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EPILEPSY IN WOMEN:
THE BIOLOGICAL BASIS FOR THE FEMALE EXPERIENCE

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NANCY FOLDVARY-SCHAEFER, DO
THE CLEVELAND CLINIC

MARTHA J. MORRELL, MD
COLUMBIA UNIVERSITY AND
THE NEUROLOGICAL INSTITUTE

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Nancy Foldvary-Schaefer, DO
The Cleveland Clinic

Martha J. Morrell, MD
Columbia University and
The Neurological Institute

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This supplement is based on the proceedings from an experts roundtable, titled "Epilepsy in Women: The Biological Basis for the Female Experience," held February 28, 2003, in New York, N.Y.

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CONTENTS AND FACULTY

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Introduction

We are very proud of this supplement, which represents the proceedings of an experts roundtable meeting titled "Epilepsy in Women: The Biological Basis for the Female Experience," held in February 2003 in New York City. More than 20 physicians and scientists participated in this event, sharing ideas and discussing innovative research that sheds light on the biological basis for gender differences in epilepsy. The experts roundtable meeting set the agenda for a series of programs and an Internet-based CME activity dedicated to educating neurologists and other health care professionals about issues critical to the treatment of epilepsy in women. As the use of antiepileptic drugs (AEDs) for disorders other than epilepsy grows, so must the awareness of all health care providers using AEDs in female patients.

We thank all of those who participated in the experts roundtable meeting for their valuable contributions, the American Epilepsy Society for sponsoring the initiative, and GlaxoSmithKline for providing an educational grant in support of these programs.

Basic concepts involving the effects of female sex steroids on central nervous system (CNS) activity are essential to understanding how epilepsy in women is influenced by changes in reproductive status and by reproductive cycles. In the first article in this supplement, neuroscientists **Sheryl Smith** and **Catherine Woolley** address the cellular and molecular effects of steroid hormones on excitation and inhibition within the CNS and describe their own recent discoveries in this area. Through multiple mechanisms, the ovarian hormones estrogen and progesterone have opposing effects on seizure threshold. Estrogen enhances excitatory input and progesterone enhances inhibitory responses, providing the basis for fluctuations in seizure expression across the menstrual cycle.

Next, **Nancy Foldvary-Schaefer**, **Cynthia Harden**, **Andrew Herzog**, and **Tommaso Falcone** review the relationship between hormones and seizures in women over the reproductive life span. Governed by the hypothalamic-pituitary-gonadal axis, the normal menstrual cycle is characterized by fluctuations in estrogen and progesterone that result in periods of seizure susceptibility. This phenomenon, known as catamenial epilepsy, affects at least one third of women with epilepsy. The pathophysiology and clinical presentation of this disorder are discussed, as are diagnostic and treatment approaches. Dr. Harden also shares data on her recent work investigating the relationship between menopause and seizure control in older women.

Reproductive health in women with epilepsy is addressed by **Martha Morrell** and **Georgia Montouris**. Women with epilepsy are at increased risk for a variety of reproductive endocrine disorders that result in menstrual cycle abnormalities and infertility. Drs. Morrell and Montouris review recent work regarding mechanisms responsible for anovulation and polycystic ovary–like syndrome in women with epilepsy. Signs and symptoms of reproductive dysfunction, both general and specific to women treated with AEDs, are reviewed.

Neurologist **Mark Yerby** and his coauthors **Peter Kaplan** and **Teresa Tran** review pregnancy outcomes in women with epilepsy, as well as the effect of pregnancy on seizures. Data are now emerging from pregnancy registries tracking the outcome of children born to mothers using AEDs during pregnancy. These data are essential for counseling women regarding AED use during pregnancy. An update on pregnancy registry findings and a practical approach for managing epilepsy during pregnancy are provided.

The effects of AED exposure on neurodevelopment are of growing concern to mothers with epilepsy and their health care providers. **Kimford Meador**, a neurologist and epileptologist, and **Mary Zupanc**, a pediatric neurologist and epileptologist, review the factors affecting neurodevelopment in

offspring of women with epilepsy and recent studies of the intelligence and educational needs of children exposed to AEDs in utero. Ongoing research, including the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study, led by Dr. Meador, is expected to clarify some of the unresolved controversies in this area.

Bone health is a major concern for all women. An association between AEDs and bone loss in adults and children was first reported more than 3 decades ago. As the use of AEDs for disorders other than epilepsy, such as pain and psychiatric and sleep disorders, continues to soar, millions of women may be at risk for bone disease. **Alison Pack** and her coauthors **Barry Gidal** and **Blanca Vazquez** review this literature and share the findings of Dr. Pack's most recent work.

Finally, **Patricia Penovich**, a leader in women's health issues in epilepsy, and her coauthors **Vasiliki Economou** and neuroscience nurse **Karen Eck** provide general recommendations for the care of women with epilepsy. They cover contraceptive options, management strategies for the treatment of women with epilepsy during pregnancy and the postpartum period, and guidelines for calcium and vitamin D supplementation and diagnostic testing for bone health.

We hope these proceedings serve as a useful guide to all health care professionals treating women with epilepsy and prescribing AED therapy, and we look forward to future advances in this important area of research.

NANCY FOLDVARY-SCHAEFER, DO
Guest Editor
The Cleveland Clinic
Cleveland, Ohio

MARTHA J. MORRELL, MD
Guest Editor
Columbia University and The Neurological Institute
New York, N.Y.

