Special Considerations for Managing Women With Epilepsy

Brought to you by Upsher-Smith with contributions from Cynthia L. Harden, MD

In recent years, there has been an increased focus on gender-related issues in women with epilepsy. Many issues are centered on hormonal fluctuations and their effect on epilepsy, drug interactions between oral contraceptives and antiepileptic drugs (AEDs), and pregnancy. In addition, there are comorbidities associated with epilepsy that occur frequently in women (eg, migraines and bone health issues).

Menstrual cycle/catamenial epilepsy

Seizures do not always occur randomly in either men or women and have been reported to group in some type of nonrandom fashion in >50% of cases.[1] Klein et al noticed an increased rate of epilepsy onset around menarche; this further supports the association between seizure activity and hormones.[2] Three years later, however, Svalheim et al published a study that could not confirm previous observations that the onset of epilepsy clusters around menarche.[3] In women with epilepsy, seizure patterns may align with a women's menstrual cycle, influenced by fluctuations in ovarian steroid hormone levels.[4] The occurrence of seizures in relation to the menstrual cycle is called catamenial epilepsy.[5] Depending on the definition, 35% to 70% of women with epilepsy are affected by catamenial epilepsy; 35% have a 2-fold or greater increase in seizure frequency related to menstruation.[6] Herzog et al have published data suggesting there are 3 patterns of catamenial epilepsy[4]:

1. Perimenstrual
2. Periovulatory
3. Inadequate luteal phase cycles

The mechanisms that underlie catamenial epilepsy have not been fully elucidated. Seizure frequency has been correlated with cyclical changes in estrogen and progesterone.[7] Estrogen is highest during the periovulatory phase and progesterone is highest during the luteal phase of normal cycles.[8] Estrogen can increase brain-derived neurotropic factor synthesis, which in turn may lead to

Dr. Cynthia L. Harden is chief of the Comprehensive Epilepsy Care Center at North Shore University Hospital and Long Island Jewish Medical Center, within the hospitals' Department of Neurology.

Prior to joining the Institute, Dr. Harden directed the International Center for Epilepsy at the University of Miami Health System. While at the University of Miami, she was Professor of Neurology at the University's Miller School of Medicine. Dr. Harden spent the majority of her career at the Weill Cornell Medical College in New York City and became Professor of Neurology there in 2007.

Dr. Harden completed her undergraduate studies at the University of Wisconsin-Eau Claire and earned her MD at the University of Wisconsin Medical School. She trained in internal medicine at St. Luke's-Roosevelt Hospital Center and completed her residency in neurology at Mount Sinai Hospital in Manhattan. Following her residency, she completed a fellowship at the Albert Einstein College of Medicine in the Bronx.

An ad hoc reviewer for *Neurology* and *Epilepsy Research*, among other journals, Dr. Harden has also authored or collaborated on nearly a score of book chapters and more than 100 peer-reviewed articles.

She is board certified by the American Board of Psychiatry and Neurology in neurology and clinical neurophysiology.

Dr. Harden is an educational consultant for EPILOG, which is supported by Upsher-Smith Laboratories, Inc.

> **"Sexual dysfunction was reported in up to 50% of women with epilepsy."**

increased hippocampal excitability.[6,9] Progesterone has been shown to have anticonvulsant properties, and its rapid decrease prior to menstruation has been suggested as a contributing factor to increased perimenstrual seizures.[10] Additionally, cyclic fluctuations in estrogen and progesterone may affect concentrations of AEDs due to the fact that estrogen and progesterone are metabolized by some of the same liver enzymes as some commonly used AEDs.[11]

Oral contraceptives

Approximately 500,000 women with epilepsy in the United States are of childbearing age.[12] In one survey in the United Kingdom of women with epilepsy aged 15-45, 17% were on oral contraceptives.[13] In this survey, more than half of the women on an enzyme-inducing AED and an oral contraceptive were on a dose of estrogen <50 μg. This dose could be associated with oral contraceptive failure and unwanted pregnancies. Another ex-US study estimates >50% of pregnant women with epilepsy had unplanned pregnancies.[14] In this study, oral contraceptive failure was noted in 27/111 unplanned pregnancies.

