Management of Epilepsy in Women

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EPILEPSY BOARD REVIEW MANUAL

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Statement of Editorial Purpose

The Epilepsy Board Review Manual is a study guide for trainees and practicing physicians preparing for board examinations in epilepsy. Each manual reviews a topic essential to the current management of patients with epilepsy.

Note from the Publisher

This publication has been developed without involvement of or review by the American Board of Psychiatry and Neurology.

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Management of Epilepsy in Women

Mona Sazgar, MD

INTRODUCTION

CASE VIGNETTE

S.B. is a 28-year-old woman with a long-standing history of focal epilepsy of right frontal lobe origin due to cortical dysplasia. She used to experience clusters of seizures 2 days prior to and throughout her menstrual bleed. Some of her seizures progressed to generalized tonic-clonic activity. In the past 2 years, she has been stable and seizure free on oxcarbazepine 900 mg twice daily with no reported seizure recurrence. She was put on folic acid 1 mg daily by her neurologist as soon as she started dating. She got married last year and is taking a birth control pill (combined estradiol/progesterone oral contraceptive). She comes to her neurologist’s office and informs her that her pregnancy test came back positive. She also has experienced 2 episodes of her typical aura in the past 2 weeks. She is worried and has many questions regarding the reason for contraceptive failure, her seizure recurrence, the effects of her seizure medication on her baby, and future directions.

Epilepsy affects approximately 1% of the population. Women comprise approximately half of the epilepsy population, including about 1.5 million women of childbearing age who live with epilepsy in the United States. Approximately 24,000 women with epilepsy in United States give birth every year. Women with epilepsy face specific challenges across their life cycle. Health care professionals involved in the care of women with epilepsy need to address difficult questions and concerns related to menses, birth control, conception, pregnancy, childbirth, breastfeeding, childcare, bone health, and menopause. However, 2 published surveys of health care professionals by Long et al, the Knowledge of Women’s Issues in Epilepsy (KOWIE) questionnaires, found that knowledge about treating epilepsy in women is lacking among health care providers.1 A total of 202 health care providers responded to the survey, 92% of whom identified themselves as physicians. Few understood the effects of endogenous steroid hormones on seizure threshold (24%) and that epilepsy is associated with an increased incidence of female sexual dysfunction (37%).2 Most respondents could not identify which seizure medications interfere with oral contraceptives. As these results indicate, there is a great need to educate health care professionals and patients with epilepsy about women’s issues in epilepsy.

CATAMENIAL EPILEPSY

In the majority of women and men with epilepsy, seizures do not occur randomly,3 but rather they tend to cluster, with more than 50% of cases showing temporal rhythmicity.4 Women with catamenial epilepsy show cyclical exacerbation of their seizures with temporal relationship to their menstrual cycles. The word catamenial is derived from the Greek word katamenios, meaning “monthly.” Sir Charles Locock first described the seizures associated with the menstrual cycle in 1857. Seizure exacerbation may occur either at the time of menstru-
oration or ovulation and is attributed to fluctuations of estrogen and progesterone and their neuroactive properties. As a rule, estrogens are proconvulsant and progesterone has anticonvulsant properties. Catamenial epilepsy is thought to be related to different responses of neurons in the cerebral cortex to sex hormones. Recent investigations by Herzog and colleagues have demonstrated the existence of at least 3 patterns of catamenial seizure exacerbation (Figure 1): perimenstrual (C1: days –3 to 3) and periovulatory (C2: days 10 to –13) in ovulatory cycles and entire luteal phase (C3: Days 10 to 3) in anovulatory cycles, where day 1 is the first day of menstrual flow and day –14 is the day of ovulation. These 3 patterns can be demonstrated simply by charting menses and seizures and obtaining a midluteal phase (days 20–22) serum progesterone level to distinguish between normal and inadequate luteal phase cycles (<5 ng/mL) (Table 1). Management of seizures in patients with catamenial epilepsy can be challenging and may include targeting the specific dates of hormonally related seizure exacerbation by increasing the baseline antiepileptic drugs (AEDs) on those dates, use of progesterone products, use of benzodiazepines such as clobazam and clonazepam, and use of acetazolamide.

**MECHANISM**

Catamenial epilepsy may result from fluctuations in levels of endogenous sex hormones (neurosteroids). Endogenous neurosteroids that modulate seizure susceptibility such as allopregnanolone and allotetrahydrodeoxy cortisol (THDOC) could play a critical role in catamenial epilepsy. It is hypothesized that the withdrawal of progesterone-derived neurosteroids can lead to enhanced excitability and predispose to seizure exacerbation. On the other hand, the plasticity in GABA_A receptor subunits may play a role in enhanced susceptibility for seizures in women with catamenial epilepsy. In animal models, prolonged exposure
to allopregnanolone followed by withdrawal, which mimics menstruation, causes marked increase in expression of \(\alpha_4\) and \(\delta\) subunits, which are linked to enhanced neuronal excitability and seizures.\(^{10,11}\) The reduced inhibition and enhanced excitability caused by neuroendocrine fluctuations can be a key factor in predisposition to catamenial seizures.

