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Clinical Updates in Women's Health Care

Seizures

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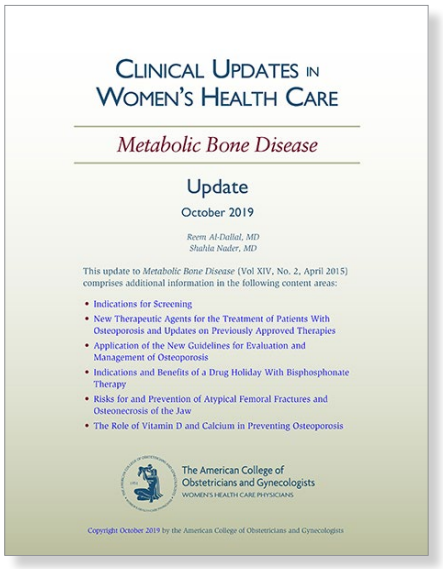
Clinical Updates in Women's Health Care

Updates



Updates to monographs in the *Clinical Updates in Women's Health Care* series are designed to provide important additional information to the content areas covered in the existing monographs. The current list includes Updates to the following titles:

- *Common Dermatologic Conditions* [Update January 2018]
- *Memory Loss and Dementia* [Update January 2019]
- *Metabolic Bone Disease* [Update October 2019]
- *Obesity* [Update August 2017]
- *Occupational Diseases and Injuries* [Update July 2016]
- *Sleep Disorders* [Update September 2015]

Contents

Continuing Medical Education

This monograph is designed to enable the obstetrician–gynecologist to do the following:

- Understand the pathophysiology and differential diagnosis of seizure disorders
- Understand how the menstrual cycle affects seizures
- Provide prepregnancy counseling with a focus on safe discontinuation of hormonal contraception and the teratogenicity of antiepileptic drugs
- Maintain seizure control during pregnancy and breastfeeding
- Provide care to postmenopausal women with epilepsy
- Initiate appropriate referrals

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a consultant and advisory board member for Invitae and provides research support for Natera; and Brandi Ring, MD, who is an owner of YouBossYou and a speaker at BossedUp. Any conflicts have been resolved through group and outside review of all content.

Foreword

Epilepsy affects 1.5 million women of childbearing age, and 24,000 women with epilepsy give birth annually in the United States. Thus, obstetrician–gynecologists (ob-gyns) not only provide obstetric care to many women on antiepileptic drugs (AEDs) but also address other reproductive health needs of these women, which often includes prescribing various hormonal therapies, such as contraception. Antiepileptic drugs can be prescribed for conditions other than epilepsy; therefore, ob-gyns should be knowledgeable of the drug–drug interactions between reproductive hormones and AEDs, which have the potential to affect the efficacy of either the hormonal therapy or the AEDs. The American College of Obstetricians and Gynecologists has published Committee Opinion No. 806, "Gynecologic Management of Adolescents and Young Women with Seizure Disorders," which is an excellent resource for the management of some of these issues in younger populations.

The authors of this monograph provide a comprehensive discussion of seizure disorders, ranging from diagnosis to management, across the entire spectrum of a woman's life. Dr. Amy Hessler completed her neurology residency at Tufts University in Boston, Massachusetts, and a clinical neurophysiology fellowship at the University of Michigan. She currently practices general neurology and women's neurology at the University of Kentucky, and her special interests include clinical epilepsy, headache medicine, and women's neurology. She is the past Chair of the Women's Issues in Neurology Section for the American Academy of Neurology where she also served as co-chair of the Sex-Related Factors in Neurologic Diseases. Dr. Katelyn Dolbec studied medicine at the University of Limerick in Ireland and completed residency in neurology at the University of Kentucky. She is currently completing a fellowship in epilepsy at Beth Israel Deaconess Medical Center in Boston.

This monograph serves as a valuable resource for providing care to women with epilepsy before and during pregnancy and through the postpartum period. The authors also have included useful information in guiding women with epilepsy through the menopausal transition and into their postmenopausal years, such as the effects of AEDs on menopausal hormone therapy and bone health.

Russell R. Snyder, MD
Editor

ABSTRACT: *Epilepsy is a common disease that affects 1.5 million women of childbearing age in the United States. Approximately 24,000 women with epilepsy give birth each year (1). The challenges for women with epilepsy extend from menarche to postmenopause, including prepregnancy, pregnancy, intrapartum and postpartum periods, menopause, and postreproductive age. The most up-to-date neurology and epilepsy guidelines provided in this monograph will enable obstetrician–gynecologists to provide care to women with this complex condition across the life span.*

Epilepsy is a major health and socioeconomic problem (2). In 2004, The World Health Organization (WHO) estimated that 50 million individuals worldwide have epilepsy (3). However, a more recent meta-analysis took into consideration both lifetime and active epilepsy cases and derived a greater number of individuals globally affected by epilepsy, potentially making epilepsy more prevalent than previously thought (2). In the United States, 1.5 million women of childbearing age have epilepsy, and 24,000 women with epilepsy give birth annually (1).

Basic Science

The International League Against Epilepsy states that epilepsy is a disease of the brain (previously considered a disorder), with the diagnosis established after one of the following (4):

1. Two unprovoked seizures occurring more than 24 hours apart
2. One unprovoked seizure with a high risk of recurrence (at least 60% over the next 10 years)
3. Diagnosis of an epilepsy syndrome based on electroencephalography, age at onset, course of epilepsy, associated neurologic and neuropsychologic findings, and underlying genetic or pathophysiologic mechanisms

The terminology has changed from partial to focal seizures within the past decade (5). However, it is important for health care professionals to be familiar with both terms because both appear in the literature and may be used by patients. The most up-to-date terminology is shown in Table 1.

Differential Diagnosis

Before a diagnosis of epilepsy is established, other transient disorders must be excluded. The obstetrician–gynecologist (ob-gyn) can initiate the evaluation by obtaining a history of the patient's transient altered awareness or abnormal physical movements and referring the patient to a neurologist for further assessment.

Table 1. Epilepsy Terminology ⇦

Old	New
Simple partial	Focal with preserved awareness
Complex partial	Focal with altered awareness
Generalized	Generalized
Secondary generalized	Focal to bilateral tonic–clonic

Not all events of altered awareness or shaking are seizures. If these transient events are seizures, the neurologist must identify the seizure type to determine the best treatment for a particular patient. Nonepileptic episodic events are relatively common and are an important consideration. These events are divided into two categories by cause:

1. Physiologic causes
2. Psychogenic causes

Nonepileptic physiologic causes include both events of neurologic and nonneurologic origin (Box 1). Syncope is an important differential diagnosis of cardiac origin, especially when accompanied by clonic movements; this is referred to as convulsive syncope and is nonepileptic in nature. The most common psychogenic cause of a nonepileptic episodic event is psychogenic nonepileptic seizure (6) (Box 1). Psychogenic nonepileptic episodic event is common in women with a history of abuse, particularly sexual abuse. The medical literature has more than 20 terms for this condition, including “pseudoseizures,” which can confer a negative connotation; therefore, "psychogenic nonepileptic seizure" is the more correct term. The condition has traditionally been thought to be the behavioral or physical manifestation of a somatoform or conversion disorder.

