Epilepsy is a condition of the central nervous system that is characterized by recurrent seizures. The goal of management is to make patients seizure free without intolerable adverse effects from treatment. Men and women differ in their physiologic makeup and therefore have different needs that must be considered when attempting to attain this goal. There are special concerns for women of child-bearing years with regard to contraception, pregnancy, and teratogenicity that should be considered during counseling and selection of appropriate treatment. There are also emerging concerns about the interaction of antiepileptic drugs and endocrine function that can affect ovarian function, induce polycystic ovary (PCO)-like syndrome, and threaten fertility. Systemic adverse effects can have a negative impact on weight, cosmetic appearance, sexual function, and bone health. Individualized treatment coupling antiepileptic drug use and the specific phase of impact of the reproductive cycle must be considered in treatment selection. Important concerns regarding long-term therapy are being raised as there are more treatment options to consider because of the plethora of new antiepileptic drugs that are available, often with more favorable pharmacokinetics and different adverse event profiles. Also, sex hormone fluctuations during maturation may exacerbate seizures at particular points during the life cycle for women, including menarche, during menses, during pregnancy, or later in the perimenopausal years, often presenting a uniquely challenging aspect to treatment. As the number of available treatment options for epilepsy increases, the optimal goal for primary care physicians is to work as a team with obstetricians, gynecologists, and neurologists in an effort to ensure the best treatment of women with epilepsy.

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nancy, inactivation of contraception by AEDs, and a heightened awareness of the possibility of birth defects should pregnancy occur. The potential for anomaly, teratogenicity, and heightened risk of a poor outcome exists, and creates a formidable obstacle for any physician and WWE who is considering becoming a mother when they are choosing therapy for epilepsy. National registries have been formed to track the outcome of women who were exposed to AEDs during pregnancy. The effect of hormonal influence on seizure frequency presents unique management challenges for women with catamenial seizures. Unique gender-based comprehensive health care involves sexual dysfunction, menstrual cycle irregularities, contraception, and pregnancy, which are special issues that are critical for the optimal treatment of WWE. Seizures may be triggered during menarche, with effects lasting through the perimenopausal period of life.  

Today, there is a greater focus on the potential for adverse cosmetic effects of treatment, such as coarsening of facial features, excessive hair growth, gingival hyperplasia, weight gain, and tremor, which can visibly alter body image and which for some patients are worse than the original condition. General health issues include maintaining ideal body weight and the integrity of bone mass, both of which are capable of being adversely affected by AED treatment. Practice parameters for treating WWE are now available to guide management. It is critical that certain practices are adhered to and supported by appropriate patient instruction. For primary care providers, an understanding of the principles of treatment is essential to the optimal treatment of WWE.

THE BALANCE OF HORMONES

A major difference between men and women is the genetically determined influence of sex hormones on biologic systems. Male and female sex steroids have profound effects on normal maturation and development and determine human sexual phenotype. The distribution of estrogen receptors in the brain changes through the process of maturation during female development. Animal studies have demonstrated that estrogen receptors are present in the neocortex of the brain during development and that they later redistribute within the limbic cortex and decrease in the neocortex after puberty. Estrogen and progesterone may influence abnormally functioning cortical neurons by altering the seizure threshold. Also, normal levels of circulating sex hormones may be altered by the AEDs used to treat seizures.

At the cellular level, estrogens bind to the γ-aminobutyric acid (GABA) type A (GABA_A) receptor site on the cell membrane and promote neuronal excitability though direct membrane and genomic effects. Altered transcription of messenger RNA–encoding cellular enzymes that regulate GABA synthesis also occurs. Synthesis of GABA, as well as of the GABA_A receptor, is reduced, thereby decreasing neuronal inhibition and facilitating seizures. Estrogen also activates the N-methyl-D-aspartate excitatory neurotransmitter receptors in the hippocampus to stimulate excitation and has been found to regulate dendritic spine density in rat hippocampi. The overall effect of estrogen on cortical neurons is to promote seizures (proconvulsant effect). Progesterone has the opposite effect on GABA_A, N-methyl-D-aspartate response, and both GABA and GABA_A receptor synthesis. Therefore, progesterone increases inhibition, decreases excitation, and reduces seizures (anticonvulsant effect).