### Abnormalities in the HPO Axis

The brain is involved in regulating sex hormones through the hypothalamic-pituitary-ovarian axis (HPO). The hypothalamus secretes gonadotropin-releasing hormone (GnRH), thereby stimulating the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the pituitary. FSH stimulates formation and growth of the ovarian follicles, which secrete estradiol (the main form of estrogen) as they develop. Estrogen, through a negative feedback mechanism, inhibits FSH but stimulates GnRH. This leads to a surge of LH, which induces oocyte maturation, ovulation, and conversion of the follicle into the corpus luteum. Ovulation marks the end of the follicular phase and the beginning of the luteal phase. Following ovulation, the corpus luteum secretes progesterone, which inhibits secretion of GnRH, FSH, and LH. If there is no pregnancy, the corpus luteum regresses and production of progesterone and estradiol declines. With lower levels of progesterone, GnRH inhibition decreases and the cycle repeats (Figure 2).

Epilepsy itself and the medications used to treat epilepsy can have direct effects on regulation of the HPO axis. Epilepsy and AEDs can target a number of brain structures, including the limbic system, amygdala, hypothalamus, pituitary gland, and peripheral endocrine glands.\(^{12}\) In women with epilepsy, there are abnormalities in the levels of sex hormones, thyroid hormones, prolactin, and vitamin D related to dysregulation of the HPO axis. The shifting levels of estrogen and progesterone can affect the seizure frequency and severity by directly affecting brain excitability.

### TREATMENT

To date there is no specific treatment approved by the US Food and Drug Administration (FDA) for catamenial epilepsy. However, there are several options that can be beneficial for patients with catamenial seizure exacerbation (Table 2). Acetazolimide, which has been in use for more than 50 years, is one of the oldest treatment options for catamenial epilepsy. There have not been any randomized clinical trials to prove the efficacy of acetazolamide in treating catamenial epilepsy. It is common practice to use 250 or 500 mg twice daily for approximately 10 days around the time of catamenial seizure exacerbation.

Benzodiazepines such as clonazepam and clonazam are used in the treatment of seizure clusters during hormonally related exacerbation of seizures. Benzodiazepines are positive allosteric modulators of GABA\(_A\) receptor and broad-spectrum anticonvulsant medications. In a double-blind, placebo-
controlled cross-over study, clobazam resulted in complete control in the majority of women during the 10-day trial period.\textsuperscript{13,14} In this study, clobazam was effective when used at a dose of 20 to 30 mg/day, administered intermittently starting 2 to 4 days before menses. The most common adverse effects of clobazam are sedation and depression.

Certain seizure medication doses can be temporarily increased during the catamenial seizure exacerbation period. This approach may not be safe with some seizure medications such as phenytoin and carbamazepine.

Synthetic progestin depot medroxyprogesterone acetate (DMPA) at a dose of 150 mg every 3 months has been used for reducing seizure exacerbation in catamenial epilepsy. Reductions in seizure frequency of up to 39% over a 1-year period have been reported.\textsuperscript{15,16} There is a risk for osteoporosis with prolonged use of DMPA, and the effects of DMPA on fertility last up to 1 year.

A National Institutes of Health–sponsored clinical trial led by Herzog and colleagues\textsuperscript{17} assessed the response to treatment with natural progesterone lozenges in women with medically refractory catamenial partial epilepsy. This was a randomized, double-blind, placebo-controlled phase 3 multicenter trial. In 294 patients randomized 2:1 to progesterone or placebo, a post hoc analysis showed significantly higher responder rate in women with perimenstrual seizure exacerbation (C1) as compared with the periovulatory (C2) and anovulatory (C3) groups. Progesterone may provide a clinically important benefit for this subset of women with perimenstrual catamenial epilepsy.

\begin{figure} 
\centering 
\includegraphics[width=\textwidth]{figure2.png} 
\caption{Hypothalamic-pituitary-ovarian (HPO) axis. FSH = follicle-stimulating hormone; LH = luteinizing hormone; GnRH = gonadotropin-releasing hormone.} 
\end{figure}
which is the most prevalent form of catamenial epilepsy. The recommended dose is 200 mg 3 times daily, which can be used around the days of hormonally related seizure exacerbation or days 14 to 28 of the cycle, with consideration for tapering up from a lower dose for 2 to 3 days at the onset of treatment and tapering down 2 to 3 days before discontinuing the therapy.

