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WOMEN WITH EPILEPSY:
Hormones, Contraception, and Treatment Options

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Women With Epilepsy: Hormones, Contraception, and Treatment Options

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**TARGET AUDIENCE**
This activity has been developed for clinicians and other health care professionals responsible for the care of women with epilepsy.

**EDUCATIONAL NEEDS**
Epilepsy is the most common neurologic disorder requiring continuous treatment during pregnancy, yet published surveys of clinical professionals responsible for the care of these women reveal considerable misunderstanding of the latest standards of care. Timing of pregnancy and contraception are crucial, long-term health concerns, especially for women with epilepsy. Furthermore, these women are more likely to experience reproductive disorders such as polycystic ovaries, early menopause, and irregular or no ovulation. Successful management of women with epilepsy demands an appreciation not only of hormonal influences on seizure activity but also of P-450–inducing anticonvulsants on oral contraceptives. Complex treatment issues that will be addressed for this particular patient population include catamenial seizures, perimenopausal and menopausal hormone replacement therapy, polycystic ovary syndrome (PCOS), and fetal exposure to anticonvulsants.

**LEARNING OBJECTIVES**
By reading and studying this supplement, participants should be able to:

- understand the influence of estrogen and progesterone on seizure activity.
- recommend appropriate methods of contraception for women with epilepsy.
- appreciate the causes and effects of PCOS.
- recognize and treat catamenial seizures.
- evaluate intervention benefits and risks of first-generation and newer anticonvulsants as well as of neurosurgical resection and vagus nerve stimulation.

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Dr. Davis has nothing to disclose.

Dr. Harden has received grant/research support from GlaxoSmithKline, Ivax Corporation, Pfizer Inc., and Schwartz. She is a consultant to Eisai Inc., GlaxoSmithKline, and UCB Pharma, Inc. and is on the Speaker’s Bureau at Abbott Laboratories, GlaxoSmithKline, Novartis AG, OrthoNeutrogena, and UCB. Dr. Harden discusses the investigational use of natural progesterone and oral contraceptives for treatment of catamenial seizures.

Dr. Pennell has received grant/research support from GlaxoSmithKline and Pfizer. She is a consultant to and is on the Speaker’s Bureau at GlaxoSmithKline and UCB. Dr. Pennell discusses the investigational use of vagus nerve stimulation for treatment of depression, topiramate for essential tremor, obesity, and pain disorders, and oxcarbazepine for neuropathy and bipolar disorder.

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Advances in Epilepsy Treatment

Page B. Pennell, MD

Epilepsy is the third most common neurologic disorder after migraine and stroke and is the most common neurologic disorder that requires continuous treatment during pregnancy. Effective treatment requires the appropriate medication for the particular seizure type and epilepsy syndrome. Newer antiepileptic agents strive to reduce drug interactions, cognitive, metabolic, and cosmetic side effects, sexual dysfunction, bone loss, and teratogenicity. Nevertheless, seizures remain uncontrolled by medications for nearly one third of patients with epilepsy, in which cases surgical intervention or vagus nerve stimulation may be appropriate.

Seizure Incidence Is High Among Elderly

Epilepsy affects all age groups and many patients are afflicted throughout their entire lifetime. The chance a single person may ever have a seizure is as high as 9%, although a third of those are benign febrile convulsions that occur in early childhood. The chance someone will develop chronic epilepsy, the recurrence of unprovoked seizures, is as high as 3%.1

Epilepsy too often is thought to strike early in life but, on the contrary, its onset actually continues throughout teenage and adulthood years. People with their first seizures in their 30s are often misdiagnosed simply because epilepsy is overlooked as an adult diagnosis. Furthermore, incidence dramatically increases after the age of 50 years, being highest among those older than 70 years of age.1 This is less surprising when it is recognized that vascular stroke, neoplasms, and degenerative diseases are common etiologies. For two thirds of all adults with epilepsy, however, the etiology is unknown.

Seizure classification depends on how much of the brain is affected by the electrical disturbance generating the seizures, which are either generalized or partial, the latter type accounting for 69% of seizures (Figure).2

Generalized Seizures

Generalized seizures affect both cerebral hemispheres from their onset and almost always produce loss of consciousness, at least briefly if not longer. Absence: Also known as petit mal seizures, absence seizures are awareness lapses that begin and end suddenly and last only a few seconds, often escaping detection. They typically begin during childhood and may persist into teenage years, but are very rare in adulthood. Tonic-Clonic: Also known as grand mal seizures, tonic-clonic seizures are the most common and familiar type of generalized seizures. They begin with stiffening of the limbs (tonic extension or flexion), which is followed by repetitive jerking of the limbs and face (clonic movements). During the tonic phase, when breathing may cease altogether, not only is a pregnant woman deprived of oxygen, but her fetus endures bradycardia far outlasting the seizure. Some individuals experience only tonic seizures, whereas others exhibit only clonic seizures, and still others display a tonic-clonic-tonic pattern. Full recovery may require hours.