PRIMARY ENDOCRINE FUNCTION

Epilepsy influences hormonal release. The hormonal cycling that normally occurs often plays a role in significantly altering seizure frequency, and the influence on seizure has frequently been observed by WWE. The monthly menstrual cycle is regulated by the hypothalamic-pituitary-ovarian axis. Gonadotropin-releasing hormones are released in a pulsatile fashion from the hypothalamus to effect pituitary production of follicle-stimulating hormone and luteinizing hormone. Increased development of the ovarian follicles during the first portion of the cycle occurs as a result of the release of follicle-stimulating hormone. The follicle secretes estrogen in the form of estradiol-promoting endometrial proliferation to augment implantation of a fertilized ovum. A feedback system within the axis allows greater release of follicle-stimulating hormone as well as luteinizing hormone when the follicle develops to the point of rupture with ovum release. The corpus luteum then forms, producing progesterone. When implantation of a fertilized ovum does not occur, after 2 weeks the endometrium is sloughed, resulting in menses.

Complex partial seizures are the most common seizure type and usually arise from medial temporal lobe structures. Epileptic activity may propagate to the hypothalamus, altering normal pituitary gonadotropin hormone release, which in turn alters sex steroid release. Anovulatory cycles, infertility, and irregular menses subsequently occur. Interictal alteration in the release of luteinizing hormone from the pituitary gland can occur in women with partial epilepsy, as well as in those with primary generalized epilepsy. The manifestations ultimately depend on the type of epilepsy and the AED used, as well as on a woman’s baseline general medical health. Elevated circadian serum prolactin levels and sex hormone–binding globulin levels are increased in women with partial epilepsy. Also, the levels of thyrotropin, luteinizing hormone, estradiol, and dehydroepiandrosterone are reduced and affected by the choice of the AED. Seizures themselves may induce further changes in the secretion of pituitary hormones. For example, prolactin levels often increase after seizures. The measurement of this hormone concentration has been used clinically to differentiate epileptic seizures by demonstrating an increase from baseline levels as opposed to nonepileptic seizures that do not show the increase. Postictal increases of cortisol and growth hormone may be measured as well.
THE EFFECT ON SEIZURE OCCURRENCE

Seizures appear to be influenced by the relationship between the proconvulsant effects of estrogen and the anticonvulsant effects of progesterone. Some WWE experience an increase in frequency or severity of seizures before or during menses.24,25 Catamenial epilepsy occurs when seizures are exacerbated primarily or exclusively during the perimenstrual period. Overall, approximately one third of WWE have seizures that increase 2-fold around menses; however, a wide range has been described because of inconsistencies in the definition of catamenial seizures.24-22,24 Although definitions have varied, a greater than 2-fold increase in seizures has been suggested.22 Women with catamenial seizures are most vulnerable to seizure increases when estrogen levels are high, and when the corpus luteum that normally secretes progesterone does not form at ovulation, the effects of estrogen go unchallenged. Three common patterns of increased seizure have been described23: immediately before menses, during the second half of menses, and at ovulation.24,25 Seizure exacerbation may occur, especially when the cycles are anovulatory.24,25 During the cycles when ovulation is absent, physiologic progesterone peaks do not occur and the estrogen-progesterone ratio remains constantly elevated. Subsequently, seizures are more frequent than when ovulation occurs. When patients have an anovulatory cycle or inadequate luteal phase, progesterone may be supplemented with exogenous progesterone to provide antiepileptic properties. A basal body temperature that increases less than 0.7°F (-17.4°C) for at least 10 days during the second half of the menstrual cycle, a serum progesterone level of less than 5.0 ng/mL during days 20 through 22, or a biopsy specimen with evidence of underdeveloped secretory endometrium 8 to 10 days after ovulation indicates that there is an insufficient progesterone response.22 Progestrone therapy (taken as 100- to 200-mg lozenges 3 times a day) during days 15 to 25 to produce luteal progesterone levels of 5 to 25 ng/mL (1-5 nmol/L), with subsequent tapering of the dosage over days 26 to 28, has effectively decreased complex partial seizures by 65% and generalized tonic-clonic seizures by 74% during a 3-year follow-up period in 1 uncontrolled study.26 Suppression of the hormone fluctuations associated with the menstrual cycle has also been evaluated using synthetic gonadotropin-releasing hormone analogues.27 Hormone therapy has been used in patients with hormone-sensitive seizures, although the risk of treatment should be discussed with the patient and with a gynecologist.

