



EPILEPSY. UPDATE.

A CASE SERIES

A CME Activity

Long-term Consequences of AED Exposure During Pregnancy

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CONTENTS

- 1 Case Studies 1 and 2
- 2 FAQs
- 3 Self-Assessment Quiz and Evaluation

Long-term Consequences of AED Exposure During Pregnancy

A long-standing concern of women with epilepsy and their physicians has been the potential deleterious effects of AEDs on the developing child. For years we have been forced to speak in generalities about this issue, but recent information, while incomplete, allows us to advise our patients with a bit more confidence. The following cases emphasize several important issues and can provide a framework with which to guide your choices.

Case 1

Samantha is a 28-year-old right-handed woman who has a diagnosis of juvenile myoclonic epilepsy (JME). She has been well controlled on extended-release valproic acid since her diagnosis at the age of 17, when she had a convulsion early one morning after a night of poor sleep and moderate alcohol use. In retrospect, she had had morning myoclonus for about a year. She was started on valproic acid at that time and has since been without convulsions and only with rare myoclonus in the setting of excessive alcohol use or medication noncompliance. She is otherwise healthy and has expressed a desire to get pregnant in the next few years. She has read that valproic acid may not be the best medication to take during pregnancy and is interested in changing medications.

Case 2

Jill is a 35-year-old woman with medically refractory temporal lobe epilepsy. Her seizures began at the age of 14 with a staring spell followed by a convulsion. Typical events are now characterized by an aura of doom and impending sadness followed by right hand automatisms and staring, lasting approximately 1 to 2 minutes. Over the years, the patient has noted that she can recognize when she has had a seizure because she finds herself in a secluded area, apparently walking away to hide. She has refused surgery despite having 8 to 10 complex partial seizures each month. She has a high

level administrative job. She recently got married and is interested in having children as soon as possible, but is concerned about the effects on the development of her baby of all the medications that she must take. She is on moderately high levels of lamotrigine (LTG) and levetiracetam (LVT).

FOLLOW-UP

Samantha was changed to LTG, conceived 5 months later, and did well with monthly serum LTG measurements and adjustments until month 6 of her pregnancy. At that time, she had a cluster of myoclonic jerks, but out of fear for effects on the baby, did not take additional LTG or lorazepam as suggested by her neurologist. Her LTG blood level was slightly low on admission to the hospital for her delivery. She otherwise did well and had a healthy baby boy who has reached all developmental milestones. Jill had monthly serum level measurements and did well throughout the entire pregnancy with slight medication modifications and delivered a healthy baby boy, also with normal developmental milestones.

DISCUSSION

There are over 1 million women with epilepsy of reproductive age in the United States and there are over 20,000 children each year born to women with epilepsy who are taking AEDs. These women are one of the few groups of young people who require chronic, potentially teratogenic medications in their reproductive years. Therefore, the first question one should ask about a woman of reproductive age on an AED is: 'Does this woman really need the medication or can she safely come off it?'

Overall, seizure control is paramount and, other than a few, most AEDs can reasonably be continued during pregnancy. The goal is to be on one AED at the lowest possible dose to control seizures to afford the best outcome for the mother and her offspring. There are no studies addressing the effectiveness of pre-conception counseling for women with epilepsy, but they should be placed on an appropriate AED regimen before conceiving. Ideally, the selected AED should control seizures and have no identified adverse effects on the offspring.

Information about these issues comes from pregnancy registries and research studies that follow women and their offspring throughout pregnancy and for several years thereafter. The main pregnancy registries are

based in North America, the United Kingdom, Europe, and Australia. Prospective research studies are currently underway looking at cognitive outcomes in children born to women with epilepsy on AEDs.

Table 1. Rate of major congenital malformations (MCMs) with AEDs.
(Ranges represent various registries and studies.)