Myoclonic: Myoclonic seizures are rapid, brief body muscle contractions that usually occur bilaterally but occasionally involve only one arm or foot. Atonic: Other names for this seizure type, which produces abrupt loss of muscle tone, include drop attacks, astatic seizures, or akinetic seizures. They may result in head drops, loss of posture, or sudden collapse. Because of their sudden onset without warning, atonic seizures often result in head injuries when victims fall with force. This seizure type tends to be drug-resistant.

Partial Seizures Are Localized

Partial seizures are more common than generalized seizures. Virtually any focal neurologic symptom may occur at the beginning, reflecting the anatomic site of origin of the seizure. These seizures may spread to produce generalized seizures, which are termed partial seizures secondarily generalized. Simple: Simple partial seizures do not impair consciousness and may involve focal motor, sensory, psychic, or autonomic symptoms. Some simple partial seizures start with a shaking hand or foot, which then spreads to an arm or a leg or side of the body (a jacksonian march). Complex: Consciousness is impaired or lost altogether during complex partial seizures. The alteration of awareness may be preceded by symptoms of the simple partial seizures. Despite an often normal appearance during these seizures, individuals are neither aware nor in control of their movements or speech. Typically, a complex partial seizure begins with a blank stare, which is followed by automatisms such as chewing movements, lip smacking, fumbling with clothing, mumbling, or repetitive unorganized...
gestures. The most common complex partial seizures arise from the temporal lobe and are one feature of temporal lobe epilepsy syndrome.

Patients with partial seizures are at very high risk of developing generalized seizures when left untreated or when treatment is stopped abruptly, such as what can occur when a patient acts without medical advice when she finds out she is pregnant.

Until relatively recently, the choice of antiepileptic medications was limited. For treatment of partial seizures, only phenobarbital, phenytoin, valproate, and carbamazepine were available; for generalized seizures, ethosuximide and valproate. Unfortunately, many patients failed to respond well to available options, either because seizure control was inadequate or side effects were intolerable.3

Even when patients with epilepsy enjoy seizure control and are leading normal lives, another concern has recently come to light. Their risk of osteopenia or osteoporosis may be high because of bone metabolism abnormalities associated with certain antiepileptic drugs. Bone mineral density is decreased in 50% of patients treated with antiepileptic drugs, partially explaining the increased fracture rates among people with epilepsy.4 The hepatic enzyme-inducing anticonvulsants phenytoin, phenobarbital, primidone, and carbamazepine all have been associated with decreased bone mineral density.

The most likely mechanism of this deleterious effect is accelerated metabolism of 25-hydroxy vitamin D with compensatory hyperparathyroidism. Adequate calcium and vitamin D intake is essential for these individuals. Furthermore, after 5 years of treatment with enzyme inducers, clinicians may want to evaluate patients for the presence of osteoporosis or osteopenia with dual-energy x-ray absorptiometry. Although valproate is an enzyme inhibitor, it may also reduce bone density, perhaps by increasing bone resorption. An even more serious risk of bone density reduction is likely among institutionalized patients whose sunlight exposure and physical activity are both limited.

What a Difference a Decade Makes

Over the past 10 years, a relative plethora of new antiepileptic drugs has been introduced. Fosphenytoin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, vigabatrin, and zonisamide all have been added to the therapeutic armamentarium against epilepsy. Gabapentin, lamotrigine, oxcarbazepine, tiagabine, levetiracetam, zonisamide, and topiramate are approved for adjunctive use in adults with partial seizures with or without generalization; oxcarbazepine and lamotrigine are also approved for monotherapy treatment of partial seizures. Topiramate and lamotrigine are approved for generalized-onset seizures in addition to partial seizures. Fosphenytoin is a parenteral prodrug of phenytoin that is more tolerable.

Many factors beyond efficacy influence choice of an antiepileptic drug. In addition to seizure type, safety issues such as organ toxicity, rash, or teratogenicity are considered. Side effects such as somnolence, ataxia, tremor, and cognitive impairment may be important. Metabolic factors affecting sexual function and fertility as well as bone health also should be recognized. Comorbidities such as psychiatric disease, headache, or pain may influence the selection as well. Finally, drug interactions can be minimized by using anticonvulsants such as gabapentin, lamotrigine, levetiracetam, and zonisamide, which do not induce drug metabolism.