Box 1. Nonepileptic Episodic Events

Physiologic Causes

Neurologic

- Migraine
- Sleep disorders (eg, parasomnia)
- Cerebrovascular disorders (eg, transient ischemic attack)
- Movement disorders (eg, tremor or nonepileptic myoclonus)

Nonneurologic

- Metabolic abnormalities (eg, toxin ingestion)
- Cardiac arrhythmias (eg, syncope)

Psychogenic Causes

- Psychogenic nonepileptic seizure

Currently, this condition is considered to have a complex, multifactorial etiology within the realm of functional neurologic disorders (7). To determine the etiology of transient events, the neurologist should obtain a detailed history from the patient and observers, perform a detailed neurologic examination, and use additional testing depending on the history and physical findings. Additional testing will most often include electroencephalography (EEG). This can be an ambulatory EEG, a routine EEG in the outpatient setting, or a hospital admission for long-term EEG monitoring, also referred to as video EEG monitoring. Unless medically contraindicated, brain imaging, most often magnetic resonance imaging, may be used to look for a cause of the seizure. Seizures can be caused by multiple underlying causes (eg, a developmental anomaly, such as cortical dysplasia, or a structural abnormality, such as a brain tumor).

Establishing an accurate epilepsy diagnosis after considering other nonepileptic etiologies is important to provide individualized care to the woman across her life span. Important considerations include contraception, pregnancy, intrapartum and postpartum concerns, and postreproductive health issues (8).

Gynecologic Management

Contraception

Women with epilepsy who use antiepileptic drugs have a risk of drug–drug interactions with combined hormonal contraception, potentially resulting in failure of either the contraceptive or the antiepileptic drug. The interaction between antiepileptic drugs and combined hormonal contraception can be complex, and both medications can have negative effects on each other when used together. Antiepileptic drugs often are used for patients with conditions other than epilepsy, such as neuropathic pain, psychiatric conditions, and migraine; therefore, it is important to consider possible interactions when discussing contraception with the patient (9).

The American College of Obstetricians and Gynecologists (ACOG) has published a Committee Opinion Number 806 entitled "Gynecologic Management of Adolescents and Young Women with Seizure Disorders" that discusses the complex interaction between contraception and antiepileptic drugs (10). Additional relevant details regarding hormonal contraception are provided in ACOG Practice Bulletin Number 206, "Use of Hormonal Contraception in Women with Coexisting Medical Conditions" (11) and ACOG Committee Opinion Number 735, "Adolescents and Long-Acting Reversible Contraception: Implants and Intrauterine Devices" (12).

The Menstrual Cycle and Its Effect on Seizures

Catamenial epilepsy is associated with a twofold or greater increase in daily seizure frequency as proposed originally in the seminal work of Herzog et al (13). This worsening of seizures may be related to the cyclic variations in serum levels of neuroactive steroid

hormones (13). One third of women with intractable focal epilepsy have a catamenial exacerbation (14).

The two most common increases in seizure pattern are during the perimenstrual period (3 days before menses and the first 3 days of menses) and the periovulatory period (mid-cycle) (10). Seizure frequency is lowest during the midluteal phase (15).

A simplified explanation of the effect of sex hormones on epileptogenesis is that **e**strogen tends to be **e**pileptogenic, and **p**rogesterone tends to be **p**rotective. A detailed overview of neurosteroids affecting the brain by direct membrane-mediated effects and receptor-mediated or genomically-mediated effects is beyond the scope of this manuscript but is available from other associations (eg, the Herzog article in the section "Resources").

Because estrogen and progesterone levels vary throughout the menstrual cycle, seizures may worsen as the serum estradiol-to-progesterone ratio changes throughout the cycle. This ratio is highest during the days before menstruation and ovulation, and it is lowest during the early phase and midluteal phase. The current theory ascribes premenstrual exacerbation to the precipitous decrease in "protective" progesterone levels, whereas the periovulatory exacerbation is caused by an increase in "epileptic" estrogen levels unaccompanied by an increase in progesterone levels until ovulation. The midluteal phase is a relatively quiescent period for seizures because it is associated by the highest levels of progesterone. The exception to this is the anovulatory cycle during which a midcycle surge in estrogen levels is unaccompanied by a surge in progesterone levels (15).

There are no approved treatments for catamenial epilepsy. Management is divided into nonhormonal and adjunctive hormonal approaches. Some antiepileptic drug levels can be safely increased during the periods of hormonal exacerbation, whereas the levels of drugs with narrow therapeutic windows cannot be increased, and the treating health care professional should consider adjunctive strategies (1, 16).

Acetazolamide is one of the oldest treatments for catamenial epilepsy dating back more than 60 years (17). In a retrospective study, a small number of women (N = 20) treated with acetazolamide, where 55% were given the drug continuously and 45% were given the medication intermittently, there was a greater than 50% reduction in seizure frequency reported by 40% of the subjects, with the response rates being similar in generalized and focal epilepsies (18). The regimen of 250–500 mg of acetazolamide daily 3–7 days before menses has been widely used (18). One small trial studied the effects of clomiphene administered in the perimenstrual pattern (ie, days 5–9 before menses) and showed an 87% seizure reduction in patients with focal epilepsy; however, one unplanned pregnancy, ovarian cysts, breast tenderness, and pelvic cramping occurred among patients in that study (19). Thus, clomiphene is not routinely recommended for seizure management in reproductive-aged individuals. In another study of 10 patients, management with gonadotropin-releasing hormone analogues resulted in seizure freedom in three patients

and a greater than 50% reduction in seizures in four patients, but long-term safety has not been established (20).

Benzodiazepines, such as clonazepam and clobazam, have been a popular adjunctive choice for patients with catamenial epilepsy. Clobazam has been found to have a greater than 50% reduction in seizure frequency in 44% of patients when administered at 20–30 mg per day for 10 days starting 2 days before the period of seizure worsening (21).

The National Institute of Health Progesterone Treatment Trial was a randomized, placebo-controlled, double-blind, phase 3 multicenter clinical treatment trial of progesterone compared with placebo for intractable epilepsy in women with and without catamenial epilepsy (22). This trial found that cyclic progesterone supplementation did not improve symptoms of the three patterns of catamenial exacerbation. The investigators speculated that the pathophysiology was likely different. However, a post hoc analysis found that a subset of women with any type of perimenstrual exacerbation caused by withdrawal of progesterone responded to cyclic progesterone treatment (23). Practical treatment guidance suggested by the investigators is to have women track perimenstrual exacerbation, and if this identifies a greater than threefold increase in seizures, progesterone supplementation may be beneficial in this select population. In the original trial, women were given progesterone lozenges, 200 mg, three times daily, on days 14–28 of the menstrual cycle (22).

In a small, open-label study, 14 patients received medroxyprogesterone, 10 mg orally, 2–4 times per day, or depot medroxyprogesterone acetate, 120–150 mg intramuscularly, every 6–12 weeks (24). The results showed a 50% reduction in seizures; however, 63% of patients developed amenorrhea (24). The study has not been replicated, and there is long-term risk of loss of bone density.

CASE NO. 1. A 42-year-old gravida 1, para 1 woman has a history of focal epilepsy that has been well controlled with levetiracetam. However, the patient now reports worsening of her seizures several days before menses for the past 5 years. Neurologic examination yields unremarkable results. Her menses are occurring every 26 days. She is prescribed a monophasic oral contraceptive pill (OCP). The seizure regimen has included levetiracetam, 1,000 mg twice daily. Because her menstruation is predictable with the OCP, and she usually has a seizure 1 day before the start of menstruation, she is started on clobazam, 15 mg once daily, from 3 days before to 3 days after menstruation. Patient returns a year later and reports that her catamenial seizures are well controlled on the clobazam.