ANTIEPILEPTIC DRUG IMPACT ON ENDOCRINE FUNCTION

The impact of drug treatment may have ramifications on endocrine function beyond the influence on seizure frequency alone. Antiepileptic drugs may affect the function of neurotransmitters, including GABA and glutamate, the major inhibitory and excitatory neurotransmitters in the brain.3 Women taking AEDs are more likely to have hormonal abnormalities of the endocrine system than those who are not, especially AEDs that are metabolized by the cytochrome P450 hepatic enzyme system. Furthermore, AEDs may affect pituitary hormone function via a direct effect on cortical input to the hypothalamic-pituitary-ovarian axis or alter gonadal hormonal feedback, which could affect gonadal and adrenal sex steroid output.3,7 Also, enzyme-inducing AEDs (EIAEDs), such as carbamazepine-oxcarbazepine, phenytoin, phenobarbital-prima- done, and topiramate, may reduce levels of circulating estrogen and progesterone in the body and alter protein binding.3,21 As a result, higher levels of steroid hormone-binding globulin and subsequently reduced unbound steroid hormones that are biologically active are available for normal function. Sex steroids appear to be neuroactive proteins. In essence, estrogen creates the cellular effect of neuronal excitability, and progesterone promotes neuronal stabilization. Enzyme induction is important not only for sex steroid availability but also for maintaining the efficacy of synthetic oral contraceptive pills.2,3,28

REPRODUCTIVE FUNCTION

As recently as the 1980s, WWE were said to be “unfit parents” and were banned from marriage and legally prevented from bearing children in some states in the United States.29 Social stigma has diminished with increasing awareness that patients with epilepsy can lead normal lives.

THE EFFECT ON OVARIAN FUNCTION

Epilepsy may be associated with a greater risk of ovarian dysfunction, leading to premature ovulatory failure, PCOs, and reduced fertility.28 Seizures or interictal epileptiform discharges can disrupt the hypothalamic-pituitary-ovarian axis, thus altering hormone secretion. The menstrual cycle may become irregular, prolonged, oligomenorrheic, or even amenorrheic.3 Fertility may also be compromised, with a greater risk of miscarriages and pregnancy-related complications when conception does occur.30,31 Polycystic ovary—like syndrome should be suspected when irregular or anovulatory menstrual cycles develop in WWE who are obese or hirsute. The syndrome is characterized by multiple cysts (at least 8), with ovarian enlargement and thickened stroma, and may be visualized on pelvic ultrasound. Altered endocrine function, including elevated androgen levels, may cause acne, excess growth of body and facial hair, weight gain, irregular menses, ovulatory failure, and infertility. Hyperinsulinemia due to insulin resistance, with PCOs, promotes androgen production. A higher incidence of PCOs32 and higher androgen concentrations33 have been noted in WWE. The cause-and-effect relationship between specific AEDs, such as valproate,33,34 that has been described, however, is controversial and requires further validation. It has been suggested that PCOs and/or hyperandrogenism often occurs in obese women who have been exposed to valproate,32,34 although this theory has not been validated by other studies and is at odds with reported clinical experience.35 Nevertheless, if women who have been treated with valporate develop symptoms of PCO-like syndrome, their physicians should
consider changing their AEDs or prescribing adjunct hormone therapy. Enzyme-inducing AEDs, such as carbamazepine, phenytoin, phenobarbital, topiramate, tiagabine, and oxcarbazepine, decrease the circulating sex steroid effect by inducing cytochrome P450 hepatic enzymatic degradation. Increases in steroid hormone–binding globulin levels reduce the unbound hormone concentrations that are available to exert the desired antiepileptic effect.

**MENARCHE TO MENOPAUSE: THE EFFECT ON SEIZURES**

Seizure patterns can change with menses, but they may also change during evolution of the female reproductive cycle from menarche through menopause. The expression of epilepsy may change over an individual’s lifetime as hormonal balance changes. Puberty, menarche, menses, and menopause are times when the reproductive hormones may have a profound impact on seizures. An increase in generalized tonic-clonic seizures has been noted during puberty. Furthermore, juvenile myoclonic epilepsy often begins during puberty. Conversely, other primary generalized epilepsies and benign partial epilepsies of childhood can enter remission. The hormonal underpinnings in these situations are incompletely understood.

