



## Seizures, AEDs and Pregnancy: A Dangerous Combination

The conversation and the clinical decision-making require finesse when these three coincide.

**A**lthough neurologists encounter many serious dilemmas in clinical care, perhaps one of the most stressful occurs when treating a woman with epilepsy who is planning on becoming pregnant or one who is already pregnant. There are many issues that cause concern. Seizures during pregnancy can injure the mother as well as the unborn child. The use of seizure medications during pregnancy can cause congenital malformations. In addition, AEDs during pregnancy have been reported to cause cognitive problems in the child, including a decrease in IQ. Should mothers with epilepsy breastfeed? How should a new mom with seizures care for her baby? These are only some of the issues that the neurologist faces in this situation. Let's take a look at each.

### Concerns Before Pregnancy

It is reasonable to re-evaluate the medication regimen of women with epilepsy prior to pregnancy, if possible. For instance, if a woman has been seizure-free for more than two years, it might be possible to discontinue medications *before she becomes pregnant*. If there are concerns about the diagnosis itself, such as the possibility of non-epileptic seizures, pre-pregnancy EEG monitoring may be useful. EEG monitoring may identify a more specific diagnosis. This information may lead to discontinuation of the AED, or perhaps a change in medication to one that would better control the patient's ictal events.

Abrupt discontinuation of AEDs is not recommended unless there is com-



PELLING evidence to support this decision. Many women, in an effort to minimize teratogenicity, stop taking their AEDs once they discover that they are pregnant. This is potentially very serious, and case reports have described women who experience an acute worsening of seizures or even status epilepticus as a result.

Of course, not all women with epilepsy are planning to become pregnant. In fact, for some the biggest concern may be pregnancy prevention in a way that minimizes interactions with their AED. Although many contraceptives are available, there are issues that women with epilepsy must know regarding oral contraceptives. The hormones in these contraceptives are broken down in the liver via the hepatic P450 system. Many AEDs are also broken down by this pathway. In fact, several of the AEDs *accelerate* the metabolic rate of the P450 system (called enzyme induction). As a result of the

increased metabolism, any other medication that is broken down by the P450 system, when taken with one of these AEDs, will be broken down more rapidly.

In short, certain AEDs will decrease the amount of hormone available for contraception: these AEDs lessen the effectiveness of certain oral contraceptives (see Table 1).

### Concerns During Pregnancy

For women with epilepsy who are planning on becoming pregnant, the best time for a visit to the neurologist occurs long before she is ready to start (or add to) her family. Again, many issues need to be discussed. Often, the majority of the discussion focuses on two issues: seizures and the potential teratogenicity of AEDs. It is important to remember that the risk of seizures during pregnancy outweighs the risk of medication adverse effects.

Of these concerns, the primary responsibility is to avoid seizures during pregnancy. Seizures can not only injure the mother but the developing baby as well. Seizure control, therefore, must be maintained throughout the pregnancy. Studies have shown that seizure patterns do not change during 60 to 70 percent of pregnancies. In 15 to 30 percent, seizures may worsen. If this occurs, the dose of medications must be adjusted to improve seizure control.

One possible explanation for a worsening of seizures during pregnancy is a decrease in AED levels. There are many factors that could account for a fluctuation in serum AED levels. During pregnancy, plasma protein binding decreases. The total levels of highly protein-bound

**Table 1. AEDs and Their Interaction with Oral Contraceptives**

Known Effect on Oral Contraceptives	No Known Effect on Oral Contraceptives
<ul style="list-style-type: none"> <li>• carbamazepine (Tegretol, Carbatrol)</li> <li>• felbamate (Felbatol)</li> <li>• oxcarbazepine (Trileptal)</li> <li>• phenobarbital</li> <li>• phenytoin (Dilantin, Phenytek)</li> <li>• topiramate (Topamax)</li> </ul>	<ul style="list-style-type: none"> <li>• gabapentin (Neurontin)</li> <li>• lamotrigine (Lamictal)</li> <li>• levetiracetam (Keppra)</li> <li>• tiagabine (Gabitril)</li> <li>• zonisamide (Zonegran)</li> </ul>

**Table 2. AEDs and Teratogenicity**

Known Effect: Pregnancy “D”	Unknown Effect: Pregnancy “C”
<ul style="list-style-type: none"> <li>• carbamazepine (Tegretol, Carbatrol)</li> <li>• ethosuximide (Zarontin)</li> <li>• phenobarbital</li> <li>• phenytoin (Dilantin, Phenytek)</li> <li>• valproate (Depakote, Depakene)</li> </ul>	<ul style="list-style-type: none"> <li>• All others</li> </ul>

medications, such as phenytoin, may decrease as a result; however, the free fraction of the drug may remain relatively unchanged. For these medications, monitoring *both* the free fraction and total amount of serum medication may be needed in order to maintain consistent serum levels throughout the pregnancy. In this way, seizure control can be maintained.

