As a group, antiepileptic drugs (AEDs) are associated with an increased risk of major congenital malformations (MCMs) (1). Older AEDs are the best studied. Valproate (VPA) is consistently associated with an increased risk of MCMs including an increased risk of spina bifida (2). Phenobarbital (PB) exposure increases the risk of MCMs, including oral clefts (3). Although not consistent among published studies, some have found an increased risk of neural tube defects in association with carbamazepine (CBZ) therapy (4, 5). Less is known about the risk of MCMs in association with newer AEDs (6).

Better understanding of these agents' impact on the developing fetus is critical, as AEDs such as lamotrigine (LTG), levetiracetam (LEV), and topiramate (TPM) are being used in increasing numbers. Internationally, the epilepsy community has established different registries to address this issue. The North American Registry was established in 1997 (7). Women using AEDs for any indication are enrolled early in pregnancy. Gathering information on AEDs used for any indication is important, as many AEDs are used for multiple indications including headaches, pain, and mood disorders. Hopefully, with increasing enrollment, there will be enough numbers to do analyses that compare outcomes among the different indications.

Hernández-Díaz and colleagues (7) presented updated analyses from the North American Pregnancy Registry. The outcomes of interest were MCMs diagnosed before 12 completed weeks after birth. It is important to note that different registries have variable periods of follow-up. For example, the EURAP register collects information through 12 months of age (8). Excluded were 1) minor anomalies, birthmarks, deformities, and anatomic findings by ultrasound not identified by examining pediatrician, 2) complications of prematurity, 3) genetic disorders, and 4) chromosomal abnormalities. The investigators identified multiple reference groups: 1) the primary reference group was women exposed to LTG; 2) an internal reference group of pregnant women without epilepsy, not taking an AED who have been recruited among friends and family of AED exposed subjects; and 3) an external reference group of 206,224 infants born at Brigham and Women's Hospital in Boston, MA. Using the LTG group as an internal comparison provides advantages, including offering a direct comparison among AEDs and minimizing confounding.

The investigators used a multivariate logistic regression analysis. Risk ratios (RRs) and 95% confidence intervals (CIs) were estimated. Multiple confounders were controlled for,
including maternal age, race, education, alcohol use, cigarette smoking, periconceptual folic acid use, illicit drug use, chronic diseases, and calendar year. Interestingly, none of these confounders affected the RR of MCMs in the exposed groups; therefore, crude RRs were provided.

In the final analysis, 4,889 out of 5,667 women taking an AED as monotherapy during the first trimester were eligible, and there were 442 eligible women out of 479 in the internal comparison group. AEDs with enrolled subjects (in order of descending enrollment) were LTG (n = 1,562), CBZ (n = 1,033), LEV (n = 450), phenytoin (PHT) (n = 416), TPM (n = 359), VPA (n = 323), PB (n = 199), oxcarbazepine (OXC) (n = 182), gabapentin (GBP) (n = 145), zonisamide (ZNS) (n = 90), and clonazepam (CZP) (n = 64). The numbers for LEV and TPM were the highest among published reports. It is difficult to draw any formal conclusions from this analysis about OXC, GBP, ZNS, and CZP, as the sample sizes were all small. Further enrollment and data from other studies are needed to better understand the effects of these AEDs on MCM outcomes.

Consistent with other studies (1, 2, 4, 8), VPA was associated with the highest MCM risk (9.3 (95% CI: 6.4–13.0)). PB was associated with a risk of 5.5% (95% CI: 2.8–9.7). LTG was associated with the lowest risk (2.0 (95% CI:1.4–2.8). The risk of MCMs in LEV exposed pregnancies was 2.4% (95% CI: 1.2–4.3). The risk among TPM users was 4.2% (95% CI: 2.4–6.8). Compared with LTG, the RR of VPA was 9.0 (95% CI: 3.4–23.3), PB was 5.1 (95% CI: 1.8–14.9), LEV was 1.2 (95% CI: 0.6–2.5), and TPM was 2.2 (95% CI: 1.2–4.0).

As demonstrated in other studies, there was a dose effect of VPA (8). Among those pregnancies with MCMs, the median daily dose was 1000 mg, whereas the median daily dose for those without was MCMs was 750 mg. Regarding the other AEDs, there was no difference in median average daily dose among exposed infants with or without MCMs. This lack of a dose effect is in contrast with the EURAP register, which revealed a dose effect for CBZ, LTG, and PB (8). In this current analysis, the investigators did not provide either the sample sizes of different dose groups as presented in EURAP study. Therefore, it is difficult to directly compare these results.

When looking at specific malformations, VPA was associated with an increased risk of neural tube defects, hypospadias, and cardiovascular malformations. Cardiovascular malformations were more commonly found among PB-exposed pregnancies. The risk of oral clefts in association with different AEDs used as monotherapy is an evolving story. The North American Registry originally published a risk of 7.3 per 1,000 among LTG monotherapy users (9). With an increased sample size the reported risk is now 4.5 per 1,000 (95% CI: 2.0–8.8). Other studies have reported even lower risks (4, 6). Similar to other studies (6, 10) the reported risk for oral clefts in association with TPM (14 per 1,000 (95% CI: 5.1–31.0)) is higher than the expected risk in the general population. This reported increased risk of oral clefts led to the current FDA Category D status.

The investigators did an exploratory analysis of the effect of seizures on the risk of MCMs. Studies found the risk to be associated with AED use (1). However, it is very difficult to compare groups of women with epilepsy who are treated versus those who are not, as they likely have different disease severity. The results of this analysis found that AED groups with higher frequency of seizures during pregnancy had lower risk of malformations. Within those AED groups associated with higher MCM risk (VPA and PB), women who had no seizures during the pregnancy had a higher risk of MCMs compared with women who had seizures. These analyses were based on small number, and the results highlight that the impact of seizures—including seizure frequency and different seizure types on pregnancy outcomes—needs further study.

In this analysis of the outcome of MCMs among women exposed to different AEDs, monotherapy, VPA, and PB were associated with this highest MCMs. LTG and LEV were associated with the lowest risk. As in other studies, TPM was associated with an increased risk of oral clefts. Further study is needed to understand the effects of OXC, ZNS, CZP, and GBP as well as the impact of seizures on developing fetuses.

by Alison M. Pack, MD, MPH

References
American Epilepsy Society

Epilepsy Currents Journal

Disclosure of Potential Conflicts of Interest

**Instructions**

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. **Identifying information.**
   
Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. **The work under consideration for publication.**
   
   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. **Relevant financial activities outside the submitted work.**
   
   This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (EGF) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

   Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

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   Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.
Section #1 Identifying Information

1. Today’s Date: May 7, 2012
2. First Name Alison   Last Name Pack   Degree MD, MPH
3. Are you the Main Assigned Author? ☑ Yes ☐ No
   If no, enter your name as co-author:
4. Manuscript/Article Title: Are Newer Antiepileptic Drugs Associated with Improved Safety In Pregnancy Compared to Older Antiepileptic Drugs? and Zonisamide Should Be Considered a First-Line Antiepileptic Drug for Patients with Newly Diagnosed Partial Epilepsy
5. Journal Issue you are submitting for: 13.1

Section #2 The Work Under Consideration for Publication
Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)? 

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

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<th>Money to Your Institution*</th>
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* This means money that your institution received for your efforts on this study.
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* This means money that your institution received for your efforts.

** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

**Section #4  Other relationships**

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

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