Menarche and menses may herald or continue to exacerbate seizures. Gonadotropin-releasing hormone secretion in children is extremely low and slowly increases for several years prior to menarche. Hormonal influences remain important in women through menopause, although information regarding these influences is limited. Menopause typically begins between the ages of 48 and 55 years, as women enter the latter third of their lifespan. Seizures may begin during menopause independent of a known symptomatic cause. Often, seizure patterns may change. Catamenial epilepsy has been associated with improvement in menopause as estrogen concentrations decline. Hormone therapy can provide a beneficial effect against the risk of osteoporosis or possibly dementia of the Alzheimer type developing. Hormone therapy consisting only of estrogen-containing preparations may worsen seizure activity, as noted by patient survey evaluation, although information is limited and the response appears to be mixed. Patients who were also taking progesterone as part of their hormone therapy were more likely to report improvement rather than worsening of their seizures. Therefore, combination therapy appears to be useful even if women have previously undergone a hysterectomy.

**SEXUALITY**

Most WWE appear to have normal sex lives, although approximately 33% to 50% of them may experience some degree of sexual dysfunction. Greater levels of anxiety and apathy related to sexual performance as well as reduced vaginal lubrication and genital blood flow and increased dyspareunia and anorgasmia during intercourse have been reported. A multifactorial cause appears operational. Important regions of cerebral cortical dysfunction, the effect of recurrent seizures and AED treatments on normal hormonal function, and the psychosocial implications of having epilepsy are involved. Sexual dysfunction is best defined for localization-related epilepsy associated with recurrent partial seizures. Seizures arising from limbic structures disrupt function in the neighboring hypothalamus and medial frontal lobe, which are important in regulating expression of libido and arousal. Also, seizures electrically alter hormonal function via pituitary secretion, creating sexual dysfunction. It has been reported that AEDs can interfere with circulating sex steroid concentrations and directly influence mood and behavior, thereby affecting sexual desire. Despite the problems encountered in WWE, evaluation is required to exclude other systemic or gynecologic causes for appropriate treatment, and counseling is also necessary.

**CONtracePTION**

Oral contraceptive pills (OCPs) are generally not associated with exacerbation of seizures; however, AEDs can reduce their efficacy. There have been some reports of seizure modification with the use of OCPs, although such modification depends on whether estrogen plus progesterone or progesterone alone is used. Enzyme induction by AEDs may substantially decrease the concentration of circulating estrogen and reduce unbound progesterone via increasing sex-hormone protein binding, making women taking EIAEDs vulnerable to contraceptive failure unless additional methods are used. The EIAED-induced compromise of hormonal contraception is true for all formulations in which a hormonal mechanism is used, including implantable and injectable forms. Circulating levels of estradiol may decrease by as much as 40% to 50% with the use of carbamazepine. The enzyme-inducing effect can be significant and may reduce the efficacy of the low-dose 35-µg estrogen-containing OCPs, thereby increasing the risk of pregnancy; therefore, higher-dose OCPs containing 50 µg of ethinyl estradiol are recommended for all women taking EIAEDs. Also, in a survey of obstetrician/gynecologists and neurologists, it was found that awareness of AED interaction with OCPs was poor. In contrast to many of the initial AEDs, including phenytoin, carbamazepine (or oxcarbazepine), phenobarbital, and primidone, many of the newer non-EIAEDs (except topiramate) do not carry similar risks of OCP inactivation. The AEDs ethosuximide, valproate, gabapentin, lamotrigine, and levetiracetam do not reduce the efficacy of OCPs. Additional agents, including tiagabine and zonisamide, have not shown inactivation of OCP effects or are unknown to inactivate OCPs. Additional methods of contraception, including the barrier method (ie, condoms or diaphragms) and foam/spermicidal jelly, should be recommended if breakthrough bleeding occurs, although its use as a clinical marker is unreliable because ovulation and pregnancy can occur despite the absence of breakthrough bleeding. Issues involving contraception are critical for all WWE of childbearing potential and should be discussed with the patient and
documented in the medical record during the course of diagnosis and treatment.

**PREGNANCY**

Epilepsy is the most common neurologic disorder in pregnant women, affecting 3 to 5 births per 1000, which accounts for 20,000 children born in the United States each year to WWE. During pregnancy, concerns arise because of the potential harm to both WWE and neonates that can result from injury incurred by unexpected seizures and because of the potential for teratogenicity induced by AEDs.

