

Rational Management of Women with Epilepsy Throughout Pregnancy

New evidence allows neurologists to more confidently answer the tough questions from women with epilepsy who wish to become pregnant.

One of the most challenging situations a neurologist can face is treating women with epilepsy who are planning to start a family. Because seizures can cause problems during pregnancy, seizure control—at least for generalized tonic-clonic seizures—must be maintained. The risk of seizures must be balanced with the risk that medications may cause birth defects. Unfortunately, despite many reports from pregnancy registries around the world, there is still no answer to the question “What anti-seizure medication is safe during pregnancy?” In addition, very few studies try to address the issue of seizures during pregnancy. What is the risk of seizures during pregnancy? Are certain women at higher risk for experiencing a worsening of seizures while pregnant? Although many questions remain unanswered, recent studies are starting to shed light on this subject.

The Problem

Several previous installments of “Epilepsy Essentials” have addressed women’s issues and epilepsy. Women pose many important questions about pregnancy: Can I get pregnant? If I do, what will happen to the baby if I have a seizure? What kinds of problems will the baby have due to the exposure to medications during pregnancy? Can I breastfeed?

Finally, and in many ways most troubling, is the question: Which medication is safest during pregnancy?

Most of these questions lack a clear answer. One of the reasons for this is that medication trials necessarily exclude pregnant women. The reason is simple: During a study, the group that receives the study treatment must be as “alike” as possible. In short, either all of the patients would need to be pregnant, or none of them can be. Excluding pregnant women, however, means that physicians end up having little or no information with which to answer these very important questions. The answer, “I don’t know,” though accurate, is not an easy one for potential parents to accept.

What the Studies Tell Us (and What They Don’t)

Several recent studies that have been published try to answer at

least some of these questions. Previous installments of “Epilepsy Essentials” have touched on problems such as impaired fertility in women with epilepsy (June 2005), the effects of antiseizure medications on bone health (April 2005 and an update in August 2008), and the teratogenicity of antiepileptic drugs (October 2008, all articles available online at practicalneurology.net). One question that has not been addressed is, “How do seizures during pregnancy affect the developing baby?”

Until very recently, this question has been difficult to answer. Many doctors used to answer the question with the very vague “rule of thirds”: “About one-third of women experience no change in their seizure frequency, one-third get worse,¹ and one-third get better.”

The European Registry for Antiepileptic Drugs and Pregnancy (EURAP) provides physicians with a much more specific and reliable response.² Published in 2006, the study showed that about two-thirds of women experience no change in their seizure frequency (the actual number is 58.3 percent; Figure 1). Of the remaining women, about 15 percent experience a worsening (15.9 percent), while 17 percent experienced more seizures (Figure 1).

With 58.3 percent of women seizure-free throughout their pregnancy, this finding is similar to the number that the Australian Registry published: 50.3 percent of women were seizure-free during their pregnancy.³ Moreover, the Australian registry showed that the best predictor that a woman would remain seizure-free during pregnancy was that she had been seizure-free in the year before becoming pregnant.^{3,4}

It should be noted, however, that in EURAP, the rate of seizure occurrence was not based on a pre-pregnancy baseline. Instead, because women are allowed to enroll up to 16 weeks pregnant, a seizure count of the first trimester is made. The second and third trimesters are then compared to the first trimester. The assessment of “worsening seizures” means that there was an increase in seizures during the later part of pregnancy. This may be an important distinction, especially since the serum levels of some anti-seizure medications can decrease through the pregnancy.

Table 1. In EURAP, 78.7% of women remained on monotherapy throughout pregnancy. This data shows the AED to which a second agent was added.

Initial AED	Percentage in whom 2nd AED added
Valproate	1.4
Carbamazepine	1.8
Polytherapy	3.0
Phenobarbital	3.4
Lamotrigine	4.6
Oxcarbazepine	4.9
Phenytoin	6.8
Other monotherapies	7.1

Fig 1a. Summary of Data from EURAP 2006

Total pregnancies: 1,956
58.3% were seizure-free throughout pregnancy; 78.7% remained on monotherapy
 15.9%: seizure frequency decreased 17.1%: seizure frequency increased; Seizure increased *equally* in 2nd & 3rd trimesters
 It is not know if the increase was:
 • Due to medication non-compliance
 • Due to decrease in serum AED levels

Fig 1b. Summary of Data from APR, 2008

Total pregnancies: 841
50.3% were seizure-free throughout the pregnancy

What Factors Might Contribute to Worsening of Seizures During Pregnancy?

When it comes to antiseizure medications and serum concentration of the drug during pregnancy, physicians have very little information. We know that many physiological changes occur during pregnancy. For instance, protein binding changes as the pregnancy progresses. This means that free level of the drug decreases.⁵ Because the body only “recognizes” the free fraction, if there is a lower free level the possibility of having more seizures goes up. Of course, this would have the greatest impact on highly protein bound medications, such as phenytoin. Perhaps this is one reason that up to 7.1 percent of women initially taking phenytoin monotherapy needed a second agent during pregnancy in order to control their seizures (Table 1).

The clearance of drugs during pregnancy can change. When clearance increases, the serum concentration of the drug decreases. How exactly these physiological changes during pregnancy affect each AED remains unclear. However, there is growing evidence that the clearance of both lamotrigine, oxcarbazepine, and levetiracetam increases significantly.^{4,6-8} For lamotrigine, clearance increases by as much as 300 percent!⁷ Oxcarbazepine levels drop to 72 percent in the first trimester, 74 percent in the second trimester, and 64 percent of pre-pregnancy values in the third trimester.⁶ Levetiracetam concentration/dose ratio decreased by 50 percent, and then returned to pre-pregnancy baseline within weeks of the baby’s birth.⁸ Unfortunately, physicians do not have the same kind of data for all available antiseizure medications.

If the serum concentration of antiseizure drug decreases during pregnancy, seizures may occur. Consider lamotrigine. During pregnancy, lamotrigine clearance can as much as triple, resulting in low serum levels. In EURAP, seizure frequency increased in 45-75 percent of women taking lamotrigine.² Unfortunately, EURAP does not collect serum antiseizure medication levels. In other words, the confirmatory evidence that decreased serum levels of lamotrigine are responsible for the seizure increase is lacking.

Another issue that may contribute to worsening seizures during pregnancy is compliance. Many women, in an attempt to minimize teratogenicity decide to stop (or reduce) the dose of antiseizure medications. How often this actually occurs is unclear. Because the pregnancy registries do not collect serum AED levels, confirmatory evidence of non-compliance is again lacking.

Conclusions

Women with epilepsy who plan to become pregnant face several challenges. The first is to maintain the (hopefully already) good seizure control that they had achieved before conceiving. In doing so, she will have the greatest likelihood of staying seizure-free throughout pregnancy. If seizure freedom can be achieved using a single AED, hopefully at a low dose, the baby faces the fewest risks. The baby will not be affected by seizures and will face the lowest risk of teratogenicity in that situation. For neurologists, information gathered by recent studies highlights the importance of pre-pregnancy planning. If the physician works closely with those planning to start a family, he or she can minimize the problems that women with epilepsy face during pregnancy. **PN**

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