The newer anticonvulsants tend to offer fewer adverse effects, fewer drug interactions, better tolerability, broader spectrum of efficacy, fewer metabolic effects, fewer cosmetic effects, and perhaps less teratogenicity than their older counterparts. On the other hand, disadvantages include slower titration for many of the medications, no intravenous formulations, more limited clinical experience, and cost factors. Furthermore, dosage adjustments may be required when renally-eliminated anticonvulsants, such as gabapentin, lamotrigine, and topiramate, are prescribed for elderly patients with compromised renal function or undergoing hemodialysis.

Despite the fact that new antiepileptic drugs gain US Food and Drug Administration approval as adjunctive therapy, monotherapy is always the goal. Compliance improved and adverse effects are fewer than with polytherapy. Cost is lower and drug interactions are less likely.

This decade has witnessed yet another important paradigm shift in the development of antiepileptic medications. Their efficacy in other indications is now being recognized. For example, lamotrigine has been approved and is gaining acceptance for bipolar disorder. Topiramate was just approved for migraine prophylaxis and may be effective against essential tremor, obesity, or pain disorders. Oxcarbazepine may be effective against trigeminal neuralgia, diabetic neuropathy, and bipolar disorder. In general, then, the use of anticonvulsant drugs, some still with consequential drug interactions, is growing quickly.

Although our new anticonvulsant medications are better in many regards, they all still have important adverse effects. Lamotrigine tends to be more activating than are other medications, so rare insomnia replaces somnolence as a sleep disturbance, myoclonus may be exacerbated, and rash or hypersensitivity can occur. Although beneficial for many patients, topiramate can produce weight loss as well as metabolic acidosis, cognitive dysfunction, nephrolithiasis, open-angle glaucoma, and oligohidrosis. Weight loss is also associated with zonisamide treatment along with irritability, cognitive dysfunction, nephrolithiasis, oligohidrosis, and rash. Oxcarbazepine may cause ataxia, diplopia, hyponatremia, and rash. Tiagabine may induce spike-wave stupor and gabapentin may cause weight gain or peripheral edema.

Treatment of Choice?

Surgical treatment of epilepsy is the treatment of choice for some patients, but precise localization of epileptogenic tissue is necessary. If patients suffer from medically refractory seizures that come from an area

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Hormonal Influences on Seizures: Treatment Considerations

Cynthia L. Harden, MD, Chair

Estrogens, androgens, and progestogens are all present in both men and women, but in different amounts. Primarily, they control and maintain the reproductive system but they also influence muscle mass, bone strength, emotions, and behavior. Their influence on neural function begins before birth, as early as 1 or 2 months after conception.

Female hormones, estrogen and progesterone, which produce opposing neural effects, generally do not cause seizures but their fluctuation often is associated with changes in seizure pattern or likelihood. It is not unusual for certain kinds of seizures to disappear at puberty, whereas others may start at this time. Many women with epilepsy suffer seizure exacerbations during ovulation or premenstrually, when estrogen/progesterone ratios alter. Women with epilepsy are more likely to have reproductive disorders such as polycystic ovaries, early menopause, and anovulatory menstrual cycles than are women in the general population.

Successful management of women with epilepsy demands an appreciation of hormonal influences on seizure activity. Complex treatment issues that will be addressed for this particular patient population include catamenial seizures, perimenopausal and menopausal hormone replacement therapy, polycystic ovary syndrome (PCOS), and fetal exposure to anticonvulsants.

Estrogen Is Proconvulsant

Two hormones, estrogen and progesterone, produce opposite effects in the brain. Progesterone has an anticonvulsant effect, making seizures less likely to occur. Estrogen is proconvulsant across the gamut of standard animal models, including kindling and audiogenic seizures as well as seizures induced chemically by pentylentetrazole or kainate. Mechanisms of seizure activity are myriad but include effects mediated by estrogen receptors, enhanced excitatory neurotransmission mediated by glutamate receptors, and decreased inhibitory neurotransmission mediated by gamma-aminobutyric acid (GABA).

Elevated estrogen/progesterone ratios during the normal menstrual cycle signify times of seizure susceptibility. Estrogen production peaks at ovulation midcycle and is followed by increased progesterone production, which subsequently plunges premenstrually. In other words, among women with regular menstrual cycles, estrogen/progesterone ratios leading to ovulation and immediately before menstrual bleeding are high.

Anovulatory cycles have no progesterone peak in the second half (luteal phase) of the menstrual cycle. Women with epilepsy have more anovulatory cycles than expected, which is another low-progesterone, seizure-permitting hormonal state.