Novel treatment for catamenial epilepsy in the future may include neurosteroids that are devoid of hormonal side effects. One candidate is ganaxolone, a synthetic analog of the neuroactive steroid allopregnanolone that has sedative, anxiolytic, and anticonvulsant effects. It is a potent and selective positive allosteric modulator of the GABA\textsubscript{A} receptor. Ganaxolone has protective antiseizure activity in rodent models of epilepsy and is being evaluated for treatment of epilepsy in humans.\textsuperscript{18} Ganaxolone has been tested in various clinical trials to assess its efficacy in the treatment of epilepsy.\textsuperscript{19,20} However, there is only limited anecdotal information supporting the efficacy of ganaxolone in women with catamenial epilepsy.\textsuperscript{21}

### REPRODUCTION DISORDERS

**DIRECT EFFECT OF EPILEPSY**

Decreased libido and infertility, polycystic ovarian syndrome (PCOS), and early menopause are among the reproductive disorders associated with epilepsy. Epileptiform discharges can alter the level of sex hormones at the hypothalamic and pituitary level.\textsuperscript{22} The amygdala, a structure closely associated with temporal lobe epilepsy, has extensive reciprocal connections with the hypothalamus. Seizures originating from the amygdala can cause disruption of the GnRH-producing cells in the pre-optic area of the hypothalamus and abnormal release of FSH and LH and sex hormones as a consequence. Seizures in this way disrupt

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**Table 2. Suggested Algorithm for Treatment of Women with Catamenial Epilepsy**

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
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</table>
| 1. Determine true catamenial epilepsy | a. Establish whether the seizures are in fact catamenial in nature using seizure diaries. Ask the patient to chart daily seizure type and frequency with simultaneous recording of ovulation and menstruation status using an ovulation kit or basal body temperature recording for 3 menses.  
   b. Determine whether there is an increase in number and severity of seizures by two-fold or higher during specific days of the patient's menstrual cycle and establish C1, C2, or C3 type of catamenial epilepsy. |
| 2. Progesterone lozenges/natural progesterone for C1 pattern | For the C1 type, consider using progesterone lozenges 200 mg 3 times daily around the days of seizure exacerbation or days 14 to 28 of the cycle. |
| 3. Synthetic progestin | Consider oral daily synthetic progestin or intrauterine device with progestin versus depot medroxyprogesterone acetate (DMPA). |
| 4. Acetazolamide | Consider using 250 mg twice daily or 500 mg twice daily around the 7 to 10 days of seizure exacerbation as determined by the seizure diary. |
| 5. Clobazam | Consider using 20 to 30 mg divided twice a day or 1 dose at night for 10 days 2 days prior to and throughout the identified seizure exacerbation dates. |
| 6. Small increase in baseline antiepileptic drug | Consider increasing dose 2 days prior to the identified period of seizure exacerbation for up to 10 days. Be cautious about phenytoin, carbamazepine, or other medications with higher risk for toxicity. |
the menstrual cycle and affect fertility. In 50 consecutive patients with temporal lobe epilepsy, Herzog et al found 56% with amenorrhea, oligomenorrhea, or abnormally long or short menstrual cycle intervals, and 68% with clearly identifiable reproductive endocrine disorders such as PCOS, hypoandrogenism, premature menopause, and hyperprolactinemia. Since the disorders of sexual function can be common in women with epilepsy, questions about sexual function should be part of the routine evaluation in the outpatient clinic.

**EFFECT OF AEDS**

The medications used to treat epilepsy can also alter reproductive function. AEDs that induce hepatic enzyme metabolism (EIAEDs) can affect the concentration of sex hormones (Table 3). EIAEDs affect liver cytochrome P450 isoforms and result in enhanced metabolism of sex hormones and potential for seizure exacerbation in women with catamenial epilepsy. In a prospective, randomized, double-blinded study by Lossius and colleagues, reversible endocrine changes in sex steroid hormone levels were observed after withdrawal of AEDs. Carbamazepine was the most commonly used drug, and withdrawal led to significant increases in serum testosterone concentrations, which resulted in sexual dysfunction.

AEDs can significantly alter circulating sex hormone levels. Morrell and Flynn studied sexual function and hormones in women aged 18 to 40 years with partial onset epilepsy and primary generalized epilepsy along with non-epilepsy controls. Compared to the controls, women with partial onset epilepsy had significantly higher sexual dysfunction scores, lower mean arousal, and higher depression scores. Women on EIAEDs had statistically higher sexual dysfunction and lower sexual arousal compared to controls. Overall, non-EIAEDs have a more favorable profile in terms of effect on sexual function.

