



## The Devil Is in the Details: Not All AED-Associated Major Congenital Malformations Are Equal

### **Valproic Acid Monotherapy in Pregnancy and Major Congenital Malformations.**

Jentink JM, Loane MA, Dolk H, Barisic I, Garne E, Morris JK, de Jong-van der Berg LTW, EUROCAT Antiepileptic Study Working Group. *New Engl J Med* 2010;362(23):2185–2193.

**BACKGROUND:** The use of valproic acid in the first trimester of pregnancy is associated with an increased risk of spina bifida, but data on the risks of other congenital malformations are limited. **METHODS:** We first combined data from eight published cohort studies (1565 pregnancies in which the women were exposed to valproic acid, among which 118 major malformations were observed) and identified 14 malformations that were significantly more common among the offspring of women who had received valproic acid during the first trimester. We then assessed the associations between use of valproic acid during the first trimester and these 14 malformations by performing a case-control study with the use of the European Surveillance of Congenital Anomalies (EUROCAT) antiepileptic-study database, which is derived from population-based congenital anomaly registries. Registrations (i.e., pregnancy outcomes with malformations included in EUROCAT) with any of these 14 malformations were compared with two control groups, one consisting of infants with malformations not previously linked to valproic acid use (control group 1), and one consisting of infants with chromosomal abnormalities (control group 2). The data set included 98,075 live births, stillbirths, or terminations with malformations among 3.8 million births in 14 European countries from 1995 through 2005. **RESULTS:** Exposure to valproic acid monotherapy was recorded for a total of 180 registrations, with 122 registrations in the case group, 45 in control group 1, and 13 in control group 2. As compared with no use of an antiepileptic drug during the first trimester (control group 1), use of valproic acid monotherapy was associated with significantly increased risks for 6 of the 14 malformations under consideration; the adjusted odds ratios were as follows: spina bifida, 12.7 (95% confidence interval [CI], 7.7 to 20.7); atrial septal defect, 2.5 (95% CI, 1.4 to 4.4); cleft palate, 5.2 (95% CI, 2.8 to 9.9); hypospadias, 4.8 (95% CI, 2.9 to 8.1); polydactyly, 2.2 (95% CI, 1.0 to 4.5); and craniosynostosis, 6.8 (95% CI, 1.8 to 18.8). Results for exposure to valproic acid were similar to results for exposure to other antiepileptic drugs. **CONCLUSIONS:** The use of valproic acid monotherapy in the first trimester was associated with significantly increased risks of several congenital malformations, as compared with no use of antiepileptic drugs or with use of other antiepileptic drugs.

### **Intrauterine Exposure to Carbamazepine and Specific Congenital Malformations: Systematic Review and Case-Control Study.**

Jentink J, Dolk H, Loane MA, Morris JK, Wellesley D, Garne E, de Jong-van den Berg L; EUROCAT Antiepileptic Study Working Group. *BMJ* 2010;341:c6581.

**OBJECTIVE:** To identify specific major congenital malformations associated with use of carbamazepine in the first trimester of pregnancy. **DESIGN:** A review of all published cohort studies to identify key indications and a population based case-control study to test these indications. **SETTING:** Review of PubMed, Web of Science, and Embase for papers about carbamazepine exposure in the first trimester of pregnancy and specific malformations, and the EUROCAT Antiepileptic Study Database, including data from 19 European population based congenital anomaly registries, 1995–2005. **PARTICIPANTS:** The literature review covered eight cohort studies of 2680 pregnancies with carbamazepine monotherapy exposure, and the EUROCAT dataset included 98 075 registrations of malformations covering over 3.8 million births. **MAIN OUTCOME MEASURES:** Overall prevalence for a major congenital malformation after exposure to carbamazepine monotherapy in the first trimester. Odds ratios for malformations with exposure to carbamazepine among cases (five types of malformation identified in the literature review) compared with two groups of controls: other non-chromosomal registrations of malformations and chromosomal syndromes. **RESULTS:** The literature review yielded an overall prevalence for a major congenital malformation of 3.3% (95% confidence interval 2.7 to 4.2) after