Examples of AEDs That Interact With Oral Contraceptives[6]
Barbiturates
Carbamazepine
Lamotrigine
Oxcarbazepine
Phenytoin
Primidone
Topiramate (>200 mg/day)

Sexual dysfunction

Sexual dysfunction was reported in up to 50% of women with epilepsy.[6] Diminished sexual desire was noted in 25% to 34% of women with epilepsy, with decreased desire seen more often in people with higher seizure frequency.[6] The causes of sexual dysfunction can be both psychosocial and physiological. Psychosocial contributors may include depression and possible anxiety over seizures during intercourse. Physiologic factors can include decreased vaginal blood flow and increased vaginal dryness in women with epilepsy.[6,15] An additional factor that can contribute to sexual dysfunction is the use of certain AEDs.[16] It is difficult to establish the role of epilepsy versus AEDs in contributing to sexual

dysfunction. Epilepsy and AEDs can alter sex hormone levels.[15] Enzyme-inducing AEDs can reduce testosterone availability and increase the metabolism of sex hormones.[16]

Infertility and polycystic ovary syndrome (PCOS)

Most women with epilepsy can conceive; however, the fertility rates of women without epilepsy were reported to be 33% higher than in women with epilepsy.[17] The reasons for this difference in fertility rates are unclear; the use of AEDs and epilepsy itself may contribute to infertility.[18] Reproductive endocrine disorders that may affect fertility in women with epilepsy include hypothalamic amenorrhea, hyperprolactinemia, and PCOS. PCOS is the leading endocrine abnormality in women of reproductive age and may occur in 6% to 8% of all women.[19] The primary features of PCOS are androgen excess, ovulatory dysfunction, and polycystic ovaries. In women with temporal lobe epilepsy, the rates of PCOS, a common cause of anovulatory cycles, range from 15% to 25%.[18] The development of PCOS in women with epilepsy is most likely due to a functional disturbance of the hypothalamic-pituitary axis.

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The issue of PCOS in women with epilepsy is confounded by the use of certain AEDs. Up to 60% of women treated with valproate monotherapy had ovaries that appeared polycystic and hyperandrogenism, common features of PCOS.[20] These features were particularly common in women who started taking valproate at <20 years old. Following an extensive literature review, Harden et al concluded that epilepsy could be a cause of PCOS, and that valproate, which can be associated with weight gain and increased androgen levels, may either be mimicking or exacerbating PCOS or be another cause of PCOS.[21]

Pregnancy

Pregnancy has the potential to alter AED disposition through increasing distribution volume, increasing renal bloodflow, altering hepatic enzyme activity, and decreasing plasma protein concentration, all of which may alter AED pharmacokinetics.[22] Research has shown that pregnancy itself can alter the concentrations of lamotrigine, carbamazepine, phenytoin, oxcarbazepine, and levetiracetam.[23]

One study has suggested that approximately one-third of women with epilepsy have more seizures during pregnancy than they did prior to pregnancy.[24] However, in the 2009 American Academy of Neurology Practice Parameter Update focusing on epilepsy and pregnancy the authors, following a comprehensive literature review,

found insufficient evidence to confirm higher rates of seizure during pregnancy in women with epilepsy.[12] Other key conclusions noted in the Practice Parameter included the following:

- Women who are seizure free for the 9 months prior to pregnancy have a high probability of remaining seizure free throughout pregnancy
- There is probably no substantially increased risk (>2 times expected) of cesarean section or late pregnancy bleeding for women with epilepsy taking AEDs
- Women with epilepsy who also smoke may have an increased risk of premature contractions, labor, and delivery

Seizure prevention offers many benefits to women with epilepsy regardless of whether they are pregnant or not. In pregnant women with epilepsy, an additional benefit of seizure prevention is protection of the fetus from maternal seizures.[25]

