By Steven Karceski, MD

AEDs and Pregnancy: The Role of Registries in Difficult Decisions

Registries from around the world offer some evidence to support treatment decisions, but there are rarely clear-cut answers.

One of the most stressful situations a neurologist can encounter is a woman with epilepsy who is either planning to become pregnant or already is pregnant. There are many issues that cause concern. However, one of the most stressful is AED teratogenicity. AEDs during pregnancy can cause congenital malformations. To the neurologist, the most concerning of these is the most severe: effects on formation of the brain and spinal cord. However, AEDs have been reported to cause cognitive problems as well, something that may not be appreciated until the child is older. These problems include decreased IQ in some children exposed to AEDs *in utero*. But there are other issues. Should mothers with epilepsy breastfeed? How should a new mom with seizures care for her baby? These are only some of the issues facing the neurologist who encounters a woman with epilepsy who is pregnant or planning to become pregnant.

Concerns During Pregnancy

The best time for a woman with epilepsy who plans to become pregnant to see her neurologist is long before she is ready to start her family (or add to it). Although many issues should be discussed, initial conversations typically center around two: what happens if seizures occur during pregnancy, and the risks of taking seizure medications during pregnancy.

Most studies show that during pregnancy the risk of seizures, especially generalized tonic-clonic seizures, outweighs the risk of medications. Seizures can injure mom or the developing baby. Seizure control, therefore, must be maintained during pregnancy. Studies have shown that seizures do not change during 60-70 percent of pregnancies. In 15-30 percent, seizures may worsen. If this occurs, the dose of medications must be adjusted to improve control of seizures. Although there may be concerns that higher doses of AEDs may cause malformations, seizure control is paramount.

Seizures worsen during pregnancy for several reasons. During pregnancy, plasma protein binding decreases, resulting in a decrease in the total level of highly protein-bound medications, such as phenytoin. The impact of this on the free fraction of the medication is less clear: in some instances the free fraction may remain unchanged. For the treating neurologist, changes in protein binding indicate a need for close monitoring of both the free fraction and total amount of serum medication. Maintaining constant serum levels throughout pregnancy may maintain seizure control.

A decrease in serum AED levels can also occur as a result of increased hepatic metabolism or increased renal clearance. For instance, the metabolism of lamotrigine can increase by as much as 300 percent[1] during pregnancy. This effect seems to stabilize by about the 32nd week of gestation; however, one must monitor levels in order to carefully adjust dosing to maintain consistent serum levels and therefore maintain seizure control.

The second issue is teratogenicity. For many years, physicians have been guided by a few specific principles. First, the older antiseizure medications (approved by the FDA before 1990) are pregnancy category "D": although there is a known risk during pregnancy, the benefits of use may outweigh risks. The newer AEDs (approved by the FDA after 1990) are pregnancy category "C": the risks of use during pregnancy are unknown. Prospective parents are counseled about these risks, as well as the risks of seizures during pregnancy.

Is there a better way to counsel prospective parents? What else do we know about AED teratogenicity? The rate of birth defects in the general population is about two to three percent. When a woman with epilepsy is taking one AED, that risk doubles (four to six percent).[2] On two AEDs, the risk is threefold (six to nine percent). On multiple AEDs, the risk is even higher; some studies have shown up to 15 percent increased risk when a person is taking three or more AEDs during pregnancy. Though imperfect in design, available studies suggest that physicians should minimize medication "burden" before pregnancy begins. This minimizes the teratogenic risk.

Although this information is helpful, most physicians and patients want to know more about AED teratogenicity. One way to better understand the effects of these medications on the developing baby is through pregnancy registries. Many countries, some in collaboration with their neighbors as has occurred in Europe, have begun to address this specific issue. In a paper published in *Neurology* in September, Dr. Meador and his colleagues summarize important information from pregnancy registries around the world.[3] He and his colleagues discuss the latest information on what is known about the risks of taking seizure medications while pregnant.

The HOPE Registry

The international Health Outcomes in

Pregnancy and Epilepsy (HOPE) registry was established to learn more about the possible effects of seizure medications (antiepileptic drugs or AEDs) on the developing baby. Information comes from pregnancy registries in North America, the United Kingdom, Australia, Sweden, Finland, and Europe. Although each registry differs slightly, their goal is similar: to collect as much information about AEDs during pregnancy.