EIAEDs can also lower the efficacy of oral and hormonal contraceptives by enhancing metabolism of both the estrogen or progesterone components. Women with epilepsy should be aware of the increased risk for contraceptive failure when taking EIAEDs and should use additional methods if they desire to avoid getting pregnant. On the other hand, pregnancy and start of contraceptive medications with an estrogenic component can significantly reduce baseline lamotrigine levels by

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**Table 3. Interactions Between AEDs and Reproductive Hormones**

<table>
<thead>
<tr>
<th>AEDs that decrease sex hormones/cause contraceptive failure (EIAEDs):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine (Tegretol)</td>
</tr>
<tr>
<td>Phenytoin (Dilantin)</td>
</tr>
<tr>
<td>Phenobarbital (Luminal)</td>
</tr>
<tr>
<td>Primidone (Mysoline)</td>
</tr>
<tr>
<td>Topiramatea (Topamax)</td>
</tr>
<tr>
<td>Oxcarbazepine (Trileptal)</td>
</tr>
<tr>
<td>Rufinamide (Banzel)</td>
</tr>
<tr>
<td>Perampanelb (Fycompa)</td>
</tr>
<tr>
<td>Clobazam (Onfi)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AEDs with least effect on sex hormones and contraceptive failure (NEIAEDs):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethosuximide (Zarontin)</td>
</tr>
<tr>
<td>Gabapentin (Neurontin)</td>
</tr>
<tr>
<td>Valproatec (Depakote)</td>
</tr>
<tr>
<td>Lamotrigine (Lamictal)</td>
</tr>
<tr>
<td>Levetiracetamba (Keppra)</td>
</tr>
<tr>
<td>Zonisamide (Zonegran)</td>
</tr>
<tr>
<td>Pregabalin (Lyrica)</td>
</tr>
<tr>
<td>Lacosamide (Vimpat)</td>
</tr>
<tr>
<td>Tiagabine (Gabitril)</td>
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</tbody>
</table>

a Weak enzyme inducers.
b Decreased free testosterone concentrations in men and increased androgen concentrations in women taking valproate.
c Increased testosterone concentrations reported in men on levetiracetam.
AED = antiepileptic drug.
increased clearance of this medication (>50%) and result in seizure breakthroughs unless the dose is adjusted.29,30

The use of valproic acid is associated with increased risk for PCOS.31–34 PCOS is characterized by enlarged ovaries with multiple small cysts and a hypervascularized, androgen-secreting stroma leading to the associated signs of androgen excess (hirsutism, alopecia, acne), obesity, and menstrual cycle disturbance (oligorrhea or amenorrhea).35 PCOS occurs in approximately 4% to 7% of women of reproductive age in the general population, but in 10% to 25% of women with epilepsy.36,37 The increased rate of PCOS among women with epilepsy is likely due to altered modulation of the HPO axis by the temporo-limbic system.

**CONTRACEPTION**

Hormonal contraception is used in a variety of formulations including oral contraceptive tablets, topical patches, intramuscular depot injections, implants, and intrauterine devices. The mechanism of action of contraceptives involves inhibiting ovulation and fertilization. Combined oral contraceptives (COC), which contain both synthetic estrogen and progestin, are the most commonly used method of contraception. The most recent COC agents contain only 20 to 35 mg of ethinyl estradiol, which is not sufficient to suppress ovulation but can control the menstrual cycle. The progestin component is responsible for the contraceptive effect of COC, including inhibition of ovulation, increased viscosity of the cervical mucus, and reduced endometrial suitability for ovum implantation.38 There are complex interactions between hormonal contraception and seizure medications. Individualized counseling is needed for women with epilepsy to avoid reducing the efficacy of AEDs or failure of contraception.

EIAEDs such as phenytoin, carbamazepine, phenobarbital, primidone, oxcarbazepine, and eslicarbazepine can result in contraceptive failure (Table 3). Perampanel and topiramate are less potent hepatic enzyme inducers and can cause contraceptive failure at higher doses.39–41 However, levetiracetam, gabapentin, pregabalin, vigabatrin, tiagabine, zonisamide, and lacosamide have no known interactions with oral contraceptives (Table 3).

The oral contraceptive failure rate is 1% in healthy women, but 3% to 6% in the population of women with epilepsy.42–44 Fairgrieve and colleagues reported that less than 55% of women with epilepsy had planned their pregnancy and contraceptive failure was the cause of 1 in 4 unplanned pregnancies.38,43 Women taking EIAEDs need to take a combination of oral contraceptive pills with at least 50 µg of estrogen, but this can significantly increase side effects including the risk for blood clots.