This patient has perimenstrual exacerbation consistent with a diagnosis of catamenial epilepsy. The treatment options are hormonal or nonhormonal. The treating neurologist chose clobazam as a short-term prophylaxis for her catamenial epilepsy as adjunctive therapy and without changes to her baseline antiepileptic drug therapy (21). Other potential treatment options include medroxyprogesterone, acetazolamide, or a short course of progesterone lozenges. The National Institute of Health Progesterone Treatment Trial failed to show benefit (22), but a secondary analysis showed benefit in women with a perimenstrual exacerbation (23).

Seizures and Reproductive Function

Reproductive dysfunction is common in women with epilepsy and manifests as menstrual disorders, hirsutism, and infertility. This may be a direct effect of seizures on the hypothalamic–pituitary–adrenal axis or from the medications used to control the seizures (25).

Menstrual disorders occur in one third of women with epilepsy, compared with 12–14% of women in the general population. Ovulation rates are substantially decreased in women with epilepsy. One third of women with epilepsy having focal seizures are anovulatory compared with 8–10% in women without epilepsy. However, there is conflicting evidence that anovulatory cycles may be more common with focal versus generalized epilepsy (26). The most common comorbid endocrine disorder is polycystic ovary syndrome (PCOS). The occurrence in women with epilepsy is 10–20% compared with 5–6% in the general population (26). Of women with epilepsy who take valproate, 45% were shown to have menstrual disorders, and of those, 90% had PCOS, hyperandrogenism, or both. Valproate-related weight gain can exacerbate the adverse endocrine effects (27). Women with epilepsy have increased rates of hypothalamic amenorrhea, functional hyperprolactinemia, and premature menopause (26). Anatomically, the amygdala has reciprocal connections with the hypothalamus. Commonly, seizures begin in the mesial temporal lobes, and this reciprocal connection can disrupt the cells that produce gonadotropin-releasing hormone in the preoptic area of the hypothalamus, which results in abnormal luteinizing hormone and follicle-stimulating hormone levels and, in turn, abnormal levels of sex hormones (25).

Antiepileptic drugs used to control seizures also are used for many other psychiatric and pain syndromes. These medications have the potential for deleterious effects, including endocrine, fertility, sexual function, and bone health. This is particularly important when prescribing the enzyme-inducing antiepileptic drugs; nonenzyme-inducing antiepileptic drugs have not been associated with these effects (10). Women with epilepsy who take carbamazepine and phenytoin (both enzyme-inducing antiepileptic drugs) are more likely to have sexual dysfunction than those who take lamotrigine or valproate (28). Lamotrigine has demonstrated improved sexual function scores compared with carbamazepine (29).

Fertility data in women with epilepsy are conflicting. An older population study found that fertility rates were reduced in women with epilepsy (30). Another population study found no difference in birth rates in women with epilepsy compared with age-matched controls (31). A more recent observational cohort study compared the fertility of 89 women with epilepsy with that of 108 age-matched controls (32). The study found that women with epilepsy, without known infertility, had comparable likelihood of achieving pregnancy. Live birth rates were comparable between women with epilepsy and women without epilepsy (median time to pregnancy was no different between the groups after controlling for key covariates).

Obstetric Management

Prepregnancy Counseling

Ideally, a woman with epilepsy would present for prepregnancy counseling. Seizure freedom 9 months to 1 year before pregnancy is the best predictor of seizure freedom during pregnancy. This seizure freedom is associated with a high likelihood (84–92%) of seizure freedom for the entire pregnancy (33). Notably, catamenial epilepsy tends to improve during pregnancy (34).

Prepregnancy counseling most likely is initiated by an ob-gyn, but comanagement with the treating neurologist is important. The neurologist may consider further steps to evaluate the patient, including inpatient EEG monitoring, epilepsy surgery, and establishing a baseline antiepileptic drug therapeutic level if and when seizure freedom is achieved. The following topics should be discussed:

- Which antiepileptic drug has the least potential risk to the fetus while maintaining seizure control?
- Should the antiepileptic drug regimen be changed if it is associated with a high teratogenic risk (such as valproic acid)? Should the antiepileptic drug dosage be decreased to the lowest level possible while still maintaining seizure control, particularly if the seizures have been well controlled?
- Should the antiepileptic drug regimen be discontinued if the patient has been seizure free for 2–4 years depending on risk factors?

With these medication changes in anticipation of pregnancy, a woman should be counselled to continue using contraception and folic acid supplementation (35).

Discontinuation of Contraception

The approach for discontinuing antiepileptic drugs is variable and often physician dependent because a standardized protocol has not been published. No recommendations are available for obtaining levels while tapering off an antiepileptic drug. One approach for monitoring antiepileptic medication levels while discontinuing combined hormonal contraception involves obtaining a level measurement of the antiepileptic drug if the patient develops any new symptoms or potential adverse effects from the medication. Otherwise, obtaining a level of the antiepileptic drug with any major change in combined hormonal contraceptive regimen is helpful in ensuring the antiepileptic drug dosage remains therapeutic.

Seizure Control During Pregnancy

The management of the pregnant women with epilepsy can be complex and requires a multidisciplinary approach. Seizures during pregnancy may lead to fetal hypoxia, acidosis, decreased placental blood flow, deceleration in fetal heart rate, maternal trauma from

a convulsion, and maternal sudden unexpected death in epilepsy (1, 36). Compared with women with epilepsy who remain seizure free during pregnancy, women with epilepsy with seizures during pregnancy have a greater risk of low-birth-weight infants, preterm delivery, and fetuses that are small for gestational age (37). The occurrence of one or more convulsions during gestation can be associated with a premature birth, increased risk of preterm delivery (up to five times), and reduced birth weight in male infants compared with the seizure-free population (36).

Unplanned Pregnancy

One study showed that almost 80% of women with epilepsy had an unplanned pregnancy, compared with 45–51% in the general population (38). Most women with epilepsy taking potentially teratogenic antiepileptic drugs reported not using any form of contraception (39). Therefore, health care professionals who provide care to women with epilepsy should discuss family planning at all visits. If an unplanned pregnancy occurs, the antiepileptic drug regimen should be changed only if the benefit outweighs the inherent risk of loss of seizure control. Ideally, this decision should be a multidisciplinary effort (36).

Antiepileptic Drug Use and Fetal Outcomes

Several large worldwide antiepileptic drug and pregnancy registries prospectively collect data about women with epilepsy or women who use antiepileptic drugs for other medical conditions and compare these data with those for healthy, age-matched controls. These registries include the Harvard University's North American Antiepileptic Drug Pregnancy Registry; the International Registry of Antiepileptic Drugs and Pregnancy, which encompasses 45 countries in Europe, Oceania, Asia, Latin America, and Africa; the Australian Epilepsy Pregnancy Register; The UK Epilepsy and Pregnancy Register; Kerala Registry of Epilepsy and Pregnancy (India); and various pharmaceutical registries.