Neonates born to WWE are at risk for preterm delivery (before the 37th week of gestation) as well as for reduced birth weights, though without a definitive relationship to specific drug therapies. There may be subsequent childhood morbidity, as well as a heightened risk of mortality, as a result of encephalopathies and cerebral palsy. Though rarely described, isolated convulsive seizures can have profound implications on fetal heart rate and have resulted in stillbirths. Even maternal complex partial seizures have been reported to affect fetal heart rate during labor. Seizures may increase in approximately 25% of patients, with those with poor control having the highest risk. Problems of maintaining compliance and pharmacokinetic changes during pregnancy may both contribute to low AED levels. Status epilepticus does not appear to be significantly increased in pregnancy.

The use of AEDs increases the risk of major fetal malformations and minor fetal anomalies. Major fetal malformations affect approximately 4% to 8% of children born to WWE, while minor anomalies in such children range from 6% to 20%. During development, the posterior neuropore closes within the first month and the palate by 6 weeks, so when pregnancy is discovered, the principal consequences of AED exposure have already been realized. The use of AEDs carries a risk of creating an AED embryopathy that includes major malformations, developmental delay, growth retardation, and hypoplasia of the midface and fingers. This risk also appears to be increased in women without epilepsy who take AEDs for other reasons.

Children of WWE may have higher rates of cognitive impairment, although long-term effects and drug-specific implications are limited. Congenital heart disease, especially septal defects, is encountered 3 to 4 times as frequently in children of WWE as in the general population. Drug-specific teratogenic effects that can be caused by the use of AEDs during pregnancy are important counseling issues. The risk of neural tube defects is 1% to 2% in patients treated with valproate and 0.5% to 1% in those treated with carbamazepine. A drug-nonspecific fetal anticonvulsant syndrome reflects the spectrum of minor anomalies that may occur with the use of all AEDs, including epicanthal folds, hypertelorism, low-set ears and hairline, nasal and nail hypoplasia, palmar creases, and minor skeletal abnormalities. Cleft lip and cleft palate occur at a rate almost 5-fold higher than that of the normal population and may require surgical correction, although many of the other facial dysmorphisms become less apparent with development. Higher AED doses and polytherapy increase the risks of teratogenic effects. It now appears evident that the use of AEDs overshadows other maternal factors, such as genetic abnormalities, as the most common cause of embryopathy of children born to WWE.

**PREPREGNANCY COUNSELING**

Prepregnancy counseling is critical for WWE who are interested in having children. Practice guidelines have been developed to assist in the treatment of WWE. Optimizing AED therapy before pregnancy is planned is the ideal, although approximately 40% of all pregnancies in the United States are unplanned. When seizures have been in remission for more than 2 years, discontinuing AEDs 6 months before conception should be considered when the risk of relapse is not excessive (as in controlled juvenile myoclonic epilepsy cases).

While most AEDs are rated by the Food and Drug Administration as category C (teratogenic in animals and unknown effect in humans), valproate, carbamazepine, and phenytoin are category D (teratogenic in animals and humans). The use of most primary AEDs for seizure control is deemed acceptable when the potential benefits of treatment outweigh the risks. While WWE will be concerned about the potential adverse effects of AEDs on their unborn children, emphasizing compliance is equally important because of the potential adverse effects of seizures on the mother and fetus. Even with compliance, psychologic changes in gut motility, hepatic clearance, expanding volume, and altered protein binding may compromise AED bioavailability and serum concentrations, increasing the risk of breakthrough seizures.

During pregnancy, regular follow-up evaluations and serial determinations of AED concentrations may require AED dose adjustments for some patients. Unbound or free AED levels should be measured to reflect the changes in pharmacokinetics during pregnancy, with dose adjustments to maintain stable free concentrations. Patients should be educated regarding birth defects with the use of AEDs, blood level monitoring, folate and vitamin K supplementation, and changes in seizure frequency. A prospective AED Pregnancy Registry is ongoing to assess the risk of AEDs during pregnancy (phone: 1-888-233-2334).

**FOLATE**

A deficiency of serum and red blood cell folate has been correlated with human fetal death and malformation. Folate supplements are recommended to reduce the risk of neural tube defects; however, supplementation may not ensure the elimination of congenital abnormalities. Moreover, the use of AEDs may reduce folate levels. Phenytoin, carbamazepine, and barbiturates are AEDs that may impair folate absorption. Valproate inhibits folate absorp-

