



Understanding the Connection Between Seizures and Women's Health

This complex relationship is poorly understood, and its adverse events too often go unrecognized. Here's how to get up to speed.

Despite the proliferation of literature on this topic, many physicians still do not recognize the association between seizures, hormones and women's health. In 2000, a survey of just over 3500 physicians was published.¹ Twenty-five percent of respondents were completely unaware of the association between hormones and seizures. In addition, 73 percent did not know which antiepileptic drugs (AEDs) interacted with oral hormones (oral contraceptives). Eighty-four percent were unaware of the reduced fertility in women with epilepsy. Finally, two-thirds did not know that the long-term use of certain AEDs has been associated with bone loss, a condition that postmenopausal women are at highest risk to develop.

In addition to these concerns, women are at increased risk for bone loss: it is now recognized that certain AEDs increase the risk of osteopenia and osteoporosis. The physician must now take this into account as well, thereby minimizing this potential long-term side effect of the treatment of epilepsy.

Hormones + Seizures = Catamenial Epilepsy

The interaction between the menstrual cycle, epilepsy and AEDs is complex. The usual cyclical changes in sex steroid hormones directly affect seizures. For women with epilepsy, this relationship becomes a concern at puberty, often beginning between the ages of 12 and 14. It is during puberty that hypothalamic releasing factors begin to act on the pituitary to stimulate the secretion of sex steroid hormones. The cyclical pattern of gonadotropin secretion in women is usually established one to two

years after the onset of puberty, marking the onset of menstruation (menarche).

For many years, women with epilepsy have noticed an association between the occurrence of their seizures and certain phases of their menstrual cycle. Not all women experience this; however, it is estimated that 30-50 percent may experience hormone related seizures. Seizures that are triggered by hormones are called catamenial. Research over the past two decades has supported this observation, demonstrating that estrogen is proconvulsant, while progesterone is anticonvulsant.

There are two times during the menstrual cycle when estrogen peaks: just before ovulation (causing release of the ovum), and just before menstruation (signaling the shedding of the endometrium). Laidlaw and Mattson have shown that catamenial seizures occur most often during these phases of the menstrual cycle.

The mainstay of treatment for catamenial seizures, as with other seizure types, is AEDs. However, when catamenial seizures do not respond completely to appropriately selected antiseizure medications, there are several additional strategies that can be considered. The first is to consider oral hormones. For most women, exogenous hormones are used as a form of contraception. The oral contraceptive acts on the pituitary-gonadal axis by interrupting the normal, intricate feedback system. By "evening out" the serum hormones during the menstrual cycle, the normal estrogen peaks are suppressed, potentially controlling estrogen-induced seizures.

AEDs and Hormones

Although hormones can affect seizures, it

has also become clear that certain anti-seizure medications may affect hormones (see Table 1). More specifically, medications which are hepatic P450 enzyme inducers reduce the effectiveness of oral hormones. Women who are taking these AEDs must be counseled regarding this interaction: the AED they are taking may erode the effectiveness of their birth control. The rate of failure of oral contraceptives, when taken with these medications, may be as high as six percent. Two strategies will help to overcome this effect. First, the type of oral contraceptive can be changed to one which contains more than 50 micrograms per day of estradiol or menstranol. Second, the woman may wish consider another strategy of birth control (barrier method, etc.).

Fertility

When compared to their unaffected siblings, women with epilepsy have an infertility rate of 40 percent. Several reasons have been proposed as a cause of this. Women with epilepsy have an increased rate of anovulatory cycles and menstrual cycle disorders, and experience a greater number of miscarriages. There are two main possible explanations: the increased risk of infertility is either due to the underlying illness (epilepsy) or it is related to the treatment (AEDs).

Whether due to seizures or AEDs, the problem likely involves disruption of the hypothalamic-pituitary-gonadal axis. In the brain, seizures interrupt the pulsatile release of hypothalamic and pituitary hormones and therefore the secretion of sex steroid hormones. Antiepileptic drugs influence the serum levels of sex steroid hormones by altering their metabolism.



