



Preventing Birth Defects by Changing Maternal Antiepileptic Drug Therapy: We've Come a Long Way, Baby

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Declining Malformation Rates With Changed Antiepileptic Drug Prescribing: An Observational Study

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Objective: Changes in prescribing patterns of antiepileptic drugs (AEDs) in pregnant women with epilepsy would be expected to affect the risk of major congenital malformations (MCMs). To test this hypothesis, we analyzed data from an international pregnancy registry (European Registry of AEDs in Pregnancy [EURAP]). **Methods:** EURAP is an observational prospective cohort study designed to determine the risk of MCMs after prenatal exposure to AEDs. The Cochrane-Armitage linear trend analysis was used to assess changes in AED treatment, prevalence of MCMs, and occurrence of generalized tonic-clonic seizures (GTCS) over 3 time periods: 2000 to 2005 ($n = 4760$), 2006 to 2009 ($n = 3599$), and 2010 to 2013 ($n = 2949$). **Results:** There were pronounced changes in the use of specific AEDs over time, with a decrease in the use of valproic acid and carbamazepine and an increase in the use of lamotrigine and levetiracetam. The prevalence of MCMs with monotherapy exposure decreased from 6.0% in 2000 to 2005 to 4.4% in 2010 to 2013. The change over time in MCM frequency after monotherapy exposure showed a significant linear trend in the crude analysis ($P = .0087$), which was no longer present after adjustment for changes in AED treatment ($P = .9923$). There was no indication of an increase over time in occurrence of GTCS during pregnancy. **Conclusions:** There have been major changes in AED prescription patterns over the years covered by the study. In parallel, we observed a significant 27% decrease in the prevalence of MCMs. The results of adjusting the trend analysis for MCMs for changes in AED treatment suggest that changes in prescription patterns played a major role in the reduction of teratogenic events.

Commentary

Major birth defects continue to represent a major public health concern worldwide and today still occur in an estimated 3% of infants born in the United States.¹ Birth defects are the leading cause of infant mortality in the United States and convey significant financial and societal costs.¹ Ongoing nationwide efforts to minimize preventable birth defects include promoting pregnancy planning, increasing folic acid supplementation, improving access to prenatal care, and education on the need to avoid exposure to harmful substances including alcohol and tobacco. Minimizing exposure to potentially teratogenic prescription medications is a growing concern, with recent estimates indicating that up to 70% of women take at least one medication during the first trimester.² For women with epilepsy, it has long been recognized that use of antiepileptic drugs (AED) during pregnancy increases the risk of birth defects.³ However, discontinuation of AED prior to conception is rarely a safe option given the risks associated with uncontrolled seizures. Fortunately, multiple international registries of pregnancy in epilepsy have provided increasing clarity on safer

AED choices for use in women of childbearing potential. It is now 15 years since these studies first provided strong evidence that the rates of congenital malformations in infants exposed to AED in the first trimester were highest for valproic acid both as monotherapy and polytherapy.³ As information about the risks of individual AED use in pregnancy was disseminated, it was observed that neurologists prescribed valproic acid less frequently and at lower doses to pregnant women with epilepsy.⁴ While the expectation was that changes in prescribing patterns should improve pregnancy outcomes for women using AED, the impact on observed birth defects had to date not been definitively explored.

Tomson et al analyzed observational data from the European Registry of AEDs in Pregnancy (EURAP) encompassing over 21 000 pregnancies in order to determine whether changes in maternal AED use temporally correlated with reductions in observed rates of major congenital malformations in exposed infants. The study compared use of specific AED in the first trimester and birth defects from a baseline sample obtained from 2002 to 2005 with subsequent time frames of 2006 to




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2009 and 2010 to 2013. The most significant finding was a decline in the prevalence of major congenital malformations among monotherapy exposed infants from a baseline of 6% down to 4.4%. Among infants with polytherapy exposures in the first trimester, major congenital malformation rates were also reduced from a baseline of 8.3% down to 6.1%. Between 2002 to 2005 and 2010 to 2013, the percentage of women on a monotherapy AED regimen who took valproic acid in the first trimester of their pregnancy declined from 23.3% to 11.5%. There was a similar decline in monotherapy exposure to carbamazepine from 32.9% down to 17.4%. There was a proportional increase in use of monotherapy levetiracetam (1.4%-16.9%) and lamotrigine (26%-41.8%). Furthermore, there was a decline in first trimester exposure to polytherapy regimens containing valproic acid from an initial 35.8% of polytherapy exposures down to 22%. Initially, the most common combination AED regimen in the registry was lamotrigine and valproic acid, utilized in 39.1% of all first trimester polytherapy exposed pregnancies. By 2010 to 2013, the most popular polytherapy was lamotrigine with levetiracetam (40.9%). Outside of changes in AED prescription patterns, the authors did not find other factors that would have impacted the change in observed birth defect rates. There were no significant changes in maternal age or percentage of women with generalized versus localization-related epilepsy between the 3 time cohorts. There was some improvement in the observed rates of folic acid supplementation prior to conception and during pregnancy from a baseline of 32.9% up to 41.6%; however, this was insufficient to explain the improved rates in infant birth defects.


An important secondary finding relates to seizure control during pregnancy. Earlier reports from both EURAP and the North American AED Pregnancy Registry indicated that seizure control during pregnancy was poorer in women taking lamotrigine and levetiracetam compared to valproic acid.^{5,6} This may have discouraged some women and their providers from changing AED prior to conception, out of concern that increased generalized tonic-clonic seizures would be an unacceptable trade-off to reducing the teratogenic risk to the developing fetus. In the current EURAP report, however, this effect was not noted. Specifically, changes in AED prescribing practice were not temporally correlated with changes in seizure, with stable rates of 17% to 19.5% of women in the 3 cohorts reporting a generalized tonic-clonic seizure during pregnancy. Similarly, there was no escalation in percentage of women experiencing convulsive or nonconvulsive status epilepticus during their pregnancies, both of which impacted less than 0.5% of study participants. The authors did note that the majority of women in the study were referred by providers with a particular interest in management of epilepsy in women, and therefore, their care might not be reflective of that observed in the broader general population.

A 27% reduction in birth defects related to AED use is a cause for celebration. To provide some perspective, the efforts

of the US government to require fortification of grain products with folic acid in 1998 decreased observed neural tube defects by 35% and are widely acknowledged as a public health success story.⁷ Neurologists should be encouraged that the time spent counseling women with epilepsy about pregnancy and adjusting AED to minimize potential teratogenic risk while optimizing seizure control has proven benefits. As rewarding as it is to see effective translation of the data gleaned from years of international pregnancy registry data collection into meaningful improvement in clinical pregnancy outcomes, there is still more work to do. While recognizing that valproic acid may be the most effective treatment for percentage of women with intractable generalized epilepsy, we must continue to strive to limit exposure to this drug in women of childbearing potential. We can continue to improve utilization of folic acid supplementation prior to conception. We need to continue to work to ensure that prevention of birth defects from AED exposure is not just a success story for women under the care of an epilepsy expert but for all women prescribed an AED for any medical indication by a neurologist, psychiatrist, or primary care provider.

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