Major congenital malformations are abnormalities that interfere with organ structure or function and often require surgical intervention or repair, including neural tube defects, cardiac anomalies, orofacial clefts, skeletal defects (particularly club foot), and hypospadias. Major congenital malformations may result from fetal exposure to antiepileptic drugs, especially during the first trimester. Most major congenital malformations occur between 3 weeks of gestation and 10 weeks of gestation. Often, at such an early gestational age a woman is unaware of pregnancy, which emphasizes the importance of regular family planning discussions. The rate of major congenital malformations in the general population is 1–3%, and the risk of fetal malformations in fetuses of women with epilepsy who do not take antiepileptic drugs is similar (10). In fetuses of women with epilepsy who take antiepileptic drugs, the overall rate of major congenital malformations is approximately twofold to threefold higher (40). A systemic review and meta-analysis

of registry data and cohort data of pregnancies of women with epilepsy, which included 65,000 women with epilepsy and 1.8 million controls (41), found that the risk of major congenital malformations was increased with antiepileptic drug monotherapy and further increased with polytherapy, especially when containing valproate, phenobarbital, or phenytoin. Therefore, these agents should be avoided during pregnancy, if at all possible. The Neurodevelopmental Effects of Antiepileptic Drugs study was a prospective observational study analyzing the cognitive effect of antiepileptic drug exposure in utero (42). Based on the results of this study, the U.S. Food and Drug Administration expanded its warning on valproate use in pregnancy to include a risk of cognitive impairment in those children exposed in utero (42).

In 2012, North American Antiepileptic Drug Pregnancy Registry published an article on the comparative safety of antiepileptic drug monotherapy during pregnancy (43). In 2016, an update to this study was published (44). Between February 1997 and December 2015, the Registry enrolled a total of 9,294 pregnant women who were taking antiepileptic drugs for any reason. Of these enrolled participants, 5,962 were taking an antiepileptic drug as monotherapy in the first trimester of pregnancy. Percentages of major congenital malformations for the commonly used drugs are shown in Figure 1. The International Registry of Antiepileptic Drugs and Pregnancy analyzed prospective data on 7,555 pregnancies, which showed the highest rate of major congenital malformations with valproate (10.3%) and the lowest with levetiracetam (2.8%) (45).

A meta-analysis of 96 studies found that several monotherapies were associated with major congenital malformations or prenatal growth alterations (46). Those therapies included the following:

- Carbamazepine (major and minor malformations)
- Clobazam (prenatal growth restriction and premature birth)
- Ethosuximide (major congenital malformations, orofacial clefts, and club feet)
- Gabapentin (cardiac malformations and hypospadias)
- Phenobarbital (major congenital malformations, prenatal growth restriction, and orofacial clefts)
- Phenytoin (major congenital malformations, orofacial clefts, and club feet)
- Topiramate (major congenital malformations, combined fetal losses, prenatal growth restriction, and orofacial clefts)
- Valproate (major and minor congenital malformations, combined fetal losses, hypospadias, orofacial clefts, and club feet)

The newer-generation antiepileptic drugs, such as lamotrigine and levetiracetam, although associated with potential teratogenic risks in utero, were not associated with significantly increased risks of congenital malformation compared with control regimens

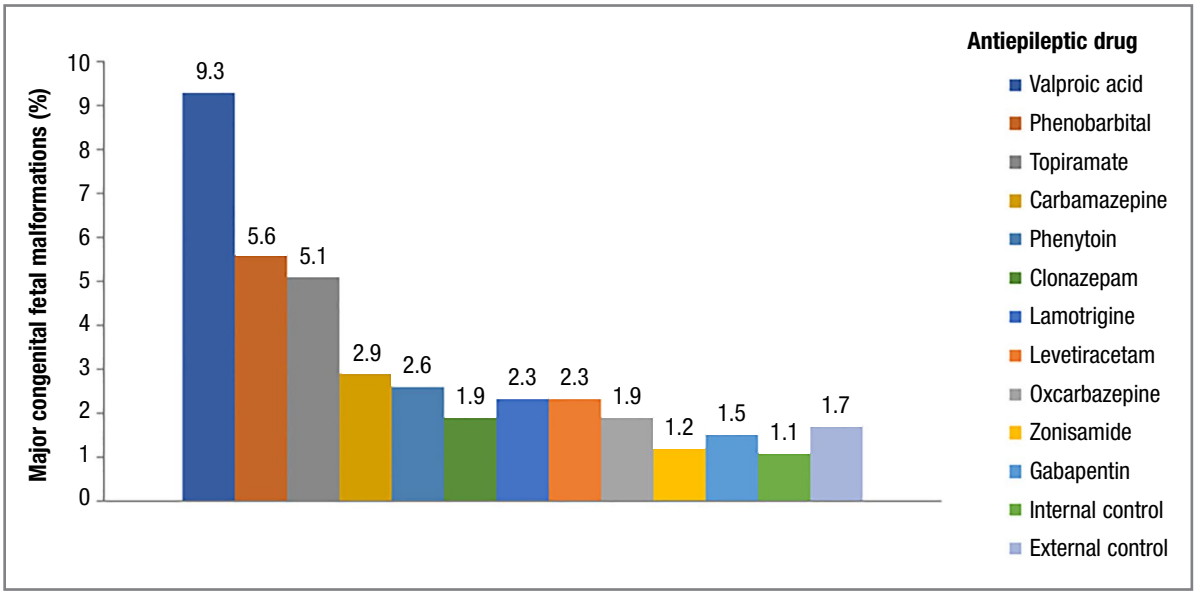

Figure 1. Major congenital fetal malformations associated with antiepileptic drug use in pregnancy. (Data from North American Antiepileptic Drug Pregnancy Registry. Update on monotherapy findings: comparative safety of 11 antiepileptic drugs used during pregnancy. Boston, MA: North American AED; 2016.) ⇦

in the study. Several polytherapy regimens also had associated major congenital malformations (46). In 2009, American Academy of Neurology (AAN) and American Epilepsy Society (AES) published a Practice Parameter Update in which they recommend the following (40):

1. The use of valproate during the first trimester should be avoided.
2. The use of polytherapy with valproate during the first trimester should be avoided.
3. The use of phenytoin and phenobarbital should be avoided to prevent impaired cognitive outcomes in the fetus.

Breakthrough Seizures and Monitoring of Antiepileptic Drug Levels

A multidisciplinary approach is ideal for monitoring levels and dose adjustments to mitigate undiscovered reductions in plasma concentrations of antiepileptic drugs with resultant breakthrough seizures. Target plasma concentration should be based on a patient's seizure history and prepregnancy levels and changed accordingly throughout pregnancy (47).

Obtaining a baseline antiepileptic drug level before pregnancy and monthly throughout pregnancy is especially important for lamotrigine, carbamazepine, phenytoin, levetiracetam, and oxcarbazepine because serum levels of these drugs are known to fluctuate throughout pregnancy. Insufficient studies do not allow conclusions to be reached regarding other antiepileptic drugs; however, most experts would recommend the same monitoring schedule to avoid decreasing serum levels and the risk of breakthrough seizures (48).

The reason for breakthrough seizures during pregnancy is most often multifactorial. When becoming pregnant, women often abruptly stop taking antiepileptic drugs out of concern that the antiepileptic drugs will harm the fetus. Hormone fluctuations, especially at 8–16 weeks of gestation; sleep deprivation; and psychosocial factors all contribute to worsened seizure control. However, the most common reason for breakthrough seizures is reduced plasma concentrations of antiepileptic drugs caused by changes in metabolism (1).