Progestin-only tablets are unlikely to be effective in women who take EIAEDs, and women who use this method are at risk for contraceptive failure. There is no evidence as to whether EIAEDs reduce the efficacy of DMPA injections, although there is a theoretical risk and it is common practice to administer the injections every 10 weeks in women using EIAEDs, as opposed to the recommended 12-week intervals for women in the general population.

Another method of contraception is levonorgestrel implants. Levonorgestrel subdermal capsules are also at risk for failure with concurrent use of EIAEDs. In a study comparing levonorgestrel subdermal implants in a control group versus a group of women with epilepsy, after 1 year 2 of the 9 women with epilepsy had become pregnant dur-
ing contraception with levonorgestrel subdermal implants. They were both on phenytoin, and their plasma concentrations of levonorgestrel were low at the time of conception. No pregnancies had occurred in 10 women in the control group.

Finally, intrauterine devices (IUDs) are T-shaped devices that are fitted into the uterus. The 2 common types are copper IUD (non-hormonal) and levonorgestrel IUD (Mirena or Skyla). These devices work locally by causing thickening of the cervical mucus. They are highly efficacious and are not affected by EIAEDs. Therefore, these devices are an effective form of contraception in women with epilepsy.

**PREGNANCY**

Each year an estimated 24,000 women with epilepsy in the United States become pregnant. Seizures during pregnancy can pose a significant risk to the fetus. Fortunately, in the majority of women pregnancy has no effect or a protective effect on their seizure frequency. However, an increased seizure risk is reported in 20% to 25% of women with epilepsy during pregnancy. There is an increased incidence of seizures during labor and delivery, with approximately 3% to 4% of women with epilepsy experiencing seizures during childbirth. About half of these seizures are generalized tonic-clonic in nature.

Seizure recurrence during pregnancy can result from sleep deprivation, anxiety, and stress provoked by the pregnancy. An increased estrogen-to-progesterone ratio, especially around weeks 8 to 16 when it reaches its peak, may also be a contributing factor. Some women may reduce or discontinue AEDs once they discover they are pregnant out of fear of harming their babies. The most common cause of seizure recurrence in pregnancy is likely reduced plasma concentration of the AEDs.

Carbamazepine levels during pregnancy were studied by Tomson and colleagues, who found that in 8 of 35 women taking carbamazepine during pregnancy total concentration of carbamazepine decreased by 9% in the second trimester and 12% in the third trimester compared to baseline. However, free carbamazepine levels did not change significantly during pregnancy compared to baseline. In the same study, in 22 women taking phenytoin monotherapy total phenytoin concentration decreased in all 3 trimesters from baseline (maximum of 61%). Free phenytoin concentrations decreased in the third trimester by 16%. Sufficient monotherapy data are not available to provide evidence for a change in levels or clearance during pregnancy for phenobarbital, valproic acid, primidone, ethosuximide, and other AEDs.

Lamotrigine metabolism through hepatic glucuronidation is enhanced during pregnancy by elevated concentrations of sex hormones. Declining plasma concentrations of lamotrigine during pregnancy, therefore, result in increased seizure frequency for more than 40% of patients. Lamotrigine clearance during pregnancy is 2 to 3 times higher than before pregnancy. The levels after delivery reach pre-pregnancy levels within 1 to 3 weeks.

Oxcarbazepine levels are also significantly affected by pregnancy, and there is a need for dosage adjustment during pregnancy. The plasma concentration of the active form of oxcarbazepine (monohydroxy derivative) declines by 36% to 50% in the late stages of pregnancy and is associated with increased seizure frequency in 50% of women.

The elimination rate of levetiracetam is significantly increased during pregnancy due to increased renal glomerular filtration in late pregnancy. The clinical relevance of this finding is unknown, but given the increased elimination rate
therapeutic monitoring of levetiracetam levels during pregnancy may be valuable.\textsuperscript{57}

The American Academy of Neurology (AAN) practice guidelines suggest checking AED levels at baseline before conception and monthly thereafter. Dose adjustment should be considered to maintain an effective and stable level throughout pregnancy, at least for women with epilepsy who are on lamotrigine, oxcarbazepine, levetiracetam, carbamazepine, and phenytoin.\textsuperscript{47} The lack of evidence for changes in other AED levels during pregnancy should not discourage monitoring the levels during pregnancy.