Antiepileptic Drug	Rate MCMs (%)
Baseline population (no AED)	1-2%
Women with epilepsy on no AEDs	1.9%
Carbamazepine	2.5-4.9%
Lamotrigine	2.9-3.2%
Levetiracetam	2-4%
Oxcarbazepine	5%
Phenobarbital	6.5%
Phenytoin	3.4-10.7%
Topiramate	4.8%
Valproic acid	6-17%
Zonisamide	7.7%

Baseline rates of major congenital malformations (MCMs) in the general population range from 1% to 2%, and women with epilepsy on AEDs have a MCM rate of from 2% to 17% (Table 1). The pregnancy registries report slightly varying rates of MCMs on different AEDs, but overall, valproic acid (VPA) is to be avoided during pregnancy. The most common AED-associated MCMs are orofacial clefts (Figures 1 and 2), midline heart defects, and neural tube defects (NTDs), such as spina bifida (Figures 3 to 5). Valproic acid has been associated with NTDs, phenobarbital with cardiac

Figure 1.



Bilateral complete cleft lip/palate. (Courtesy of Dr John Mulliken, Department of Surgery, Children's Hospital, Boston, MA.)

Figure 2.



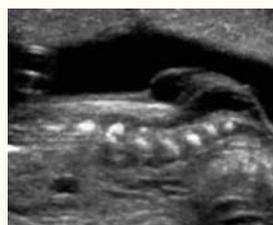
Right unilateral incomplete cleft lip/palate. (Courtesy of Dr John Mulliken, Department of Surgery, Children's Hospital, Boston, MA.)

Figure 3.



Spina bifida (e.g., lumbosacral meningocele). (Courtesy of Dr Joseph Madsen, Department of Neurosurgery, Children's Hospital, Boston, MA.)

Figure 4.



Lumbosacral meningocele as viewed through ultrasound. (Courtesy of Dr Judy Estroff, Department of Radiology, Children's Hospital, Boston, MA.)

Figure 5.



Lumbosacral meningocele as viewed through magnetic resonance imaging (MRI). (Courtesy of Dr Judy Estroff, Department of Radiology, Children's Hospital, Boston, MA.)

malformations and cleft palate, and carbamazepine with cleft palate and NTDs. While there are only small numbers of offspring studied on the newer AEDs, they seem to have a MCM rate just slightly higher than that of the general population. Of the newer AEDs, LTG is well studied with a MCM rate of about 3%, as noted in over 1200 pregnancies. The North American Pregnancy Registry reported a 25-fold higher rate of cleft palate and lip as compared to the general population, but subsequent population-based investigations showed that this specific malformation is not increased in users of LTG. There is no information at present regarding MCMs after in utero exposure to pregabalin.

AED polytherapy has a higher rate of MCMs than monotherapy, and especially if the combination includes VPA. Overall, AED monotherapy appears to carry the

Continued on page 3 (Reverse side)

same MCM risk as no treatment. Minor congenital malformations are not always noted because they are difficult to detect at birth.

Cognitive effects of fetal exposure to AEDs are an important area of active research for which we have no final conclusions because of the long follow-up times required. Valproic acid, phenytoin, and phenobarbital are the three AEDs reproducibly shown to have adverse cognitive outcomes. Older reports showed that VPA exposure increased the risk of lower IQ. While there were significant confounders to these studies, such as maternal IQ, social environment, and length to follow-up, recent studies have corrected for these factors, showing that verbal IQ is lower, particularly with third trimester exposure.

Phenytoin is associated with fetal hydantoin syndrome, which is characterized by a low IQ, microcephaly, and characteristic facial features. Phenobarbital also is associated with a lower verbal IQ. Carbamazepine has not been shown to be associated with adverse cognitive outcomes. There have been no significant cognitive effects seen with the newer AEDs, but the numbers of enrolled patients are few and studies are still ongoing. The cognitive outcomes of AED exposure of infants through breast feeding have not been adequately evaluated. A small amount of medication gets into the breast milk; the more highly protein-bound medications are excreted in very small, almost undetectable, quantities into the breast milk. Seizures themselves are potentially harmful to the offspring. Generalized seizures during pregnancy can cause uterine hypoperfusion, fetal bradycardia, and acidosis, as well as trauma. Complex partial seizures may have some of these risks, but simple partial seizures likely have no consequence on blood flow to the uterus or developing fetus. One to two generalized seizures will likely have no significant effect on fetal development, but more may lead to obstetrical and fetal complications such as intrauterine growth retardation and premature labor. Status epilepticus

in pregnancy occurs about 1% to 2% of the time and almost all offspring survive. For more than 60% of women with epilepsy, seizure control is similar to that before pregnancy if they comply with their prescribed medications. Across many studies, approximately 3% to 5% of women with epilepsy have a seizure in the peripartum period. Remaining seizure-free during pregnancy outweighs the risks of AED use in pregnancy.