Lamotrigine and levetiracetam are commonly used in pregnancy because of their safety profiles. A retrospective study of 115 pregnant women found that the average serum clearance increased by 191% for lamotrigine and by 207% for levetiracetam compared with the baseline before pregnancy (49). Despite increasing dosage, seizures occurred in 38.4% of women during pregnancy, most often in the second trimester. This occurred more frequently if a woman had seizures in the year before pregnancy or had focal epilepsy. Lamotrigine is metabolized through hepatic glucuronidation, and its level is thought to be increased in pregnancy because of increased concentration of circulating sex hormones. In one study, the levels of lamotrigine returned to nonpregnant baseline within a month after delivery (50). Plasma concentration of levetiracetam also appears to decrease between the first trimester and second trimester and decreases significantly in the third trimester. Postpartum levels can increase to prepregnancy values within 2 weeks. Therefore, the levels should be checked carefully after delivery and regimen adjusted accordingly (50, 51).

Folic Acid Recommendations

Based on available evidence, the AAN and AES recommend supplementation with 0.4 mg of folic acid per day before and during pregnancy in women with epilepsy and those without epilepsy (48). Higher dosage of folic acid is not recommended because of insufficient data, and this recommendation is consistent with recommendations of multiple institutions nationwide, including ACOG (52). Studies examining a different dosage of folic acid in women with epilepsy are lacking, and research is needed to see if higher dosages would be beneficial for women with epilepsy who take antiepileptic drugs that interfere with folic acid metabolism (48).

CASE NO. 2. A 24-year-old woman, at 20 weeks of gestation, with a history of well controlled generalized epilepsy presents to the emergency department after a witnessed generalized tonic–clonic seizure lasting 2 minutes. She has a long-term history of generalized epilepsy after receiving the diagnosis at age 16 years. Levetiracetam and lacosamide have not controlled her seizures well. Therefore, she was subsequently started on lamotrigine. Currently, her seizures are well controlled with lamotrigine, 100 mg, twice daily. She had been seizure free for the preceding 1 year before pregnancy. She does not report any missed doses, any recent illnesses, or sick contacts. On examination, she is somnolent but easily arousable, and she is not able to recall any details of the seizure. Her neurologic examination yields normal results. She undergoes routine workup for causes of

breakthrough seizures, including toxic metabolic causes, which reveals a mild leukocytosis without shift but no other metabolic derangements. The results of chest radiography and urinalysis are unremarkable. Her lamotrigine level is checked and found to be subtherapeutic at 1 microgram per milliliter (normal range is 1.5–10 micrograms per milliliter).

Although lamotrigine is an appropriate antiepileptic choice for many women during pregnancy, it requires close monitoring to avoid subtherapeutic levels and resultant breakthrough seizures. Lamotrigine is metabolized through hepatic glucuronidation, and clearance is enhanced during pregnancy, which can contribute to decreased serum levels of lamotrigine. The American Academy of Neurology practice guidelines have suggested that a baseline lamotrigine level should be obtained before pregnancy and monitored regularly thereafter. The most frequent guidance is to check the levels monthly during pregnancy. If the levels are found to be low, the regimen should be titrated up throughout the pregnancy based on the monthly antiseizure medication levels (48).

CASE NO. 3. A 24-year-old gravida 1, para 0 woman with generalized epilepsy comes for a prenatal visit at 5 weeks of estimated gestational age (3 weeks after fertilization). She began having seizures at age 15 years. She was started on valproate before immigrating to the United States. She recalls her last tonic–clonic seizure 2 weeks ago. She is taking valproate, 750 mg, orally twice daily. She also takes a daily multivitamin. Neurologic examination yields normal results.

Valproate substantially increases the risk of neural tube defects. The neural tube develops within 28 days of fertilization. Additionally, the data from the Neurodevelopmental Effects of Antiepileptic Drugs Study found that valproate exposure in utero had worse neurocognitive outcomes in children (42). Because she is presenting within 5 weeks of gestation, it will be advantageous to switch the patient to a safer medication. Levetiracetam is chosen for its safety profile. To facilitate an abrupt discontinuation of valproate and to achieve a therapeutic dose of levetiracetam quickly, a 2,000 mg intravenous loading dose of levetiracetam is administered. Subsequently, she is started on levetiracetam, 1,000 mg, orally twice per day, and instructed to continue supplementation with folic acid, 0.4 mg per day orally. An alternative to levetiracetam would be lamotrigine (44). However, valproate is an enzyme inhibitor, resulting in higher serum concentrations of lamotrigine. Therefore, it is necessary to slowly titrate lamotrigine dosage to decrease the patient's risk of adverse effects, specifically Stevens–Johnson syndrome.

Obstetric Complications

Overall, there is no conclusive evidence of increased complications for women with epilepsy during pregnancy (33). Increased risk of cesarean delivery, late pregnancy bleeding, and premature labor and delivery were observed except in those patients who smoked. Individual studies have demonstrated increased obstetric risks; however, more data are needed to determine the underlying cause (ie, the epilepsy itself or the newer antiepileptic drugs used to treat the epilepsy) (53). One study suggested an increased risk of maternal mortality (54). It did not find a particular reason but suggested obstetric complications, complications from seizures, and sudden unexpected death from epilepsy.

Postpartum Management

The 2009 AAN/AES Practice Parameter concluded that a number of antiepileptic drugs are transferred into the breast milk; however, no further conclusions could be determined (48). Breastfeeding has many medical and psychologic benefits for the woman and the infant. However, the transfer of antiepileptic drugs into the breast milk can have adverse effects for the infant. Some antiepileptic drugs, such as barbiturates, benzodiazepine, lamotrigine, and ethosuximide, have the potential to reach significant serum levels. Therefore, the infant should be monitored by parents and pediatrician for adverse effects, particularly sedation (55).

The Neurodevelopmental Effects of Antiepileptic Drugs Study studied the potential deleterious effects of breastfeeding during antiepileptic drug therapy on cognitive outcomes (specifically, the intelligence quotient) in children who were previously exposed to antiepileptic drugs in utero. If the child was exposed to a single antiepileptic drug (ie, carbamazepine, lamotrigine, phenytoin, or valproate), no difference in cognitive outcomes at age 3 years was found whether the child was breastfed or not (56).

Women with epilepsy should consider pumping breast milk and having someone else feed the baby at night to avoid sleep deprivation leading to breakthrough seizures. When bathing the newborn, tub baths should be avoided, particularly if the woman with epilepsy is alone. Ideally, dressing and diaper changes should be performed on the floor to avoid the risk of falls from the changing table or a bed. If the woman with epilepsy has frequent seizures, she should avoid carrying the newborn when alone (57).

Considerations for Aging Women

Timing of Menopause

Women with epilepsy are at risk for premature menopause, change in seizure frequency related to menopause or hormone therapy (HT), and physiologic changes affecting metabolism of antiepileptic drugs. Bone health is another important consideration.

Several studies have recognized early onset of perimenopausal symptoms in the late fourth decade or early fifth decade in women with epilepsy. The risk of premature menopause is four times greater in women with epilepsy than in women without epilepsy (58). The frequency of seizures was seen as a risk factor for the development of earlier menopause (58). Women with fewer than 20 lifetime seizures had less risk of earlier menopause (ie, average age at menopause was 50–51 years) than women who had monthly seizures (average age at menopause was 46–47 years). There was no association between early menopause and a particular antiepileptic drug. Therefore, it was thought that the premature menopause was likely caused by epilepsy itself and the interictal activity on the hypothalamic–pituitary–gonadal axis (59).