**FETAL RISKS WITH SEIZURE RECURRENTS DURING PREGNANCY**

A generalized tonic-clonic seizure and postictal hypoxia can result in significant lactic acidosis as a result of lack of respiratory oxygen. Lactic acid can transfer to the fetus and result in fetal hypoxia and acidosis. Teramo and colleagues studied 3 women with epilepsy who experienced generalized tonic-clonic seizure during labor.\textsuperscript{58} There were marked changes in fetal heart rate for up to 60 minutes after the seizure. There was also a risk for increased uterine contractions during and after a seizure, resulting in decreased arterial blood flow to the placenta. A fall as a result of seizure may result in trauma to the uterus and possible placental abruption. The number of stillbirths (fetal death after 22 completed weeks of pregnancy) is slightly increased—1.2 to 1.3 times—in women with epilepsy.\textsuperscript{49}

To avoid the potential harmful effects of convulsive or prolonged partial seizures on the fetus and expectant mother, all efforts must be made to avoid these types of seizures during pregnancy. This means that AED use is indicated in the majority of women with epilepsy, despite potential risk for fetal malformation.\textsuperscript{59} Pre-pregnancy counseling and planning should include discussing the need for medication, type of medication, use of monotherapy, and obtaining baseline levels of AEDs. The levels should be monitored monthly during pregnancy and adjusted in case of significant drop or signs of seizure recurrence. In case of any seizure recurrence and fall, the patient should be immediately evaluated by the obstetrician clinic to ensure maternal and fetus well-being. The delivery should be arranged in a hospital that can handle the possibility of seizure recurrence during pregnancy and delivery.

In summary, for a pregnant woman with epilepsy, her neurologist should work closely with her high-risk obstetrician to manage her throughout the pregnancy, delivery, and immediate postpartum period. Proper management will minimize the risk for both mother and fetus.

**TERATOGENIC EFFECTS OF AEDS**

The majority of women with epilepsy give birth to normal, healthy children. There is a modestly increased risk for major congenital malformations, about 1.5- to 2-fold, among offspring of women treated for epilepsy during their pregnancy. Increased risk for congenital malformations in children of women with epilepsy was reported as early as the 1960s.\textsuperscript{60} Since then, numerous studies confirmed a greater risk for major congenital malformations among children of mothers treated for epilepsy during their pregnancy. The overall prevalence of congenital malformations in children of women with epilepsy was systematically reviewed during a meta-analysis of 59 studies, and the risk was estimated to be increased 3 times compared with healthy women.\textsuperscript{61} This increased risk could be a result of AEDs used during pregnancy or other factors related to maternal epilepsy. Overall, in a pooled analysis of data from 26 studies, the malformation
rate was 6.1% in children of women with epilepsy, as compared with 2.8% in children of untreated women with epilepsy and 2.2% in healthy women in the general population. Polytherapy in women with epilepsy carries a higher risk of fetal malformation of approximately 6.8%, as compared with monotherapy with a risk of 4%. The teratogenic side effects of AEDs appear to be dose dependent. There is an increased risk due to high doses as opposed to low doses of valproic acid, carbamazepine, phenobarbital, and lamotrigine. With valproic acid, the risk increases at doses above 700 mg/day.

In the North American AED Pregnancy Registry (NAAPR), lamotrigine monotherapy during pregnancy was associated with a 1.9% risk for malformation in the fetus. Carbamazepine monotherapy carried a risk of 3.0%, phenytoin 2.9%, phenobarbital 6.5%, and valproic acid 10.7% in the offspring of women with epilepsy. Polytherapy with lamotrigine and valproic acid resulted in a malformation rate of 9.1%, and with carbamazepine and valproic acid the rate was 15.4%. A recent meta-analysis of women exposed to topiramate during their pregnancy confirms that first-trimester exposure to topiramate is associated with a 6-fold increased risk of oral clefts. In March 2011, the FDA moved topiramate to a category D pregnancy label. Data on other newer AEDs are insufficient but so far do not indicate an alarmingly high risk with gabapentin, oxcarbazepine, and levetiracetam.

In summary, the majority of women with epilepsy will require continuing their AEDs during pregnancy to prevent seizures and potential harmful effects to their baby. A planned pregnancy and pre-pregnancy counselling should include simplifying the medication regimen and an attempt to use monotherapy at the lowest effective dose to minimize the teratogenic effects of AEDs.

FOLIC ACID SUPPLEMENTATION

Some AEDs, such as valproic acid, carbamazepine, phenobarbital, phenytoin, and primidone, alter folic acid metabolism and may decrease folic acid levels in the blood. Folic acid deficiency can increase the risk of neural tube defects and folic acid supplementation is recommended for women with epilepsy who are planning pregnancy, as it is for all women of childbearing age when not using contraception. The effective dose of folic acid is a matter of debate as there is insufficient data for clear advice regarding the dose. A systematic review by Wald et al concluded that 5 mg of folic acid daily in women without epilepsy renders 85% protection against neural tube defects. Folic acid studies in women with epilepsy do not show convincing evidence regarding the dosage needed in this population. The dose recommended by the AAN is a minimum of 0.4 mg folic acid supplementation daily prior to conception and throughout the pregnancy. A dose of 4 to 5 mg daily in women taking carbamazepine, phenobarbital, phenytoin, primidone, and valproic acid is common practice.