*References 2-6, 13, 20, 21, 31, 37, 41, 48, 50, 51.*
tion indirectly by preventing enzymatic conversion of folate to the active metabolite folinic acid. Lamotrigine was originally developed to have antifolate properties, though without notable effect on folate absorption.\textsuperscript{63} Folate requirements for WWE are extrapolated from the general population because of the limited outcome data that are available for WWE. The optimal dose is as yet unknown. Current recommendations include primary prophylactic use of at least 0.4 mg/d for all women of childbearing potential,\textsuperscript{2} although while no optimal dose has yet been identified, higher maintenance doses of 0.4 to 5.0 mg/d are often used for secondary prevention in patients with epilepsy. Lower doses of 0.4 mg/d are effective in preventing neural tube defects in the general population,\textsuperscript{64} with reports of a graded effect of folate deficiency on the occurrence of neural tube defects often prompting the use of higher doses in epilepsy management.\textsuperscript{65} For WWE who are at increased risk of giving birth to an infant with neural tube defects (eg, a personal and/or family history of neural tube defects or treatment with valproate or carbamazepine), a dose of 4 to 5 mg/d is advised, although a potential adverse impact on seizure frequency is unclear.\textsuperscript{2,6,37,50,63}

**VITAMIN K**

Routine peripartum intramuscular administration of vitamin K to prevent hemorrhagic disease of the newborn is now standard after all deliveries.\textsuperscript{66} Hemorrhagic disease of the newborn, which may occur during the first week after delivery, was most commonly described in breastfed children whose mothers had not received vitamin K supplements. In children of WWE who were treated with EI AEDs, a unique presentation of neonatal hemorrhage due to internal bleeding that is potentially fatal may occur on the first day of birth.\textsuperscript{2,6,37,50,54,66} Prevalence averages 10%, with a mortality rate of more than 30%.\textsuperscript{2} The cause is not entirely clear, although the hemorrhage may result from a deficiency of vitamin K–dependent clotting factors caused by EI AEDs. Enzyme-inducing AEDs that cross the placenta may induce vitamin K deficiency in the fetus, with reduced clotting parameters measurable in cord blood.\textsuperscript{67} Oral vitamin K, given to the mother at 10 mg/d for the last 4 weeks of pregnancy may reverse the effect in conjunction with routine intramuscular administration.\textsuperscript{68}

**PERIPARTUM CARE**

Only 1% to 2% of WWE will experience a tonic-clonic seizure during labor, and another 1% to 2% will experience one during the 24 hours after delivery.\textsuperscript{37} Delivery should take place in a care unit that is capable of providing emergency obstetric service, although most women have normal vaginal deliveries.\textsuperscript{69} Serial seizures during labor may be managed with lorazepam therapy, and an elective cesarean section may be appropriate if frequent seizures occur in the last weeks of pregnancy.\textsuperscript{37} Serum AED concentration monitoring should continue after delivery, with a return to prepregnancy states, which is typically noted within 2 months.\textsuperscript{5} Additional postpartum precautions, besides monitoring changes in AED levels, include ensuring regular sleeping habits and outlining precautions for optimal neonate and mother safety during ongoing evaluation of daily activities.

**INFANT FEEDING**

Breastfeeding is also an important component of counseling with respect to pregnancy. The proven benefits include protection from infections, which likely results from passive transfer of immunoglobulins in breast milk. Antiepileptic drugs are expressed in breast milk in an inverse relationship to the degree of protein binding. Highly protein-bound AEDs demonstrate low drug levels in breast milk. Caution is still required, and it may be helpful to check AED levels in neonates after 1 to 2 weeks of nursing if clinical complications are suspected.\textsuperscript{70} Barbiturates, especially, may produce sedation as well as withdrawal symptoms when breastfeeding ceases. If sedation occurs or poor feeding is evident, breastfeeding should be curtailed. Rarely, consequences of AED-induced hematologic and hepatic consequences have been reported, although, in general, the benefits of breastfeeding outweigh the risks, and breastfeeding is therefore recommended as an option for WWE.\textsuperscript{3}

**GENERAL HEALTH**

Throughout the life cycle, overall health may be affected by the particular AED chosen for treatment of epilepsy. For WWE, the adverse cosmetic effects of AEDs are well known and include coarsening of facial features, alterations in hair growth, joint contractures, tremors, and weight gain. Weight gain most frequently occurs with valproate use in about 40% of women,\textsuperscript{72} although it can also occur with the use of gabapentin and carbamazepine.\textsuperscript{60} Alternatively, topiramate, zonisamide, and felbamate may cause weight loss.\textsuperscript{73} Excessive weight is a known primary risk factor for systemic morbidity and mortality, including hypertension, type 2 diabetes mellitus, coronary artery disease, and stroke.\textsuperscript{73} Furthermore, it has been suggested that hyperinsulinemia resulting from insulin resistance due to excessive weight may be responsible for endocrine disorders such as PCO-like syndrome that are caused by hyperandrogenism.\textsuperscript{74} Other adverse cosmetic events include alopecia due to valproate use, with hair regrowth of a different texture, and excessive face and arm hair growth due to phenytoin use. Coarsening of facial features and gingival hyperplasia may also occur with phenytoin use.

