs (with the exception of 5-minute Apgar scores) or admissions to the neonatal intensive care unit, after adjusting for maternal age, race, and gestational age.

In my view, the data from this study—although advancing the field and representing one more step forward in scientifically delineating the relative risks of antidepressants during therapy—don't let the clinician off the hook, because the clinician can neither discount the impact of exposure to the medicine or to the disorder. Therefore, patients and their doctors again are left making these individual decisions based on the patient's wishes, available reproductive safety data, and the severity of the underlying psychiatric disorder.

DR. COHEN directs the perinatal psychiatry program at Massachusetts General Hospital, Boston, which provides information about pregnancy and mental health at www.womensmentalhealth.org. He also is a consultant to manufacturers of SSRIs.



BY LEE COHEN, M.D.