BREASTFEEDING

Breastfeeding is associated with reduced risk of lower respiratory tract infections, atopic dermatitis, asthma, acute otitis media, gastroenteritis, obesity, diabetes, childhood leukemia, sudden infant death syndrome, and necrotizing enterocolitis. Despite the clearly known benefits of breastfeeding, many women with epilepsy hesitate to breastfeed their newborns due to the potential risk of exposure of their infants to AEDs through breast milk. All AEDs can pass into the breast milk to a certain degree, but the amount transferred through breast milk is much less than the amount transmitted through the placenta to the fetus. Most medications have
a low transfer rate into the breast milk, especially the medications with higher protein binding affinity such as carbamazepine, phenytoin, and valproic acid.

Serum levels of valproic acid in infants of mothers who breastfed their babies were measured to be 0.9% to 2.3% of the mother’s serum level. There is only one known adverse report associated with valproic acid use during breastfeeding, where an infant developed thrombocytopenia and anemia while breastfed on valproic acid. The Neuropsychological Effects of Antiepileptic Drugs (NEAD) study did not demonstrate any deleterious effects of breastfeeding during valproate therapy on cognitive outcomes in children who were previously exposed to valproate during their mother’s pregnancy. This study also did not find any neurocognitive side effects of carbamazepine, lamotrigine, and phenytoin in breastfed infants.

For phenytoin, the drug levels in infants are lower than 5% of maternal plasma concentrations. One report in 1954 described decreased suck, drowsiness, and methemoglobinemia in an infant breastfed on phenytoin.

Plasma levels of carbamazepine in breastfed infants are very low, with a milk/maternal plasma ratio of 0.64 to 0.79. Only 2 reports of liver dysfunction exist in breastfed infants of mothers who were taking carbamazepine.

Lamotrigine shows a milk/maternal plasma ratio of 41.3%, with an infant plasma concentration of 18.9% of maternal plasma concentrations. Mild thrombocytosis was the only reported side effect in breastfed infants of mothers who continued lamotrigine while breastfeeding.

Levetiracetam shows a milk/maternal serum ratio of 1.05 (range 0.78–1.55), and the infant’s level is approximately 13% of the mother’s serum level. Despite the high transfer rate, the infant serum level stays low, suggesting that the amount the infant absorbs is low.

Topiramate shows a milk/maternal plasma ratio of 0.86 (range 0.67–1.1). Between 2 and 3 weeks after delivery, the infant’s serum level of topiramate is barely detectable and no clear adverse events are reported in breastfed infants of mothers taking topiramate. Zonisamide also has not been associated with any adverse events in breastfed infants.

For barbiturates and benzodiazepines, the risk–benefit ratio should be evaluated more carefully. Despite low levels of phenobarbital and primidone in breast milk, there are reports of sedation, lethargy, weight loss, and higher drug levels in the child than in the mother.

In summary, breastfeeding is encouraged in women with epilepsy who took AEDs during pregnancy. Except for barbiturates and benzodiazepines, the reported side effects in infants who are breastfed on other AEDs have been rare or infrequent, and the benefit may outweigh the risks.

PERIMENOPAUSE AND MENOPAUSE

Perimenopause is characterized by decreased ovarian progesterone secretion, resulting in increased occurrence of anovulatory menstrual cycles. During the early stages of perimenopause, estrogen secretion remains high, which creates an excitatory environment and contributes to seizure exacerbation in women with catamenial epilepsy. When menopause establishes due to the diminished levels of FSH and hypogonadal state, seizures stabilize.

Harden and colleagues reported the results of a questionnaire which was sent to women with epilepsy currently in menopause and perimenopause seeking information regarding the course of their
epilepsy and treatment. Two thirds of women with “hot flashes” and recent onset of menstrual changes reported an increase in seizures. A high percentage of these women took synthetic hormonal replacement therapy (HRT), which was significantly associated with seizure exacerbation. A history of catamenial seizures also correlated with seizure exacerbation during the perimenopause state. The menopausal group reported decreased seizure frequency.

A follow-up randomized, double-blind, placebo-controlled trial of HRT in menopausal women with epilepsy using 0.625 mg conjugated equine estrogen/2.5 mg medroxyprogesterone (CEE/MPA) found that seizure frequency significantly increased in a dose-related manner with the use of HRT in this formulation. The study was terminated after a small number of participants were randomized due to increased risk of breast cancer with this form of HRT.