Osteopathies are being reported with increased frequency. The epilepsy population is at increased risk for metabolic bone disease and subsequent fracture. Women reach their peak bone mass in the third decade of life and then lose bone slowly until menopause, when bone loss accelerates. Metabolic bone disease has been a recognized consequence of the use of hepatic EI AEDs, including phenytoin, phenobarbital, and carbamazepine,\textsuperscript{75,76} which have also been associated with bone health abnormalities, including osteomalacia, osteopenia, and osteoporosis. The mechanism is thought to be caused by reduced levels of active vitamin D, with subsequent decreased calcium absorption.
and increased parathyroid hormone concentrations. Valproate is not an hepatic EIAED; however, it has been linked to impaired bone health in children77 and adults,79 likely through a different mechanism. In children born to WWE, short stature, reduced bone formation, and low bone mass have occurred to a greater extent after exposure to multiple AEDs than after exposure to a single AED.79 Delayed sexual maturation has also been reported.80 Additional studies concerning the effects of newer AEDs and bone health are needed. Because of this recognized chronic complication of AED use, early measures of bone health should be considered. All patients who have been taking AEDs for more than 5 years should undergo dual-energy x-ray absorptiometry. Vitamin D and calcium should be supplemented if necessary. Weight-bearing exercises, adequate light exposure, cessation of smoking, and limiting caffeine intake should be encouraged. If metabolic bone disease is recognized early, it may be reversed with treatment, which would have a favorable effect on reducing morbidity and mortality resulting from long-bone fractures.

TREATMENT OPTIONS

The classification of epilepsy is foremost in the selection of AED therapy, with treatment being dependent on the diagnosis of partial or generalized epilepsy.12 Recently, there has been a surge in the number of new AEDs that are available for the treatment of epilepsy.95 The choice of AED should be based on the stage of the woman’s reproductive age, including efficacy for her type of epilepsy and the potential for adverse events, interaction with contraception, and teratogenicity. There may be false comfort in assuming that older AEDs are safer just because they have been used more extensively. For example, previous recommendations for the use of phenobarbital during pregnancy now appear less tenable and, in fact, are potentially more harmful than “newer” agents. A deficiency of the detoxifying enzyme epoxide hydrolase, increased free radicals, and drug-induced folic acid deficiency have been postulated96 as teratogenic mechanisms caused by the use of AEDs. The newer AEDs that are devoid of hepatic enzyme induction, such as gabapentin, lamotrigine, and levetiracetam, do not appear to significantly alter gonadal hormones.81 Whether these agents will find a role as initial therapies for WWE will require further investigation.

In catamemial epilepsy, other types of treatment, including perimenstrual acetazolamide therapy, premenstrual AED pulse therapy, and hormone therapy, have a unique role in the treatment of WWE. For patients with an inadequate luteal phase or anovulatory cycle, a relative lack of progesterone may be supplemented with exogenous progesterone to provide antiepileptic properties. In one study,26 100- to 200-mg lozenges taken 3 times a day decreased complex partial seizures by 65% and generalized tonic-clonic seizures by 74% during a 3-year follow-up period.

The effectiveness of AED treatment not only depends on the efficacy of agents to reduce or control seizures but also encompasses drug tolerability. Fewer than 50% of patients become seizure free with the first AED used,82 and only 70% of patients remain seizure free.83 Surgical treatment of epilepsy surgery continues to be underused in most cases, including those involving WWE. Age has not been a barrier in patients who have been successfully treated from the neonatal period84,85 to the postmenopausal period.86 Epilepsy surgery during pregnancy is rare, although it has been performed with successful results for both mother and newborn (S.R.B., oral communication, May 17, 2002).