FAQs Frequently Asked Questions

When should an AED be changed to avoid adverse outcomes on the offspring?

Before conception is the best time to change an AED, if possible. Many physicians consider reproductive issues before starting a woman with epilepsy on AEDs, but for women considering starting a family, many ongoing medication regimens can be optimized to minimize adverse effects on the offspring. Unfortunately, many women do not see an obstetrician until the end of the first trimester, at which point all major organ systems are formed and major congenital malformations (MCMs) will already have taken place. Ideally, the patient and her neurologist should discuss her reproductive plans months to years in advance of conception. Suddenly stopping or changing AEDs during pregnancy is often difficult, given the risk for seizures. The key to a healthy pregnancy in a woman with epilepsy is compliance with physician visits and measuring monthly serum AED levels. Only in rare, select cases would discontinuing VPA be a reasonable option during pregnancy. If VPA is the only medication that has controlled seizures, it may be unreasonable to change it.

What factors other than AEDs increase risk for MCMs?

Birth defects result from genetic and environmental influences. A family history of MCM increases the risk of a child with a MCM. Genetic counseling may be considered in some women with epilepsy with a family history of a MCM and on an AED. Other medical problems, such as obesity and diabetes, are known to increase the risk of MCMs, as do alcohol, tobacco, and illicit drugs.

When and how should I suggest folic acid to prevent MCMs?

Folic acid intake during early pregnancy significantly reduces the risk of neural tube defects (NTDs). Regular prenatal vitamins contain about 400 µg of folic acid. In Europe, many epileptologists recommend 5 mg for women with epilepsy, but the optimal dose of supplemental folic acid in women with epilepsy on AEDs has not been formally studied. Many AEDs are known to lower serum folic acid levels, but folate supplementation in animals exposed to phenytoin did not decrease embryotoxicity. In addition, serum folate levels are the same in children with NTDs and controls. Recommendations for folic acid use in the U.S. are therefore largely arbitrary and range from 1-4 mg per day. Folic acid is not harmful at these doses and there is a theoretical benefit.

Where can I direct women for information about pregnancy registries for women with epilepsy?

Information is available from the Food and Drug Administration Office of Women's Health at <http://www.fda.gov/womens/registries/>, through the Epilepsy Foundation www.epilepsyfoundation.org, the Epilepsy Project www.epilepsy.com/epilepsy/links_pregnancy, and through Massachusetts General Hospital www.aedpregnancyregistry.org; 1-888-233-2334.



ABOUT THE AUTHOR

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KNOWLEDGE GAP ADDRESSED

Current practice recommendations in the general neurology community are limited and need to be supported. This activity will make the general neurologist more aware of the complex issues involved in treating patients with epilepsy and be able to apply the appropriate resources.

LEARNING OBJECTIVES

- Evaluate risk of AEDs for successful pregnancies in women with epilepsy and manage these appropriately to enhance quality of life.
- Recognize that treatments may have consequences for women's ability to bear healthy children and how best to address these consequences.
- Given that women with epilepsy want to have children as part of a normal life, determine the best ways to address the issue of adequate seizure control while minimizing risk to the fetus.
- Recognize the barriers that women with epilepsy may encounter in an effort to sustain an optimal quality of life.

TARGET AUDIENCE

General neurologists, nurses, and other healthcare professionals involved in the care of patients with epilepsy.

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Opinions expressed with regard to unapproved uses of products are solely those of the faculty and are not endorsed by the American Epilepsy Society or any manufacturers of pharmaceuticals.

FACULTY DISCLOSURES

Drs. Austin, Bertram, Donner, Gilliam, and Goodkin – have indicated they have nothing to disclose.