Women with epilepsy who have had a catamenial pattern of epilepsy are particularly prone to worsened seizures during perimenopause. During this time, estrogen levels gradually decrease, and cyclic luteal phase progesterone surges are absent in anovulatory cycles. The estrogen-to-progesterone ratio generally is high and unpredictable. However, despite worsening during perimenopause, once menopause is achieved, the ratio decreases as does the number of seizures. Studies have shown that women with epilepsy can have a change in seizure frequency as they transition into menopause; therefore, careful monitoring of antiepileptic drugs may be required (60).

Hormone Therapy

Hormone therapy had been suggested to worsen seizure activity in women with epilepsy. Therefore, a double-blind, randomized, placebo-controlled trial on the effect of HT on seizure occurrence in menopausal women with epilepsy was undertaken (61). However, when the Women's Health Initiative (WHI) study showed that HT (0.625 mg conjugated equine estrogen plus 2.5 mg medroxyprogesterone acetate or conjugated equine estrogen–medroxyprogesterone acetate [CEE/MPA]) was associated with increased risk of breast cancer and stroke (62), the HT in women with epilepsy study was stopped early because of these safety concerns. A small number (n = 21) of patients did complete the study. After a 3-month prospective baseline, women were randomized to placebo, CEE/MPA daily, or a double-dosage of CEE/MPA for 3 months. Conjugated equine estrogen–medroxyprogesterone acetate and its dosages for the trial were chosen based on their wide usage. Furthermore, the same regimens were used in the WHI study. Results indicated that patients who used CEE/MPA had an association with dose-related increase in seizure frequency. However, a small number of participants may limit generalizability of this conclusion. Additionally, several women on lamotrigine had increased clearance (25–30%) while taking HT (61).

Despite the potential to worsen seizures in women with epilepsy, HT may be needed to manage perimenopausal symptoms, such as hot flushes, which may lead to sleep deprivation and further a risk of seizures. Some experts advocate a combination of a single estrogen compound, such as 17-β-estradiol, with a micronized progesterone to limit the exacerbation of seizures with CEE/MPA formulations (61).

Age-related physiologic changes decrease the overall clearance of antiepileptic drugs by 20–40% (63). This change is multifactorial because of other medical conditions and drug–drug interactions (eg, warfarin and valproate). A decrease in renal excretion rate and drug metabolism that occur with age are particularly important to consider with those antiepileptic drugs that are highly protein bound, because a decrease in serum albumin occurs with age. Carbamazepine and phenytoin plasma concentrations are variable in the aging patient (61).

Bone Health

Bone disease is an important consideration for women with epilepsy. Fracture rates are increased two to six times in children and adults with epilepsy compared with the general

population (64). The causes include an increased risk of osteoporosis, low bone density, falls resulting from seizures, effects of antiepileptic drugs leading to incoordination, lack of calcium intake, and decreased quality of bone because of the loss of estrogen (64).

Epilepsy and antiepileptic drug use have deleterious effects on bone health. Numerous mechanisms, including increased bone turnover, reduced bone mineral density, and possibly decreased quality of bone have been implicated in the development of secondary osteoporosis (65). Osteomalacia associated with antiepileptic drug treatment was noted in early studies (65). However, most of the patients in these studies were institutionalized and had poor diets confounding the assessment. Bone biopsies did not reveal osteomalacia. As mentioned earlier in this section, causes of fractures in women with epilepsy are likely multifactorial. For example, seizures themselves can lead to falls. The enzyme-inducing antiepileptic drugs have negative effects on bone health demonstrated in multiple studies (65). Data are lacking regarding the newer antiepileptic drugs. Therefore, women with epilepsy and those using antiepileptic drugs should be treated with adequate calcium and vitamin D supplementation (65). See the section "Resources" for ACOG's guidance regarding osteoporosis and further information regarding bone disease.

CASE NO. 4. A 50-year-old woman has a history of hot flushes and longstanding focal epilepsy. She has been seizure free for 2 years, but in the past 2 months she has had three seizures. These seizures typically start with a rising sensation in her stomach and then, per her husband, she stares with occasional abnormal mouth movements and picking at her clothing. The seizures last 45 seconds and are followed by 30–45 minutes of confusion. She then gets intense fatigue, so she takes a 2–3-hour nap. In her mid-20s, she also had seizures that occurred 1–2 days before her menses, and her neurologist believed this was catamenial epilepsy. She had a pregnancy at age 28 years and another at age 30 years. She did not have recurrence of the catamenial seizures. She is adamant that she has adhered to her regimen of oxcarbazepine, 600 mg, orally twice per day, and this has not been changed by the pharmacy to another preparation. Over the past 6 months her otherwise regular menses have become irregular. She is also experiencing frequent hot flushes.

The likely diagnosis is breakthrough seizures caused by hormone fluctuations related to perimenopause. The oxcarbazepine dosage is increased to 900 mg, orally twice per day, and she does not report any further seizures. Women with epilepsy who have previously had a catamenial pattern of epilepsy are particularly prone to worsened seizures during perimenopause. Increasing the dosage of antiepileptic drugs may be necessary to control these breakthrough seizures. The patient can be counselled that once menopause is achieved, the seizures may be stabilized (60).

Complementary and Alternative Medicine

The use of cannabis throughout pregnancy has been discouraged given the potential for health risks and lack of sufficient data to determine its safety profile in pregnancy (66). The use of cannabidiol in individuals with epilepsy has been studied only in children with refractory epilepsy (67). Its effect on contraceptive efficacy and teratogenic potential are unknown (10).

Antiepileptic drug therapy is the most studied form of seizure control and has been proved effective. Therefore, the use of alternative therapies should not be a cause for discontinuation of an antiepileptic drug regimen. There is no general consensus regarding medical alternatives that are best for women with epilepsy, including pregnant women. In some cases, the use of certain herbal supplements in pregnancy, such as blue cohosh, has been associated with severe adverse effects (68). The use of any essential oils or herbs that are known to interact with antiepileptic drugs should be avoided to ensure that the medication remains therapeutic.

Referral

Epilepsy is a common disease, and ob-gyns are likely to encounter women with epilepsy in their practice. Therefore, ob-gyns should be familiar with this and other seizure disorders as well as antiepileptic drugs. However, collaboration with a neurologist often is required. Box 2 contains important management questions to consider before consulting with or referring a woman to a neurologist.

Box 2. Referral Guide

Prepregnancy

- The following issues should be addressed:
  - — Has a diagnosis of epilepsy been established? Has a neurologist been identified who can provide care to a woman with epilepsy who uses contraception and is considering pregnancy?
  - — Has the line of communication been established with a treating neurologist?
  - — In anticipation of attempting to become pregnant, is the patient seizure free? The period of 9 months to 1 year without seizures predicts high likelihood of seizure freedom during pregnancy.
  - — Has a prepregnancy antiepileptic drug level been checked to serve as a baseline during pregnancy?
  - — Has the patient started supplementation with at least 0.4 mg of folic acid daily?

Pregnancy

- A line of communication should be established with a treating neurologist.
  - — Has the woman notified her neurologist that she is pregnant?
- A potential enrollment of the patient in North American Pregnancy Registry (see the section "Resources") should be discussed during clinic visit.