Women with epilepsy are at risk for early ovarian failure due to HP axis dysfunction. Klein and colleagues reported a premature ovarian failure rate of 14% in women with epilepsy as compared with a rate of 3.7% in healthy control women. Women with premature ovarian failure and early menopause were more likely to have a history of frequent seizures as well as catamenial epilepsy.

In summary, women with catamenial epilepsy are at risk for seizure exacerbation during the perimenopause state. Their seizure medications may need to be adjusted to higher therapeutic levels. Once menopause is achieved, the doses may be reduced back to their baseline. The CEE/MPA formulation of HRT needs to be avoided in these patients; for women in whom hot flashes are disturbing sleep, consultation with the patient’s gynecologist is warranted to explore other hormonal treatment approaches.

### BONE HEALTH

Long-term treatment with AEDs can put patients with epilepsy at increased risk for bone loss, low bone mineral density (BMD), and fractures. Abnormal bone health is associated with epilepsy and independently with EIAEDs. Cytochrome P450-inducing AEDs are reported to be associated with bone loss. Persons with epilepsy have a risk for fracture that is 2 to 6 times higher than that of the general population. Falls as a result of seizure or secondary to AED-induced loss of balance can increase fracture risk.

Phenytoin and phenobarbital are most consistently associated with low BMD. Long-term gabapentin use in several studies was associated with bone loss at the hip and spine. Findings with carbamazepine and valproic acid and lamotrigine are mixed. In a systematic review of the literature, Vestergaard reported that only 3 out of 11 carbamazepine monotherapy studies and 6 out of 11 valproic acid monotherapy studies showed a significant reduction in BMD. Pack and colleagues studied the effect of AED monotherapy on bone density after 1 year of treatment in premenopausal women. In 23 women who were taking lamotrigine monotherapy, there was no detectable adverse effects on bone turnover or BMD. However, Guo et al examined bone mass in children treated with long-term valproate and combination lamotrigine therapy. They reported that this combination was associated with short stature, low BMD, and reduced bone formation. They suggested that these alterations may be mediated primarily through reduced physical activity rather than through a direct link to the valproic acid or lamotrigine therapy. Oxcarbazepine and topiramate were studied for their effects on BMD, and no significant bone loss was found. Koo et al studied 61 patients with recent-onset epilepsy re-
Managing monotherapy with levetiracetam, and found no decrease in BMD.93

Levels of active vitamin D metabolites such as 25-hydroxy-vitamin D may be low in people with epilepsy who are on EIAEDs. Elevated bone turnover markers in these patients reflect increased bone remodeling and are associated with a higher rate of bone loss and are independent predictors of bone fracture.81,83,94–97

Monitoring of calcium and vitamin D metabolites is important in patients who take EIAEDs. Current guidelines suggest that 25-hydroxyvitamin D concentrations should be above 30 ng/mL. A higher dose of vitamin D supplementation may be needed in these patients. Dual energy X-ray absorptiometry (DEXA) scan should be performed periodically to monitor BMD. If osteopenia or osteoporosis is detected, consideration should be given to starting bisphosphonates or other therapeutic agents, increasing calcium and vitamin D supplementation, and/or replacing EIAEDs. The patient may benefit from referral to an endocrinologist.

CONCLUSION

Women with epilepsy face challenges across their life cycle. The challenges start with puberty and menses, and continue throughout their life, including birth control, conception, pregnancy, childbirth, breast feeding, childcare, bone health, and menopause. Health care professionals must remain informed and up to date regarding the specific issues in the care of women with epilepsy. In the case of patient S.B., her seizures were consistent with catamenial epilepsy (C1 or perimenstrual type). She should have been informed of the risk of contraceptive failure with EIAEDs such as oxcarbazepine and offered an additional alternative contraception method such as IUD. She needs counseling regarding the potentially teratogenic side effects of oxcarbazepine and the fact that it is a pregnancy category C medication; however, the risk of seizures during this pregnancy may be higher than the risk to the fetus from exposure to oxcarbazepine. Detailed level 4 ultrasound at around week 17 of pregnancy and close follow up with a neurologist/epileptologist and high-risk obstetrician are recommended throughout her pregnancy. Other investigations, including assessment of serum alpha-fetoprotein level and amniocentesis, may be offered to her depending on detection of any fetal abnormalities with the ultrasound. She needs monthly monitoring of her oxcarbazepine levels and adjustment of the dose in case of a significant drop in the medication levels. She may need immediate dose adjustment for oxcarbazepine since her auras, which are simple partial seizures, have recurred, likely secondary to hormonal changes in her body and her pregnancy.

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