Decreases in AED levels can also occur as a result of increased hepatic metabolism or increased renal clearance as well. For instance, the metabolism of lamotrigine can increase by as much as 300 percent!<sup>1</sup> This effect seems to stabilize by about the 32nd week of gestation; however, monitoring levels will be needed in order to carefully adjust dosing of medication to maintain consistent serum levels.

The second issue is teratogenicity. The older antiseizure medications are pregnancy category “D”: there is a known risk when used during pregnancy. However, the benefits of their use may outweigh these risks during pregnancy. The newer

AEDs are pregnancy category “C”: the risks of their use during pregnancy are unknown (see Table 2).

When confronted with these choices, most women are understandably concerned. They are required to make a choice between medicines that are known to cause problems versus ones for which the risk is unknown. Of the AEDs, valproate has consistently been shown to cause congenital malformations based on information from pregnancy registries in the United States, United Kingdom, Sweden and Finland.<sup>1</sup> Many physicians agree that this medication should be avoided, if possible during pregnancy.

How to best counsel a woman regarding the other AEDs is less clear. In general, birth defects occur at a rate of about two to three percent. When a woman is taking one AED, that risk is double (four to six percent).<sup>2</sup> If the woman is taking two AEDs, the risk is threefold (six to nine percent). For women on multiple AEDs, the risk is even higher—some studies have shown up to 15 percent

when a person is taking three or more AEDs during pregnancy. An attempt to minimize medications before pregnancy might help to reduce this risk. Though never proven with a randomized study, administration of folate (0.4 to 4.0mg per day) may also help to reduce the risk of congenital malformations, and has led to the general recommendations to take folic acid before and during pregnancy.

In an effort to better understand the effects that these medications have on the developing baby, many countries have started pregnancy registries. These are designed to determine the rate of congenital malformations in babies who are born to women with epilepsy. In addition, there is an ongoing study headed by Kimford Meador in which the IQs of the parents *and* children are being carefully reviewed. This research may help us to better understand which medications affect the later cognitive development of children who were exposed to AEDs *in utero*. Ideally, this information will soon be available to all neurologists, hopefully allaying some of these concerns.

### Labor and Delivery

Seizures do sometimes occur during labor and delivery. Some estimate a seizure risk of one to two percent during labor and delivery, and another one to two percent in the early postpartum period. Other sources describe a seizure risk of up to five percent during this time.<sup>1</sup> The increase in seizures in part may be related to changes in serum levels of AEDs that occur towards the end of the pregnancy.

### Breastfeeding

Many new mothers are concerned that these medications may cross over into the breast milk. Although the concentration that crosses over is low for most AEDs, there are a few exceptions. For instance, phenobarbital can cross over in a ratio of 0.7 to 0.9 compared to serum.<sup>2</sup> This may lead to neonatal sleepiness, poor feeding and “failure to thrive.” If this occurs, give

consideration to an alternative form of neonatal nutrition.

Lamotrigine is secreted into breast milk, and may result in concentrations *higher* than that which occurs in maternal serum. However, the newborn also breaks down this medication quicker than an adult. It remains unclear whether this observation leads to a clinically significant problem. Overall, women with epilepsy are encouraged to breastfeed as the potential benefits outweigh these concerns.

### Care for the Newborn

Because new babies require much attention and frequent feeding, new moms are likely to become sleep deprived, which can in turn lead to a worsening of seizures. If possible, the new mother should work out a feeding schedule with her significant other. One possibility is that the partner be involved in some of

the feedings, using stored breast milk or formula. This would allow the new mom a change to obtain an adequate amount of rest, hopefully avoiding this seizure trigger.

Newborn infants should never be bathed in a bathtub. Mothers with an active seizure disorder should discuss this with their doctors: if a seizure were to occur during bathtime and the mother lost awareness, even briefly, the baby could drown. New moms with epilepsy should feed their babies while sitting on the floor or in the middle of the bed. Here again, if a seizure were to occur, there is less chance that the baby would be dropped and therefore injured.

### Conclusions

Women with epilepsy who are planning on having a baby should talk with their doctors as early as possible. Ideally, this

discussion would occur long before the person was actively trying to conceive. In this way, the optimal medication, dose and treatment plan can be discussed. Frequent medication levels and subsequent dose adjustments can be reviewed. Concerns about labor and delivery, breastfeeding and new infant care should be carefully addressed. The goal is to optimize the care of both the woman with seizures, to minimize fetal exposure to medications, and to prevent injury to the newborn child. **PN**

1. Kalviainen R, T Tomson. "Optimizing treatment of epilepsy during pregnancy." *Neurology* 2006;67:S59-S63.

2. Yerby MS and SD Collins. "Pregnancy and the Mother." In: *Epilepsy: A Comprehensive Textbook*, edited by J Engel and TA Pedley. Lippincott-Raven Publishers, Philadelphia 1997.

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