exposure to carbamazepine monotherapy in the first trimester. In 131 registrations of malformations, the fetus had been exposed to carbamazepine monotherapy. Spina bifida was the only specific major congenital malformation significantly associated with exposure to carbamazepine monotherapy (odds ratio 2.6 (95% confidence interval 1.2 to 5.3) compared with no antiepileptic drug), but the risk was smaller for carbamazepine than for valproic acid (0.2, 0.1 to 0.6). There was no evidence for an association with total anomalous pulmonary venous return (no cases with carbamazepine exposure), cleft lip (with or without palate) (0.2, 0.0 to 1.3), diaphragmatic hernia (0.9, 0.1 to 6.6), or hypospadias (0.7, 0.3 to 1.6) compared with no exposure to antiepileptic drugs. Further exploratory analysis suggested a higher risk of single ventricle and atrioventricular septal defect. **CONCLUSION:** Carbamazepine teratogenicity is relatively specific to spina bifida, though the risk is less than with valproic acid. Despite the large dataset, there was not enough power to detect moderate risks for some rare major congenital malformations.

### Commentary

The researchers in these two published reports used a fresh approach to an old dilemma, resulting in the addition of valuable detailed information about the specific structural teratogenic risks associated with the use of valproic acid (VPA) and of carbamazepine (CBZ) during the first trimester of pregnancy.

Most antiepileptic drug (AED) pregnancy registries prospectively follow a cohort of women on AEDs and record outcomes. Comparisons are usually made with a group of healthy control women without epilepsy and on no AEDs and occasionally with women on other AEDs. These traditional pregnancy registry studies have limited power to detect increased risk for specific, individual major congenital malformations (MCMs), as most occur quite rarely. A recent extensive evidence-based review of published studies, the *Practice Parameter Update: Management of Women with Epilepsy—Focus on Pregnancy* report from the American Academy of Neurology (AAN) and the American Epilepsy Society (AES), concluded that it is possible that valproate (VPA) as monotherapy and probable that VPA as part of polytherapy contribute to the development of MCMs compared with women without epilepsy who are untreated with AEDs (1). However, because the majority of the women with epilepsy require treatment during the childbearing years, it is more helpful to the clinician to differentiate risks among AEDs. The AAN/AES practice parameter update concluded that it is highly probable that intrauterine first-trimester VPA monotherapy exposure has a higher risk of MCMs compared with women on CBZ and possible compared with phenytoin or lamotrigine. For the appropriate epilepsy syndrome, this conclusion would favor the use of CBZ over VPA but falls short of providing the detailed information needed for adequate counseling when treating women with epilepsy who plan to become pregnant or during their pregnancy.

What clinicians and patients really want to know is not only the magnitude of the risk for any type of MCM, but what types of MCM are more likely to occur. MCMs are defined as an abnormality of an essential anatomical structure present at birth that interferes significantly with function or that requires major intervention. Not all MCMs are similar in severity, degree of intervention required, or in their impact on quality of life. For example, studies have demonstrated the devastating impact on a child born with spina bifida as well as on the

entire family (2, 3). For specific MCMs, the AAN/AES practice parameter update was only able to conclude that VPA exposure probably contributes to neural tube defects (spina bifida) and facial clefts and possibly contributes to hypospadias. The conclusions for other AEDs were more limited: it is possible that CBZ contributes to posterior cleft palate, that phenobarbital contributes to cardiac malformations, and that phenytoin contributes to cleft palate (1). Although the association did not hold up in this the AAN/AES practice parameter update, previous smaller studies have raised the concern that CBZ could be linked to an increased risk of spina bifida.

These two studies by Jentink et al. employed a reverse approach by using 19 population-based registries of congenital anomalies from 14 countries, the European Surveillance of Congenital Anomalies (EUROCAT) antiepileptic-study database. The registries covered 3,881,592 live births and stillbirths in 1995 to 2005, with 98,075 births that involved an MCM. The investigators performed each study in two steps. For VPA, they first combined data from eight published studies to identify MCMs that may occur at a greater frequency than expected among offspring exposed to VPA during the first trimester. They identified 14 specific MCMs with a higher prevalence than in the EUROCAT reference group of 3.8 million. The investigators then conducted a population-based, case-control study to test their hypotheses, using the EUROCAT antiepileptic-study database. They compared the odds of exposure with VPA monotherapy among cases (for each of the 14 MCMs) with the odds of exposure in two groups of controls—a group with MCMs other than those under study and a group with MCMs associated with chromosomal abnormalities. The investigators went on to determine exposure to VPA monotherapy during the first trimester compared with the absence of exposure to AEDs and with exposure to an AED monotherapy other than VPA. The investigators used a nearly identical approach for CBZ monotherapy, combining data from 8 cohort studies to identify MCMs that may occur at a greater frequency than expected.