The babies are evaluated for both major and minor congenital malformations. Major malformations include problems with major organs such as the heart, skeleton, or brain. Major malformations can affect the way that the baby grows and develops. The significance of minor malformations is more difficult to determine. Minor malformations may not cause medical problems during the person's life. As a result, the greatest amount of attention to date has been focused on major malformations.

When it comes to patient registries, more is better. A larger number of people translates into much higher confidence in the results. More than 5,500 women have enrolled in the North American registry. There are more than 5,400 in the UK registry, approximately 1,000 in Australia, and roughly 9,000 in Europe. The data from these registries do not tell neurologists about every AED. This is partly because the number of women taking each AED is different: we know more about the medications that are most commonly prescribed in monotherapy.

The North American registry has given doctors information about phenobarbital, valproate, lamotrigine, and carbamazepine. The rate of major malformations is 6.5 percent with Phenobarbital, 10.7 percent with valproate, 2.7 percent with lamotrigine, and 2.5 percent with carbamazepine.

In the United Kingdom and Australia, information has emerged for valproate, carbamazepine, and lamotrigine. In the UK, the risk of major malformations is 6.2 percent for valproate, 2.2 percent for carbamazepine, and 3.2 percent for lamotrigine. In Australia, it is 13.3 percent for valproate, three percent for carbamazepine, and 1.4 percent for lamotrigine.

In the Finnish and Swedish registries, information is available for valproate and carbamazepine only. In Finland, there is a 9.7 percent risk of major malformation when the baby is exposed to valproate, and four percent with carbamazepine. In Sweden, it is 10.7 percent for valproate, and 2.7 percent for carbamazepine.

What Do Registry Data Really Say?

The authors of the recently published paper admit that there are limitations to the information contained within patient registries.[3] One key item is the fact that not all women with epilepsy who become pregnant are enrolled in these registries. Therefore, the information may be biased. For example, what if many of the women who enrolled had done so because they were worried about the risks of AEDs? What if many of these women had already experienced problems during previous pregnancies? In other words, they may have decided to enroll because of their concerns about having another baby with problems. If a previous pregnancy predicts risk in subsequent pregnancies, then the end result in this case would be that the registry would overestimate the risk of birth defects.

Another issue is that the registries did not differentiate between epilepsy syndromes. Instead, all women with all kinds of epilepsy were enrolled. As discussed in previous installments of "Epilepsy Essentials," there are many kinds of epilepsy. Epilepsy type could possibly contribute to the risk of congenital malformations.

Finally, information about confounding factors may not be known through these registries. For instance, what other medications (prescribed or over-the-counter) were used during the pregnancy? How did mom's diet contribute to the development of congenital malformations? Did she take vitamins such as folate? Did she smoke? Did she use illicit drugs? Obviously, any of these factors might influence the outcome of the pregnancy and therefore the pregnancy registry data.

Difficult Choices

Women with epilepsy face a difficult choice. They may need to choose a medication that is known to cause problems versus ones for which the risk is unknown. The pregnancy registry data has consistently shown that valproate causes congenital malformations in 6.2 to 13.3 percent of babies exposed in utero. The use of phenobarbital may also be a concern, as 6.5 percent of babies exposed to this (the North American registry) had congenital malformations. As a result, many physicians agree that valproate and possibly phenobarbital should not be first line agents during pregnancy. If valproate is the best agent for the woman with epilepsy, minimizing the dose in an effort to minimize this risk seems prudent.

Doctors and patients want the same thing: good information. Although the answer for valproate seems clear, the answer for other medications remains vague. Valproate is only one of many currently available AEDs. What do the pregnancy registries tell us about the rest? At this point, physicians must wait until more women are enrolled in these registries. The registries are ongoing, and, as a result, the information will continue to emerge. With good information, both the doctor and the patient can make better decisions about their health care. **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.

3. Meador KJ, PB Pennell, CL Harden, JC Gordon, T Tomson, PW Kaplan, GL Holmes, JA French, WA Hauser, PG Wells, JA Cramer. "Pregnancy registries n epilepsy: A consensus statement on health outcomes." Neurology 2008;71:1109-1117.

Steven Karceski, MD is Associate Clinical Professor of Neurology at the College of Physicians and Surgeons of Columbia University.