Treatment of Catamenial Seizures

As many as one third of women with seizures may have catamenial epilepsy, a term that refers to women whose seizures are exacerbated at certain times of the month. Based on estradiol and progesterone neuroactivity, three hormonally based patterns of catamenial epilepsy are recognized (Figure on page 6).1 The most common pattern of catamenial seizure exacerbation is premenstrual, which involves seizures a few days before or during the first few days of menses. The second most common is periovulatory, and the third catamenial pattern is seizure exacerbation throughout the entire second half of the menstrual cycle, or the luteal pattern.1,2

Diagnosis of catamenial seizures can be made through careful assessment of menstrual and seizure diaries and characterization of cycle type and duration.

A variety of therapies for catamenial seizures has been proposed, including conventional anticonvulsants, acetazolamide, and hormonal therapy. Efficacy of these treatments, however, has been evident only from small, unblinded studies or anecdotal reports. Controlled trials to evaluate the underlying pathophysiology of catamenial seizures, as well as its treatment options, are needed.

**Anticonvulsants:** Neurologists who work in epilepsy consider catamenial seizures challenging to manage with antiepileptic medication. Too often a patient’s seizures are well controlled except premenstrually, a specific time of vulnerability. Increasing doses of antiseizure medicines premenstrually may be beneficial, but not all medications can be abruptly increased. Phenytoin, for example, may easily reach a toxic level if its dose is increased even slightly. Although premenstrual dose increases may prove effective for some patients, serum concentrations should be monitored to avoid underdosing or overdosing for most medications.

**Acetazolamide:** Although acetazolamide has been used over the years, there are no convincing data demonstrating its efficacy, but anecdotal reports have been published. Furthermore, there is some evidence of tachyphylaxis with acetazolamide. In other words, its effectiveness diminishes over time.

**Oral Contraceptives:** Animal models suggest that the most effective approach may be to provide hormones via oral contraceptives. By virtue of a very stable hor-
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Menopause and Epilepsy

Women with catamenial seizure patterns may experience hormonal sensitivity at perimenopause and menopause. Moreover, the estrogen/progesterone ratio may continue to explain the likelihood of seizures during these times. During perimenopause, rising estrogen levels and falling progesterone levels may enable seizures. Conversely, lack of hormonal cycling at menopause may have a beneficial effect on seizure occurrence.

Women in perimenopause (determined by hot flashes and changes in menses) with partial or primary generalized epilepsy (n=39) reported increased seizures, particularly if they were taking synthetic hormone replacement therapy (P=0.001).

PCOS, Epilepsy, and Valproate

PCOS and epilepsy seem to be related. Women seem to have PCOS features at the onset of the diagnosis of epilepsy, and neurologists should identify women who need evaluations for PCOS. It is not known what precipitates PCOS but epilepsy is likely a cause, possibly from central luteinizing hormone (LH) dysregulation. Because the anticonvulsant valproate produces effects that look like PCOS, it is at least a confounding factor when evaluating PCOS in women with epilepsy.

PCOS: PCOS is now defined as polycystic ovaries, and the presence of one of the following two criteria: (1) oligo- or anovulation, and (2) clinical or biochemical evidence of hyperandrogenism. It occurs in 5% to 8% of the general population. Polycystic ovaries are present in 20% to 30% of premenopausal women and do not predict ovulatory dysfunction. When accompanied by any sign of PCOS, however, polycystic ovaries are associated with subfertility. Moreover, PCOS often is associated with hirsutism, irregular menstrual cycles, infertility, or obesity. Among 30% to 35% of women (with or without obesity) with PCOS, insulin resistance is a concomitant endocrine characteristic. Also common in PCOS is an elevated ratio of LH to follicle-stimulating hormone (FSH), an endocrine abnormality shared by men and women with epilepsy.

Epilepsy: There appears to be an elevated risk of PCOS among women with epilepsy, even in the absence of antiseizure medicine. The incidence of PCOS was about 11% among premenstrual women with focal epilepsy, whether they were administered carbamazepine, valproate, or an antiepileptic agent at all. Another study found polycystic ovaries among 41% of women with idiopathic (primary) generalized epilepsy and 26% of women with localized epilepsy but only 16% of women without epilepsy. Similarly, anovulation occurred in 27%, 14%, and 11% of women with idiopathic generalized epilepsy, localized epilepsy, and no epilepsy, respectively. From this same study, an elevated LH/FSH ratio, another marker of PCOS, was evident among women with epilepsy and highest among women with idiopathic generalized epilepsy taking valproate.