EPILEPSY ESSENTIALS

By Steven Karceski, MD

Table 1. AED Interactions with Oral Contraceptives

Known Effect on Oral Contraceptives	No Known Effect on Oral Contraceptives
carbamazepine (Tegretol, Carbatrol)	gabapentin (Neurontin)
felbamate (Felbatol)	lamotrigine (Lamictal)
oxcarbazepine (Trileptal)	levetiracetam (Keppra)
phenobarbital	tiagabine (Gabitril)
phenytoin (Dilantin, Phenytek)	zonisamide (Zonegran)
topiramate (Topamax)	

Table 2. AEDs and Teratogenicity

Known Effect: Pregnancy “D”	Unknown Effect: Pregnancy “C”
carbamazepine (Tegretol, Carbatrol)	All others
ethosuximide (Zarontin)	
phenobarbital	
phenytoin (Dilantin, Phenytek)	
valproate (Depakote, Depakene)	

Pregnancy

There are two main concerns that a woman with epilepsy faces during pregnancy. First, a generalized tonic-clonic seizure (GTC) during pregnancy might cause falls, injuring both mother and child. A GTC may cause premature labor and delivery, necessitating life supportive measures for the newborn. In addition, the use of AEDs carries a risk of teratogenicity (see Table 2).

The older AEDs are all pregnancy category D, which means that there is a known risk of birth defects; however, the benefits of their use may outweigh these risks. The newer AEDs are pregnancy category C: the risk of use during pregnancy is unknown. Most studies suggest that the infants of women who take one AED during pregnancy have a two-to-threefold increased risk of birth defects. With more than one AED, the risk is even higher. When the two concerns are compared, the risk that ongoing seizures pose is greater than the risk of the antiseizure medication. This has led to the current recommendation: to maintain seizure control during pregnancy using the lowest dose of medication.

In addition to maintaining seizure control, women should take folate (folic acid), a vitamin that is important to the formation of the central nervous system. Ideally, folate should be taken before pregnancy occurs. It should be continued through pregnancy and during breastfeeding. Because so many pregnancies are unplanned, most physicians begin counseling patients about the importance of taking multivitamins and folate during their “reproductive years.” However, the recommended range is anywhere from 400ug (the amount contained in a usual multivitamin) to 4mg of folate. There are no prospective studies to guide physicians in selecting the optimal dose.

Bone Health

Recent evidence has demonstrated an association between long-term use of AEDs and bone loss. Women, especially postmenopausal women, have a higher risk of developing bone loss than men. However, both men and women on long-term AEDs have been shown to have an increased risk of osteopenia and osteoporosis. This topic was

addressed in April’s Epilepsy Essentials: it is the older AEDs (carbamazepine, phenobarbital, phenytoin, and valproate) that are most often associated with this problem.

Conclusions

The relationship between seizures, epilepsy, AEDs, hormones and the female reproductive cycle remains under-recognized. The normal cyclical changes in hormone levels, needed to signal ovulation and menstruation, can be seizure-provoking. In these instances, when AEDs fail to completely control seizures, oral hormones may be of benefit. The occurrence of seizures can affect the normal cyclical release of hypothalamic releasing hormones, directly affecting fertility and reproductive cycles.

Anti-seizure medications can also affect the hypothalamic-pituitary-gonadal axis, impairing fertility. In addition, AEDs, especially the enzyme-inducing agents, can lower the serum concentration of sex steroids: for women taking oral contraceptives, this means that the exogenous hormones will be less effective. For women who are trying to conceive, the issue of teratogenicity must be addressed. Finally, in all people with seizures, long-term exposure to these medications may cause adverse effects. More specifically, they may be at higher risk of developing bone density problems, increasing the risk of fractures. Hopefully, research will continue to illuminate the complex relationship between epilepsy, its treatment, and their combined effect on the body. **PN**

1. Morrell MJ, Sarto GE, Shafer PO, Borda EA, Herzog A, Callanan M. “Health issues for women with epilepsy: a descriptive survey to assess knowledge and awareness among healthcare providers.” *J Womens Health Gen Based Med.* 2000 Nov;9(9):959-65.

2. Morrell MJ. “Hormones and epilepsy through the lifetime.” *Epilepsia* 1992;(S4):S49-S61.

3. Pack AM, Morrell MJ, Marcus R, Holloway L, Flaster E, Done S, Randall A, Seale C, Shane E. “Bone mass and turnover in women with epilepsy on antiepileptic drug monotherapy.” *Ann Neurol.* 2005 Feb;57(2):252-7.

Steven Karceski, MD is Assistant Clinical Professor of Neurology at the College of Physicians & Surgeons of Columbia University and Director of the Columbia Epilepsy Center at the Atlantic Neuroscience Institute.