(continued)

Box 2. Referral Guide *(continued)*

- The antiepileptic drug levels (ideally trough levels) should be checked at least monthly during pregnancy. It is important to understand that the most common reason for breakthrough seizure is reduced medication concentration, especially lamotrigine, during the third trimester; however, levetiracetam also can have increased clearance and needs to be adjusted.
- In anticipation of delivery, any potential obstetric complications should be identified.

Postpartum Period

- After delivery, antiepileptic drug levels can return to baseline within 2–4 weeks
  - — Has a 2-week postdelivery level been checked, particularly if the dosage was increased during pregnancy?
- The following breastfeeding considerations should be discussed:
  - — Is the patient taking an antiepileptic drug with high transfer into breast milk?
  - — Has the pediatrician been made aware of the effects of the antiepileptic drug on the infant, ie, sedation?

Postreproductive Period

- Often, catamenial epilepsy improves in menopause. However, if the woman is perimenopausal and her seizure control has worsened, she should be referred to the neurologist to consider adjusting her antiepileptic drug regimen.
- The negative effect of the patient's antiepileptic drug regimen on bone health should be assessed.
- The patient should be prescribed adequate calcium and vitamin D supplementation, if needed.

Key Points

At each stage of the life cycle, women with epilepsy have challenges related to antiepileptic drugs as well as the epilepsy itself. Reproductive-aged women with epilepsy have additional concerns related to contraception, prepregnancy, pregnancy, and menopause. These patients can be successfully treated, but a multidisciplinary approach between an ob-gyn and the neurologist is necessary to optimize care of these women. The following key points should be useful to ob-gyns in providing care to patients with seizure disorders:

- In the United States, 1.5 million women of childbearing age have epilepsy and 24,000 women with epilepsy give birth annually (1).
- The importance of establishing an epilepsy diagnosis after considering other nonepileptic etiologies is important for appropriate management of a woman across her life span.

- Women with epilepsy who use antiepileptic drugs have a risk of drug–drug interactions with combined hormonal contraception, potentially resulting in decreased efficacy of either the contraceptive or the antiepileptic drug.
- The two most common increases in seizure frequency are during the perimenstrual period (3 days before menses and the first 3 days of menses) and the periovulatory period (midcycle) (10). Seizure frequency is lowest during the midluteal phase.
- Generally, estradiol is considered "epileptogenic," and progesterone is "protective."
- Treatment for catamenial epilepsy is divided into nonhormonal and adjunctive hormonal approaches. Most commonly, catamenial epilepsy is treated with benzodiazepines and, in certain cases, with medroxyprogesterone.
- Reproductive dysfunction is common in women with epilepsy and manifests as menstrual disorders, hirsutism, and infertility.
- Fertility in women with epilepsy is comparable to that in women without epilepsy.
- Seizure freedom for 9 months to 1 year before pregnancy is associated with a high likelihood (84–92 %) of remaining seizure free during pregnancy (33).
- Risk of seizures during pregnancy includes maternal injuries and maternal sudden unexpected death in epilepsy. Potential fetal risks include hypoxia, acidosis, decreased placental blood flow, deceleration in fetal heart rate, and maternal trauma.
- Women with epilepsy experiencing breakthrough seizures have a greater risk of giving birth to infants with low birth weight, preterm delivery, and fetuses that are small for gestational age (37).
- Use of valproate, phenobarbital, and topiramate during pregnancy is associated with the highest risk of major congenital malformations (41). The American Epilepsy Society has issued a position statement on the use of valproate in women of childbearing potential (see the section "Resources").
- Fetal exposure to valproate was associated with a decreased intelligence quotient (42). As a result, FDA expanded its warning on valproate use to include a risk of cognitive impairment in those children exposed in utero.
- Measuring a baseline antiepileptic drug level before pregnancy and then monthly for the rest of pregnancy is important, particularly for lamotrigine, carbamazepine, and phenytoin because of metabolic changes during pregnancy.
- Lamotrigine and levetiracetam have increased serum clearance during pregnancy; therefore, careful monitoring of serum levels is required.
- Postpartum levels can increase to prepregnancy values within 2 weeks. Therefore, the levels should be checked carefully after delivery, and regimens should be adjusted accordingly (50, 51).
- Folic acid supplementation should remain at 0.4 mg per day before pregnancy and during pregnancy (48).
- No conclusive evidence of increased obstetric complications has been reported for women with epilepsy. Some studies have demonstrated increased obstetric risks;

however, more data are needed to determine if the epilepsy itself or the newer antiepileptic drugs used to treat the epilepsy are the underlying cause.

- Breastfeeding is beneficial, but some antiepileptic drugs can pass into breast milk and cause sedation in the infant (48).
- Women with epilepsy have a variety of perimenopausal and menopausal issues, including a risk of premature menopause, change in seizure frequency related innately to menopause or associated with HT, and physiologic changes affecting metabolism of antiepileptic drugs.
- Epilepsy and antiepileptic drug use have deleterious effects on bone health, leading to falls and to secondary osteoporosis, respectively. Women with epilepsy who use antiepileptic drugs should have adequate calcium and vitamin D intake.

Resources

American College of Obstetricians and Gynecologists

Gynecologic management of adolescents and young women with seizure disorders: ACOG Committee Opinion No. 806. American College of Obstetricians and Gynecologists. Obstet Gynecol 2020;135:e213–20.

Use of hormonal contraception in women with coexisting medical conditions. ACOG Practice Bulletin No. 206. American College of Obstetricians and Gynecologists. Obstet Gynecol 2019;133:e128–50.

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The following list is for information purposes only. Referral to these sources and websites does not imply the endorsement of the American College of Obstetricians and Gynecologists. This list is not meant to be comprehensive. The exclusion of a source or website does not reflect the quality of that source or website. Please note that websites are subject to change without notice.

Websites

North American AED Pregnancy Registry
The North American AED (Antiepileptic Drug) Pregnancy Registry is the first hospital-based registry established to determine the safety of seizure medications that can be taken by women during pregnancy. Participants are interviewed at enrollment, at 7 months of gestation, and after pregnancy (8–12 weeks after delivery). Patients without epilepsy also are needed as controls.
North American AED (Antiepileptic Drug) Pregnancy Registry. North American antiepileptic drug pregnancy registry. Available at: https://www.aedpregnancyregistry.org/. Retrieved September 23, 2020.

(continued)

Resources *(continued)*

American Epilepsy Society
American Epilepsy Society provides resources for patients and clinicians, reviews of ongoing studies, and links to position statements.
American Epilepsy Society. Available at: https://www.aesnet.org/clinical_resources/women_with_epilepsy. Retrieved September 23, 2020.

Epilepsy Foundation
Epilepsy Foundation provides comprehensive patient education materials.
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American Academy of Neurology and American Epilepsy Society 2009 Practice Parameters

Harden CL, Hopp J, Ting TY, Pennell PB, French JA, Hauser WA, et al. Practice parameter update: management issues for women with epilepsy--focus on pregnancy (an evidence-based review): obstetrical complications and change in seizure frequency: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology 2009;73:126–32.

Harden CL, Meador KJ, Pennell PB, Hauser WA, Gronseth GS, French JA, et al. Practice parameter update: management issues for women with epilepsy--focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology 2009;73:133-41.