Valproate: Various theories have been proposed to explain the higher prevalence of PCOS among women with epilepsy,
including the effects of antiepileptic drugs, especially valproate. Valproate does trigger weight gain but whether it causes insulin resistance without weight gain remains uncertain. Valproate has been associated with polycystic ovaries, anovulation, and hyperandrogenism.

**Congenital Malformations**

In teratology studies in epilepsy, major malformations are defined as structural abnormalities with surgical, medical, or cosmetic consequences that are recognized during the first 5 days of life. Common cardiac defects include ventricular septal defect, aorta coarctation, tetralogy of Fallot, aortic valve stenosis, or mitral valve hypoplasia. Neural axis defects include spina bifida, cleft lip, cleft palate, and limb defects such as club foot or hip dysplasia. Anticonvulsant embryopathy, which includes these major malformations, along with microcephaly, growth retardation, and hypoplasia of the midface and fingers, is increased in infants exposed to anticonvulsant drugs in utero.

Pregnancy registries are a new method of assessing fetal risks. Patients interested in the lamotrigine registry must be enrolled by a healthcare provider to collect information on timing, dose, and duration of the drug exposure, estimated delivery date, and sufficient contact information to allow for follow-up of the subsequent pregnancy outcome. Another pregnancy registry levetiracetam, has been established to advance scientific knowledge about safety and outcomes associated with pregnant women being treated with levetiracetam. To ensure broad program access and reach, either a healthcare provider or the patient may initiate enrollment and information will be collected on the children up to age 5.

Patients may also enroll in the first hospital-based registry established to determine the safety of seizure medications that can be taken by women during pregnancy. This registry, the North American Pregnancy Registry, encompassing the United States and Canada, began enrolling pregnant women in February 1997. Findings from this very large registry indicated that major malformations were much more likely after exposure to maternal phenobarbital or valproate monotherapy. More specifically, malformation rates were 6.5% and 10.7% following monotherapy with phenobarbital or valproate, respectively, compared with 1.6% in the general population and 2.9% following all other anticonvulsant monotherapies.

Further evidence of anticonvulsant-induced malformations has been collected in a variety of national sources. In Italy, 5.3% of infants born to women treated with anticonvulsants (N=517) had major malformations. A population-based study in Iceland found that the risk of major congenital malformations among women treated with anticonvulsants was 2.7 times that in the general population. Among 983 offspring born in Japan, Italy, and Canada to women treated with anticonvulsants, the incidence of congenital malformations was 9%, nearly three times the incidence (3.1%) among offspring without anticonvulsant exposure. This same study also concluded that teratogenic risk was reduced when polypharmacy and high valproate levels were avoided. On the other hand, monotherapy with valproate or carbamazepine did increase malformation risk (4.9%), based on data pooled from the Netherlands, Germany, and Finland (N=1,379), although this risk was much higher following phenobarbital combined with ethosuximide (9.8%) or with phenytoin, carbamazepine, or valproate (11%).

Second-generation anticonvulsants may be safer. Among 414 first-trimester exposures to lamotrigine monotherapy, the risk of major malformations was lower than that reported following exposure to older anticonvulsants (2.9%) but still higher than among the general population. Exposure to monotherapy with gabapentin (N=44) or levetiracetam (N=3) during pregnancy led to no malformations.

**Conclusions**

Because estrogen is proconvulsant, elevated estrogen/progesterone ratios may exacerbate seizures at ovulation and premenstrually during normal menstrual cycles, during cycles without adequate luteal phases or ovulation, and during perimenopause. Treatment of patients with catamenial seizures includes premenstrual dosage increases of standard antiepileptic drugs, oral contraceptives to stabilize the hormonal environment, and natural progesterone to influence inhibitory neurotransmission.

PCOS and epilepsy seem related, perhaps via LH dysregulation. Among women with PCOS, insulin resistance is a concomitant endocrine malady as is an elevated LH/FSH ratio, an abnormality shared by men and women with epilepsy. Because valproate produces PCOS-like effects, it is at least a confounding factor when evaluating PCOS in women with epilepsy.

Pregnancy registries are beginning to...
provide valuable assessment of fetal risk following exposure to antiepileptic drugs. Evidence indicates that anticonvulsant-induced congenital malformations can be reduced by avoiding polypharmacy and high valproate levels. Information regarding newer antiepileptic agents should prove most helpful.

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of the brain that enables surgical avoidance of memory, language, and primary motor areas, epilepsy surgery is warranted. The prototype is mesial temporal lobe epilepsy with an 80% cure rate.

In a randomized, controlled trial comparing treatment of temporal lobe epilepsy with optimal antiepileptic medication or surgery (N=80), findings 1 year later were striking. The cumulative proportion of patients who were free of seizures impairing awareness was 58% among those treated with surgery. In stark contrast, only 8% of those treated with medication reached this control status (P<0.001). When subjects with only auras were included, the cure rate improved to nearly 80%.