Dr. Cascino – Honoraria: AAN, AES; Contracted Research: NeuroPace; Grants: Epilepsy Phenome Genome Project.

Autumn M. Klein, M.D., Ph.D. – Honoraria: *The New England Journal of Medicine*, Headache Cooperative of New England, Massachusetts Medical Society, PriMed.

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Fred Lado, M.D., Ph.D. – has indicated he has nothing to disclose.

EDITORIAL REVIEWERS

Paul Shea and Kay Sloves – have indicated they have nothing to disclose.

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To obtain credit you must read the newsletter and answer the Self-Assessment Quiz and CME Evaluation Survey. Mail them to:

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A CME certificate will be sent to you within 3 weeks should you obtain a grade of 75% (3 of 4 answers correct) or more.

1. Which one of the following newer antiepileptic drugs (AEDs) has the most outcome data on the rate of congenital malformations in offspring born to women taking these medications?

- a. Levetiracetam
- b. Lamotrigine
- c. Topiramate
- d. Zonisamide

2. True or False, AED monotherapy at the lowest possible dose allows the best possible outcome for children born to women with epilepsy.

3. If possible, which AED should be avoided in pregnant women and women of child bearing age?

- a. Lamotrigine
- b. Levetiracetam
- c. Carbamazepine
- d. None of the above

4. True or False, women with epilepsy taking valproic acid have been shown to give birth to offspring with a higher rate of adverse cognitive outcomes compared to the control population.

Please circle the correct answers:

1. a b c d 2. T F 3. a b c d 4. T F

CME EVALUATION SURVEY

Complete the Evaluation (please be sure to indicate how long it took to complete this activity). The amount of time you attest to on this evaluation will be reflected on your certificate.

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Was the activity effective in meeting the identified learning objectives?

SCALE: 5=Excellent 4=Very Good 3=Satisfactory 2=Fair 1=Poor

Evaluate risk of AEDs for successful pregnancies in women with epilepsy and manage these appropriately to enhance quality of life.

5 4 3 2 1

Recognize that treatments may have consequences for women's ability to bear healthy children and how best to address these consequences.

5 4 3 2 1

Given that women with epilepsy want to have children as part of a normal life, determine the best ways to address the issue of adequate seizure control while minimizing risk to the fetus.

5 4 3 2 1

Recognize the barriers that women with epilepsy may encounter in an effort to sustain an optimal quality of life.

5 4 3 2 1

2. Questions Relating to Your Intent to Make Practice Changes

Based upon your participation in this CME activity, please answer the following:

Did the information in this activity increase your ability to counsel your female patients who have epilepsy and wish to have children?

YES NO

Did the information in this activity increase your confidence in discussing relative risks of AEDs to successful pregnancy for your patients?

YES NO

Will the information in this newsletter alter or influence the discussions that you have with women of childbearing age about selecting medications when trying to achieve adequate seizure control?

YES NO

Can we contact you in a follow-up survey to measure the impact of this educational intervention?

YES NO

3. Based on your participation in this CME activity, which of the following strategies do you now plan to use in your practice that you haven't used before? (Check all that apply)

I will counsel my female patients on achieving optimal seizure control with minimal pregnancy risk.

I will recommend AEDs with lower incidences of major congenital malformations for my female patients who wish to become pregnant.

I will consider AED titration to a minimum effective dose to achieve seizure control in my female patients to minimize potential risk to a developing fetus.

I will advise my female patients about the risk of not achieving adequate seizure control during pregnancy versus the potential adverse effects of AEDs.

4. Are there any barriers to implementing these strategies? (Check all that apply)

- Time
- Cost
- Staffing
- Institutional treatment algorithm differences
- Formulary
- Patient adherence
- Other: _____

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Just Right Too Advanced Too Basic

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If trade names were used, trade names of all products discussed were used.

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Yes	No
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8. Based upon the topic of this case series, "Long-term Consequences of AED Exposure During Pregnancy," please list additional topics that you would like to hear about that will better help you manage your patients.

1.) _____

2.) _____

9. Are you interested in the following modalities of learning? (Check all that apply)

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Thank you for your participation.