Harden CL, Pennell PB, Koppel BS, Hovinga CA, Gidal B, Meador KJ, et al. Practice parameter update: management issues for women with epilepsy--focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology 2009;73:142–9.

Other Publications

American Epilepsy Society. Position statement on the use of valproate by women of child-bearing potential. Chicago, IL: AES; 2019. Available at: https://www.aesnet.org/sites/default/files/file_attach/AES-Position_Statement_on_the_Use_of_Valproate_by_Women_of_Childbearing_Potential.pdf. Retrieved September 22, 2020.

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Test Your Clinical Skills

Complete the answer sheet at https://learning.acog.org/clinicalupdates/ and receive 5 continuing medical education credits.

Directions: Select the one best answer or completion.

1. The diagnosis of epilepsy is made after how many unprovoked seizures?
   A. One
   B. Two
   C. Three
   D. Four

2. An example of a physiologic nonepileptic cause of seizure is
   A. conversion disorder
   B. hypochondriasis
   C. pseudoseizure
   D. syncope

3. The least common time for catamenial seizures is during which menstrual phase?
   A. Midluteal
   B. Midfollicular
   C. Midmenstrual
   D. Periovulatory

4. Which of the following drugs is not recommended for treatment of catamenial epilepsy?
   A. Acetazolamide
   B. Clobazam
   C. Clomiphene
   D. Clonazepam

5. What percentage of women with epilepsy who have focal seizures are anovulatory?
   A. 8–10
   B. 11–20
   C. 21–30
   D. More than 30

6. If a woman with epilepsy has been free of seizures for 1 year, what is her likelihood of staying seizure free during pregnancy?
   A. 8–10%
   B. 20–28%
   C. 56–68%
   D. 84–92%

7. A study cited by the authors found an unplanned pregnancy rate of 45–51% in the general population. What was the unplanned pregnancy rate in women with epilepsy according to the same study?
   A. 20%
   B. 40%
   C. 60%
   D. 80%

8. The International Registry of Antiepileptic Drugs and Pregnancy found the lowest rate of major congenital anomalies in offspring when the pregnant woman was taking
   A. levetiracetam
   B. phenobarbital
   C. phenytoin
   D. topiramate

9. The most common reason for breakthrough seizures in pregnancy is
   A. changes in metabolism
   B. hormone fluctuations
   C. psychosocial factors
   D. sleep deprivation

10. How often should serum levels be measured in a pregnant patient with epilepsy who is taking lamotrigine?
    A. Weekly
    B. Monthly
    C. Every 6 weeks
    D. Each trimester

11. The risk of premature menopause for women with epilepsy is how many times greater than the risk for women without epilepsy?
    A. Two
    B. Three
    C. Four
    D. Five

12. Seizure frequency in women with epilepsy during perimenopause is related to blood
    A. estrogen levels
    B. progesterone levels
    C. estrogen-to-progesterone ratio
    D. testosterone levels

13. How much do age-related physiologic changes decrease clearance of antiepileptic drugs?
    A. By 10%
    B. By 30%
    C. By 50%
    D. By 70%

14. Which vitamin supplementation do the authors recommend for women with epilepsy and those taking antiepileptic drugs?
    A. A
    B. B
    C. C
    D. D

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Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Answers

1. B, 2. D, 3. A, 4. C, 5. D, 6. D, 7. D, 8. A, 9. A, 10. B, 11. D, 12. C, 13. B, 14. D

Forthcoming and Current Titles

Each monograph in *Clinical Updates in Women's Health Care* is an overview of a topic of importance to obstetrician–gynecologists in practice. Upcoming titles include the following:

- Incidental Findings at the Time of Cystoscopy
- Upper Gastrointestinal Tract, Biliary, and Pancreatic Disorders

Updates

Also available at https://www.acog.org/clinical/journals-and-publications/clinical-updates are the following content updates:

- *Common Dermatologic Conditions* (January 2018)
- *Memory Loss and Dementia* (January 2019)
- *Metabolic Bone Disease* (October 2019)
- *Obesity* (August 2017)
- *Occupational Diseases and Injuries* (July 2016)
- *Sleep Disorders* (September 2015)

List of Titles

2021

Seizures (Vol. XX, No. 1, January 2021)

2020

Overactive Bladder (Vol. XIX, No. 1, January 2020)
Multiple Sclerosis (Vol. XIX, No. 2, March 2020)
Aging Women and the Office Assessment (Vol. XIX, No. 3, May 2020)
Systemic Lupus Erythematosus (Vol. XIX, No. 4, July 2020)
Anorectal Disorders (Vol. XIX, No. 5, September 2020)
Travel Medicine (Vol. XIX, No. 6, November 2020)

2019

Surgical Considerations (Vol. XVIII, No. 1, January 2019)
Evaluation and Management of Lipid Disorders (Vol. XVIII, No. 2, March 2019)
Acute Cough (Vol. XVIII, No. 3, May 2019)
Migraine and Other Headache Disorders (Vol. XVIII, No. 4, July 2019)
Back Pain (Vol. XVIII, No. 5, September 2019)
Diabetes Mellitus (Vol. XVIII, No. 6, November 2019)

2018

Common Dermatologic Conditions (Vol. XVII, No. 1, January 2018)
Arthritis (Vol. XVII, No. 2, March 2018)
Asthma (Vol. XVII, No. 3, May 2018)
Incidental Radiologic Findings (Vol. XVII, No. 4, July 2018)
The Role of Physical Therapy in Obstetric–Gynecologic Practice (Vol. XVII, No. 5, September 2018)
Perioperative Pain Management (Vol. XVII, No. 6, November 2018)

2017

Liver Disease: Reproductive Considerations (Vol. XVI, No. 1, January 2017)
Structural Heart Disease (Vol. XVI, No. 2, March 2017)
Arrhythmias (Vol. XVI, No. 3, May 2017)

Gynecologic and Obstetric Care for Breast Cancer Survivors (Vol. XIV, No. 4, July 2017)
Mood and Anxiety Disorders (Vol. XVI, No. 5, September 2017)
Ischemic Heart Disease (Vol. XVI, No. 6, November 2017)

2016
Hypertension (Vol. XV, No. 1, January 2016)
Thrombosis, Thrombophilia, and Thromboembolism (Vol. XV, No. 3, May 2016)
Polycystic Ovary Syndrome (Vol. XV, No. 4, July 2016)
Challenging Patient Encounters (Vol. XV, No. 5, September 2016)
Liver Disease: General Pathophysiology, Diagnosis, and Management (Vol. XV, No. 6, November 2016)
Liver Disease: General Pathophysiology, Diagnosis, and Management Supplement (Vol. XV, No. 6, November 2016)

2015
Metabolic Bone Disease (Vol. XIV, No. 2, April 2015)

2014
Nutrition (Vol. XIII, No. 3, July 2014)
Adverse Drug Reactions (Vol. XIII, No. 4, October 2014)
Memory Loss and Dementia (Vol. XIII, No. 5, November 2014)

2013
Obesity (Vol. XII, No. 1, January 2013)
Exercise (Vol. XII, No. 2, April 2013)
Allergies (Vol. XII, No. 4, October 2013)
Thyroid Disorders (Vol. XII, No. 5, November 2013)

2012
Sleep Disorders (Vol. XI, No. 3, July 2012)
Anemia (Vol. XI, No. 5, November 2012)

2010
Occupational Diseases and Injuries (Vol. IX, No. 3, July 2010)

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