Vagus Nerve Stimulation
Vagus nerve stimulation becomes an interesting option. The vagus nerve stimulator is a pulse generator implanted under the chest skin with a subdural wire to the vagus nerve in the neck. Electrical impulses delivered to the vagus nerve not only reduce seizure frequency and severity but also improve quality at least a 50% seizure reduction for 37% of the patients after 1 year and 43% after 2 and 3 years. Most common adverse events postimplantation were hoarseness and paresthesia. Although this intervention is not curative as surgery is and it seldom yields complete seizure control, vagus nerve stimulation often enables patients to reduce medications, thus substantially reducing side effects. Instead of adverse effects on sleep, mood, and cognition, vagus nerve stimulation positively affects alertness, postictal recovery, seizure clustering, and other measures of quality of life; in fact, approval is being sought for depression.

Conclusions
The newer anticonvulsants tend to offer fewer adverse effects, fewer drug interactions, better tolerability, broader spectrum of efficacy, fewer metabolic effects, fewer cosmetic effects, and perhaps less teratogenicity. Neurosurgery for temporal lobe epilepsy can produce an 80% cure rate. When refractory patients are poor candidates for surgical resection, vagus nerve stimulation usually reduces seizure frequency and severity, and improves quality of life. Future treatment modalities already being investigated with clinical trials include new antiepileptic drugs, neurosteroids, hormonal therapies, direct thalamic stimulation, gene therapy, and preemptive seizure detection followed by local stimulation or drug delivery.

References
Women with epilepsy too frequently receive inadequate counseling regarding contraception and pregnancy. A national survey of practicing neurologists and obstetricians revealed incomplete understanding of drug interactions between antiepileptic drugs and oral contraceptives. Less than 4% of respondents knew the effects of several common anticonvulsants on oral contraceptives. Moreover, risk of congenital malformations associated with fetal anticonvulsant exposure was underestimated by 44% of surveyed neurologists and 23% of the obstetricians. In another survey of healthcare professionals likely to provide care to women with epilepsy, most respondents could not identify which antiepileptic drugs interfere with oral contraceptives. Thus, women with epilepsy have higher rates of infertility, reproductive endocrine disorders, oral contraceptives and were unaware that antiepileptic drugs interfere with oral contraceptives. Another survey revealed that 44% of surveyed neurologists and 23% of the obstetricians reported that women with epilepsy were more likely to have infertility issues. Moreover, risk of congenital malformations associated with fetal anticonvulsant exposure was underestimated by 44% of surveyed neurologists and 23% of the obstetricians. In another survey of healthcare professionals likely to provide care to women with epilepsy, most respondents could not identify which antiepileptic drugs interfere with oral contraceptives. Thus, women with epilepsy have higher rates of infertility, reproductive endocrine disorders, and sexual dysfunction.

Most healthy women use contraception throughout most of their reproductive years—as many as 30 of the roughly 36 years between menarche and menopause. Epilepsy is a chronic medical condition that requires special considerations to ensure maternal and fetal health; pregnancy may be high risk, medications may be teratogenic, and risk of unwanted pregnancy may be higher when commonly used antiepileptic medications induce metabolism of contraceptive steroids.

Nevertheless, a few antiepileptic drugs do not interact with oral contraceptives, including newer, better tolerated drugs gabapentin, levetiracetam, tiagabine, and zonisamide. Furthermore, efficacy of hormonal contraceptives for women with epilepsy can be improved, simply by avoiding low-dose products when anticonvulsants are enzyme inducing.

Methods of Contraception Without Interaction Potential

Given that many anticonvulsants are hepatic P-450 enzyme inducers, which reduce circulating levels of concomitant medications such as oral steroid-induced hormones, certain methods of contraception may be more appropriate for women with epilepsy than are others.

Sterilization: In the United States, more women rely on sterilization for contraception than any other method, especially after the age of 35 years. Clearly this method is reliable and safe for women with epilepsy. Its reversibility, however, is problematic for young women wanting children at a later point in their lives.

Methods of Contraception Without Interaction Potential

Barrier Methods: Barrier methods obviously create no concerns with respect to antiepileptic drug interactions. Importantly, however, these methods are less effective than are other methods of contraception, even among diligent users. For example, among women depending on male condoms for contraception, nearly 15% become pregnant within a year. Likewise, approximately a 20% annual pregnancy rate follows reliance on female condoms, diaphragms, cervical caps, or spermicides. This high pregnancy rate is especially adverse for chronically ill women taking teratogenic medication. Furthermore, female barrier methods are not widely used or accepted; among women at risk of pregnancy, the proportion who use the diaphragm declined from 5% in 1988 to 2% in 1995.