PREECLAMPSIA/ECLAMPSIA

Preeclampsia/eclampsia, otherwise known as toxemia of pregnancy, is a syndrome that is characterized by pregnancy-induced hypertension, often with edema and proteinuria, as well as more generalized multisystem abnormalities that often involve the kidneys, the liver, coagulation, and the nervous system.87 Vascular endothelial dysfunction along with hypertension produces cerebrovascular spasm with ischemia, hemorrhage, or cerebral edema, especially at posterior watershed zones, often resulting in seizures.87,88 When seizures or coma supervenes, the condition is referred to as eclampsia. Worldwide, eclampsia is the leading cause of maternal death during pregnancy and is commonly seen in overweight primigravidas and in African Americans.89 Hypertension is characterized by a blood pressure reading of at least 140/70 mm Hg, proteinuria of at least 300 mg/24 h, and edema that typically involves the face, arms, and legs. Severe preeclampsia is present when the blood pressure reading is higher than 160/110 mm Hg on 2 occasions, 6 hours apart, during bed rest, with proteinuria of 5 mg/24 h or +3 to +4 by dipstick.90

A significant part of the neurologic morbidity arises from accelerated hypertension that overwhelms cerebral autoregulation, with resultant ischemia and transecthymal flow of fluid and proteins. Subsequently, this pathologic cascade of events may result in focal neurologic deficits, coma, or death. Multifocal intracerebral lesions may involve cortical and subcortical regions.91 The posterior watershed zones are preferentially affected, producing ischemia, hemorrhages, and edema. When the occipital lobe is involved, visual function is disturbed and produces the perception of streaks of light, from which the name eclampsia is derived.

In preeclampsia, the diagnostic feature is hypertension, although other features are often absent at the time of seizure. Premonitory symptoms include headache, agitation, right upper abdominal quadrant pain, and hyperreflexia. In rare instances, hypertension may be minimal, or missed, with seizures appearing with few heralding features. Diagnosis is particularly problematic in the postpartum period. Late postpartum seizures (occurring more than 48 hours postpartum), which also often present with few heralding features, are increasingly recognized in the literature.87,92,93 At the time of seizure, hypertension can be identified on magnetic resonance imaging scans that show typical watershed curvilinear T2-weighted high-signal changes.94

After lengthy debate, it is now clear that magnesium sulfate therapy can stop seizures in eclampsia,95-97 probably by stabilizing endothelial dysfunction and prevent-
ing the consequences of impaired cerebral autoregulation. In animal models, magnesium sulfate has not been shown to be an anticonvulsant per se.98 Seizures may persist in 10% of patients with eclampsia who are treated with magnesium sulfate, and there is experience in the use of phenytoin for seizure prophylaxis, supplemental to magnesium sulfate.99

The neurologic effects of ischemia associated with eclampsia are usually reversible, and the primary goal of treatment is the expedient delivery of a viable child.87-90 Delivery usually leads to rapid resolution of the process, but magnesium sulfate may be used for 24 hours after the latest seizure, whether it occurs prepartum or postpartum.

Overall, the prognosis for patients with preeclampsia/eclampsia is favorable, but cerebral hemorrhage may cause 15% to 20% of the deaths seen in eclampsia.100,101 Aggressive management of hypertension is usually instituted with labetalol or hydralazine therapy, and long-term prognosis depends on the reversibility and the extent of injury to the multiorgan system. Recurrent eclampsia occurs in up to 21% of patients.101

CONCLUSIONS

Women face unique challenges in the management of their epilepsy throughout life.102 The diagnosis of epilepsy should always be reconfirmed and the seizures classified for appropriate medical or surgical therapy. Special issues often arise because of the hormonal influence on normal and abnormal neuronal function. Counseling on interpersonal relationships, sexual dysfunction and fertility, contraceptive failure, and isosexual behaviors may help cultivate evidence-based results on all these issues. Education may help cultivate individual participation toward individualized treatment. Women who plan pregnancy ideally should be seizure free during monotherapy, and they should have their drug therapy discontinued if their risk of relapse is low before conception. The ideal drug of choice during pregnancy is the one that permits freedom from seizure without adverse effects, based on the individual seizure type(s). In the future, individual AEDs that are “relatively safe” to use during pregnancy may be determined, but at this time all AEDs should be viewed as potential teratogens. Multiple AEDs are now available, enhancing the treatment options for WWE. Improvements in the pharmacokinetic properties of the newer AEDs may have less of an impact on hormonal dysfunction and deleterious effects on reproductive and bone health, as well as demonstrating improved overall safety and tolerability. Understanding the unique aspects of treating WWE is essential for proper counseling and management.

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