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Birth defects

One of the greatest challenges in managing pregnant women with epilepsy is that of potential teratogenicity associated with many AEDs. An exhaustive discussion of this topic is outside the scope of this paper; this section is only meant to provide a broad overview of some of the risks associated with AED use during pregnancy. It has been well established that the use of older-generation AEDs is associated with a 2- to 3-fold increased risk of major birth defects.[26] For example, exposure to valproate during pregnancy is associated with a risk of major congenital malformations.[25] There are, however, still knowledge gaps related to the teratogenic potential with many newer AEDs. Recent publications in this area give epileptologists more information to consider when caring for women of childbearing age with epilepsy. Molgaard et al conducted an extensive study of 837,795 live births recorded by Danish health registries to determine the association between fetal exposure to newer-generation AEDs and the risk of major birth defects. Authors reported that the use of oxcarbazepine (Pregnancy Category C) and lamotrigine (Pregnancy Category C) during the first trimester were not associated with a moderate or greater risk of major birth defects as seen with older drugs, though they could not exclude a minor excess in risk of major birth defects or risk of specific birth defects.[26-28] They also found that topiramate (Pregnancy Category D as of March 2011), gabapentin (Pregnancy Category C), and levetiracetam (Pregnancy Category C) did not appear to be major teratogens, but the study could not exclude minor to moderate risks of major birth defects.[26,29-31] Another recent study has reported a dose-dependent risk of major congenital malformations with carbamazepine (Pregnancy Category D), lamotrigine (Pregnancy Category C), valproic acid

(Pregnancy Category D), and phenobarbital (Pregnancy Category B) and offers prescribers more valuable information to assess the teratogenicity of particular treatment regimens before a woman becomes pregnant.[28,32-35]

Folic acid is recommended for all women who could become pregnant in order to reduce the risk of neural tube defects (NTDs) in the fetus if a woman does conceive.[23] A daily supplement of at least 0.4 mg of folic acid is recommended for women of childbearing age. Women with epilepsy may also decrease the risk of major congenital malformations, particularly NTDs, with folic acid supplementation. Certain AEDs can reduce serum folic acid levels by causing increased metabolism of folic acid.[6,36] Epileptologists may recommend doses of folic acid as high as 4 mg per day in women depending on patient-specific factors, such as the AED they are taking.[6] Folic acid itself may also affect blood levels of AEDs, namely phenytoin, necessitating careful monitoring and potential dose adjustment.

Menopause

Data suggest that women with epilepsy reach menopause approximately 3 years earlier than women without epilepsy.[37] Higher seizure frequency may be associated with earlier onset of menopause. While the exact cause of the early cessation of the normal reproductive cycle is unknown, it is hypothesized that it occurs because women with epilepsy often have abnormal secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Inadequate concentrations of LH and FSH can cause anovulation and amenorrhea.

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Just as hormonal issues associated with menarche and pregnancy can affect epilepsy, the onset of menopause can also affect epilepsy. One study reported that women with catamenial seizure exacerbations during their reproductive years had significant changes at perimenopause and menopause: during perimenopause this subset of women experienced an increase in seizures; however, after menopause, they had a reduction in seizure frequency.[38]

Bone health

It is well known that the postmenopausal state is associated with bone health issues, such as osteoporosis, in women without epilepsy. What may be less well known is that women with epilepsy are at greater risk of osteoporosis, due in part to metabolic effects of certain AEDs on bone turnover.[39,40] CYP P450-inducing AEDs can adversely affect bone metabolism by increasing inactivation of vitamin D, leading to decreased absorption of calcium. Cummings et al demonstrated that Caucasian women 65 and older taking AEDs were twice as likely to experience hip fractures than women

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65 and older who were not taking AEDs.[41] Studies examining the management of osteoporosis in postmenopausal women with epilepsy are very rare and more research is needed to better understand this group.

Migraines

Migraines occur more commonly in women than in men, and up to 20% of people with epilepsy experience migraines.[42,43] It is hypothesized that the increased comorbidity of epilepsy and migraines may be due to the excessive neocortical excitability associated with both conditions.[44] Due to the similar underlying mechanisms, several AEDs are also indicated to prevent migraines, such as those that affect glutamate receptors, which are involved in both migraine and epilepsy.[42,45] Topiramate and divalproex sodium are AEDs that are indicated for migraine prophylaxis.[29,45,46]

Summary

In recent years, there has been an increased focus on gender-related issues in women with epilepsy. The management of women with epilepsy can be complicated due to the effects of hormonal fluctuations and comorbid conditions.

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