Hormonal Contraceptives: Benefits and Risks in Epilepsy

Oral hormonal contraceptives are the most popular reversible method among American women. They are reliable, safe, and, when used properly, highly effective. Typical users, however, experience annual pregnancy rates of 2% to 7%. For women with epilepsy and concomitant endocrinologic disorders, oral hormonal contraceptives provide additional benefits. Irregular menstrual cycling, chronic anovulation, and high androgen levels respond to hormonal contraceptives, which regulate cycles, reduce testosterone levels, and offer protection from endometrial and ovarian cancer.

Since the pill’s introduction, doses of estrogen and progestins have declined substantially. With respect to safety, the many marketed formulations are now all low dose; oral contraceptives in development contain even lower doses. This dose reduction extends a degree of comfort to healthy patients wanting as little exogenous hormone as possible. Low-dose oral contraceptives, however, increase the risk of ovulation and pregnancy among women taking enzyme-inducing anticonvulsants.

Progesterone-Only Pill: Because estrogen-containing oral contraceptives are associated with venous throm-
boembolism, the progesterone-only pills are preferred by some providers for chronically ill women. In the case of women with epilepsy, however, this method of contraception is a poor choice for those taking enzyme-inducing anticonvulsants. Progesterone-only pills are very low dose, even when compared with the amount of progesterone in combined estrogen-progesterone oral contraceptives.

**Patch or Ring:** Newer methods of contraception offer different delivery systems such as the skin patch and vaginal ring. Because these methods are not oral, physicians may wonder if they are less susceptible to drug interactions. Since almost all steroid metabolism, regardless of how delivery to the system is accomplished, is affected by hepatic P-450 enzymes, these methods are also vulnerable to drug interactions. No studies have compared oral and transdermal effects on contraceptive efficacy. Because the patch and ring are comparable to lower-dose (20 µg/day) birth control pills, these low-dose methods should be avoided by women taking enzyme-inducing antiepileptic drugs.

**The Tricycle:** Approved by the US Food and Drug Administration in late 2003, this contraceptive method reduces the number of menstrual cycles to four per year by extended administration of ethinyl estradiol and levonorgestrel, the hormones commonly used in other oral contraceptives. Thus, these oral contraceptives are comparable to other marketed pills but administered in a novel regimen; active pills are taken for 84 days before a week of placebo, thus extending the menstrual cycle. Especially among women whose seizures are worse during menstrual periods, this method might be particularly beneficial, but is still subject to potential drug-drug interactions.

**Depot Medroxyprogesterone Acetate (DMPA):** This progesterone-only method of contraception is very effective and convenient with nearly 100% contraceptive efficacy using four intramuscular injections per year. Although women often experience irregular bleeding, long-term use typically results in amenorrhea. Reversible bone mineral density loss may occur during DMPA use. Although probably not an important concern for healthy women, women with anticonvulsant-induced bone changes might be more susceptible to DMPA-induced bone changes. Drug interactions are less of a concern with this high-dose method. Contraceptive levels are still likely even in the face of anticonvulsant-induced reductions, making this an appropriate choice for women with epilepsy.

**Emergency Contraception:** Considering the risks of unplanned pregnancies in women with epilepsy, emergency contraception should always be made available. These progesterone-only pills delay or inhibit ovulation and can decrease the risk of pregnancy up to 5 days after unprotected intercourse. They are very safe—they are neither an abortifacient nor a teratogen. As yet, there are no published data on how anticonvulsants may affect the pharmacokinetics of this method. Reductions in serum hormone levels are expected, given known anticonvulsant effects on other levonorgestrel-containing oral contraceptives.

**Some Anticonvulsants Jeopardize Contraception**

Drug metabolism is accomplished, primarily hepatically, by CYP 450 enzymes. The CYP3A enzyme family is responsible for hepatic metabolism of approximately 60% of currently available drugs; common substrates for CYP3A include ethinyl estradiol and common inducers include carbamazepine, phenobarbital, and phenytoin.

First-generation anticonvulsants include phenobarbital, phenytoin, primidone, carbamazepine, ethosuximide, and valproate; second-generations; include felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, vigabatrin, and zonisamide; both groups contain enzyme inducers. Hepatic enzyme-inducing antiepileptic drugs—phenobarbital, phenytoin, carbamazepine, felbamate, oxcarbazepine, phenobarbital, primidone and topiramate—increase metabolism of ethinyl estradiol, progestogens, and their circulating concentrations by as much as 40%. Oral contraceptives may also affect anticonvulsant levels. For example, plasma lamotrigine levels are reduced by more than 50% during oral contraceptive administration.