For the case-control study of VPA using the EUROCAT antiepileptic-study database, pregnancies involving spina bifida had an adjusted odds ratio (OR) of 12.7 (CI: 7.7–20.7) for VPA exposure versus no AED exposure. Five other MCMs had significantly increased adjusted ORs of 2.2 to 6.8 (vs no AED): atrial septal defect, cleft palate, hypospadias, polydactyly, and



craniosynostosis. Even more helpful to treating clinicians were the findings from comparisons with the other AED monotherapy regimens. The findings again showed a relative increase and were almost identical with the following two exceptions: the OR for craniosynostosis was no longer significantly increased in the VPA group, but the ventricular septal defect was increased in the VPA group. The adjusted OR for spina bifida and VPA exposure versus other AED monotherapy exposures was 5.7 (CI: 2.6–12.3).

For the CBZ analysis, five types of MCM were identified in the literature review and were considered *indications* to be tested in the case-control study. Based on an abstract report from the North American AED pregnancy registry, the authors decided to include the additional indication for the risk of cleft palate (4). For the case-control study of CBZ using the EUROCAT database, spina bifida was the only specific MCM significantly associated with exposure to CBZ monotherapy, with an OR of 2.6 (CI: 1.2–5.3) compared with nonchromosomal controls and 4.2 (CI: 1.5–11.2) compared with chromosomal controls. However, in the comparison for other AED monotherapies excluding VPA, exposure to CBZ showed no difference in the association with spina bifida, with an OR of 1.1 (CI: 0.4–3.6). There were differences when comparing directly with VPA monotherapy, with findings favorable for CBZ. The OR were significantly lower for CBZ compared with VPA exposure for spina bifida and for hypospadias. In contrast to other reports, the risk for isolated cleft palate and for cleft lip with or without palate was not higher in the CBZ monotherapy group compared with controls or other AEDs.

The remarkable finding is the consistency of a higher risk for MCMs for VPA echoed throughout several pregnancy studies around the world and now supported by a very different methodologic approach. These studies more clearly identify which MCMs are likely to occur with the use of VPA, includ-

ing in comparison with other AEDs as a group and to CBZ in isolation. However, the one finding of an association of spina bifida with first-trimester CBZ use should also be considered when counseling women of childbearing age, especially given the severity and impact of this type of MCM. The findings from this research group further underscore the message that by choosing to prescribe any AED other than VPA, the clinician is automatically lowering the risk for future pregnancies. This should be a guiding principle when treating adolescent girls and women with epilepsy.

by Page B. Pennell, MD

#### References

1. Harden CL, Meador KJ, Pennell PB, Hauser WA, Gronseth GS, French JA, Wiebe S, Thurman D, Koppel BS, Kaplan PW, Robinson JN, Hopp J, Ting TY, Gidal B, Hovinga CA, Wilner AN, Vazquez B, Holmes L, Krumholz A, Finnell R, Hirtz D, Le Guen C. Practice parameter update: management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): Teratogenesis and perinatal outcomes: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology* 2009;73:133–141.
2. Abresch RT, McDonald DA, Widman LM, McGinnis K, Hickey KJ. Impact of spinal cord dysfunction and obesity on the health-related quality of life of children and adolescents. *J Spinal Cord Med* 2007; 30(suppl 1):S112–S118.
3. Holmbeck GN, Devine KA. Psychosocial and family functioning in spina bifida. *Dev Disabil Res Rev* 2010;16:40–46.
4. Hernandez-Diaz S, Smith CR, Wyszynski DF, Holmes LB. Major malformations among infants exposed to carbamazepine during pregnancy (Teratology Society Abstracts). *Birth Defects Res A Clin Mol* 2007;79:357.



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