What is the consequence of decreased steroid levels? Are residual levels high enough to inhibit ovulation? If ovulation occurs, does pregnancy? It is known that women occasionally ovulate during contraceptive treatment with levonorgestrel implants or the progestosterone-only pill, yet they do not become pregnant because of contraceptive effects such as those on cervical mucus. Until studies are designed specifically to address these issues, a conservative treatment approach is prudent.
Because unplanned pregnancies among women with epilepsy can be hazardous, treating physicians must be particularly diligent. When an enzyme-inducing anticonvulsant is the most effective agent for a woman of childbearing age, her oral contraceptive should contain at least 50 µg ethinyl estradiol to prevent insufficient protection. DMPA injections may want to be given every 10 (rather than 12) weeks to women taking enzyme-inducing medications. In addition to using higher dosages of oral contraceptives, use of a second method of contraception may be recommended for these women.

Which Anticonvulsants Do Not Interact With Contraceptives?

Prescribing physicians should not presume that any antiepileptic drug will affect hormonal methods of contraception (Figure on page 10). Anticonvulsants that do not induce hepatic enzymes do not interact with combined oral contraceptive pills, progestrone-only pills, medroxyprogesterone injections, or levonorgestrel implants. They include vigabatrin, gabapentin, tiagabine, lvetiracetam, valproate, zonisamide, ethosuximide, and the benzodiazepines.

Particularly levetiracetam appears devoid of significant enzyme-inducing or -inhibiting properties. In a double-blind, placebo-controlled study (N = 18), levetiracetam affected neither the pharmacokinetics of oral contraceptives containing ethinyl estradiol and levonorgestrel nor contraceptive efficacy, on the basis of serum progesterone and luteinizing hormone (LH) levels. In an open-label, crossover study (n = 26), zonisamide affected neither the pharmacokinetics of oral contraceptives containing ethinyl estradiol and norethindrone nor serum LH, follicle-stimulating hormone, or progesterone levels.

Conclusions

Hormonal contraception is safe and effective for women with epilepsy as long as sequential drug interactions with enzyme-inducing anticonvulsants are considered. No such interactions have been reported with vigabatrin, gabapentin, tiagabine, levetiracetam, valproate, zonisamide, ethosuximide, or the benzodiazepines. When an enzyme-inducing drug is the most effective anticonvulsant, compensatory contraceptive measures should be taken. Higher-dose oral contraceptives, more frequent DMPA injections, switching to a progesterone IUD, and use of a second method of contraception are all valuable options.

References

Women With Epilepsy: Hormones, Contraception, and Treatment Options

CME Post-Test and Evaluation

Release Date: August 2005
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Instructions: For each question or incomplete statement, one answer is correct. Circle the most appropriate response.
Six correct responses are required for credit.

1. Which of the following antiepileptic agents does not induce P-450 enzymes?
   a) zonisamide  c) levetiracetam  e) a + c
   b) oxcarbazepine  d) a + b

2. Which of the following contraceptive methods is inappropriate for women taking enzyme-inducing anticonvulsants?
   a) depot medroxyprogesterone acetate
   b) progestosterone-only pill
   c) progestosterone intrauterine device
   d) a + b
   e) b + c

3. Which of the following statements is true?
   a) Oxcarbazepine is approved for monotherapy of partial seizures.
   b) Petit mal seizures are also known as simple partial seizures.
   c) Temporal lobe resection can be an effective cure for epilepsy.
   d) a + c
   e) b + c

4. Epilepsy is the most common neurologic disorder requiring continuous treatment during pregnancy.
   a) true  b) false

5. Newer antiepileptic drugs generally:
   a) enable more rapid dose titration.
   b) are associated with fewer side effects.
   c) induce fewer drug-drug interactions.
   d) a + b
   e) b + c

6. Treatment recommendations for catamenial seizures include which of the following?
   a) increased estrogen therapy before ovulation
   b) reduced antiepileptic medications before ovulation
   c) natural progesterone during the luteal phase
   d) a + b
   e) b + c

7. Which of the following statements about polycystic ovary syndrome (PCOS) is true?
   a) An elevated risk of PCOS characterizes women with epilepsy.
   b) PCOS often is accompanied by insulin resistance.
   c) Epilepsy and PCOS share an elevated LH/FSH ratio.
   d) a + b
   e) a + b + c

8. Female hormones, estrogen and progesterone, produce similar proconvulsant effects.
   a) true  b) false

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