Cellular and molecular effects of steroid hormones on CNS excitability

SHERYL S. SMITH, PHD, AND CATHERINE S. WOOLLEY, PHD

ABSTRACT

The steroid hormones 17β-estradiol (estradiol) and progesterone not only regulate the reproductive system but have other central nervous system effects that can directly affect a variety of behaviors. Generally, estradiol has been shown to have activating effects, including the ability to increase seizure activity, while progesterone has been shown to have depressant effects, including anticonvulsant properties. Because levels of these hormones fluctuate across the menstrual cycle, it is important to understand how changes in these hormone levels may influence levels of excitability in the brain, especially in women who have seizure patterns that are related to their menstrual cycle, a phenomenon known as catamenial epilepsy. This paper reviews the effects of estradiol and progesterone on excitatory and inhibitory neurotransmitters, respectively, and the possible cellular and molecular mechanisms underlying the changes in brain excitability mediated by these hormones.

In addition to their well-known effects on reproductive actions mediated through classic nuclear receptors, the ovarian hormones 17β-estradiol (estradiol) and progesterone can also exert nonclassic effects on the central nervous system (CNS) that alter a variety of behaviors. Estradiol has been shown to have activating effects on mood (euphoria, anxiety, or antidepressant effects), cognition, sensory response, motor behavior, and seizure activity.[1,2] Progesterone produces effects that are generally opposite to those produced by estradiol.[1] Increases in circulating levels of progesterone have been correlated with depressant effects, including anxiolytic[3] and anticonvulsant[4,5] effects. At higher doses, this hormone is sedative and can act as a general anesthetic,[6] an effect first demonstrated by Hans Selye in the 1940s.[7]

From the Department of Physiology and Pharmacology, SUNY Downstate Medical Center, Brooklyn, N.Y. (S.S.S.), and the Department of Neurobiology and Physiology, Northwestern University, Evanston, Ill. (C.S.W.).

Address: Sheryl S. Smith, PhD, Associate Professor, Department of Physiology and Pharmacology, SUNY Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, NY 11203; e-mail:sheryl.smith@downstate.edu.

Hormones and epilepsy across the menstrual cycle

Despite the fact that these hormones have very well-characterized effects on nuclear receptors, many of these nontraditional effects in the brain may be due to nonclassic actions of the hormones on conventional neurotransmitters. Estradiol and progesterone, or their metabolites, acutely potentiate responses to excitatory (estradiol) or inhibitory (progesterone metabolites) neurotransmitters in a rapid fashion (seconds to minutes) and, after chronic exposure or withdrawal (days to weeks), produce structural, synaptic, or molecular effects by which both hormone systems increase CNS excitability.

Across the menstrual cycle, estradiol is elevated in the second half of the follicular phase and increases to a peak at midcycle, while progesterone is primarily elevated during the luteal phase and declines before menstruation begins. The contrasting effects of these hormones in activating or depressing CNS function, respectively, may have implications for behavior or perhaps even epilepsy across the cycle.

Catamenial epilepsy is a change in seizure frequency or severity across the menstrual cycle;[8] increases in seizure severity have been reported at the midcycle peak in ovarian hormones and also during the late luteal phase, during the decline in ovarian hor-

mones—a period that may be a time of hormone withdrawal.

THE BASIS OF ESTRADIOL'S EXCITATORY EFFECTS

One cellular mechanism contributing to the excitatory effects of estradiol is its ability to rapidly increase responses of neurons to the excitatory neurotransmitter glutamate **(Figure 1A)**.[9–11] Glutamate, in turn, can activate a number of receptor subtypes, including those selective for AMPA and kainate, the typical glutamate receptors responsible for fast synaptic transmission at excitatory synapses in the brain. These receptors are composed of four subunits, and once bound, the transmitter gates open a channel that allows Na^+ in to depolarize the neuron, thereby increasing its activity. The NMDA-selective subtype of glutamate receptor, however, requires extensive depolarization before channel gating occurs, owing to a Mg^{2+} block that is unblocked by depolarization. The NMDA receptor is permeable to both Na^+ and Ca^{2+}. The Ca^{2+} influx that accompanies NMDA channel activation may contribute to neuronal plasticity, as well as neural degeneration under excessive activation, as is sometimes seen during seizure states.

This potentiating effect of estradiol on excitatory synaptic transmission influences both the non-NMDA[12–15] and the NMDA[16] types of glutamate receptors, the former due to a G-protein–dependent mechanism involving protein kinase A activation.[13] This rapid effect of estradiol may underlie the observation that direct application of estradiol to the cortex of an animal can produce de novo ictal discharges.[17]

In contrast to estradiol's rapid effect, more prolonged exposure to estradiol results in structural and functional changes at excitatory synapses that selectively enhance neurons' sensitivity to NMDA receptor–mediated synaptic input. These effects have been mostly studied in the hippocampus, which is often a site for the initiation and propagation of limbic seizure activity. Excitatory synapses on neurons in the hippocampus are formed by presynaptic axonal varicosities, from which neurotransmitter vesicles are released, and postsynaptic dendritic spines, which are small thornlike protrusions that densely cover the dendrites of neurons.

Anatomic studies in animals such as rats have shown that 3 days' exposure to elevated estradiol levels increases the number and density of dendritic

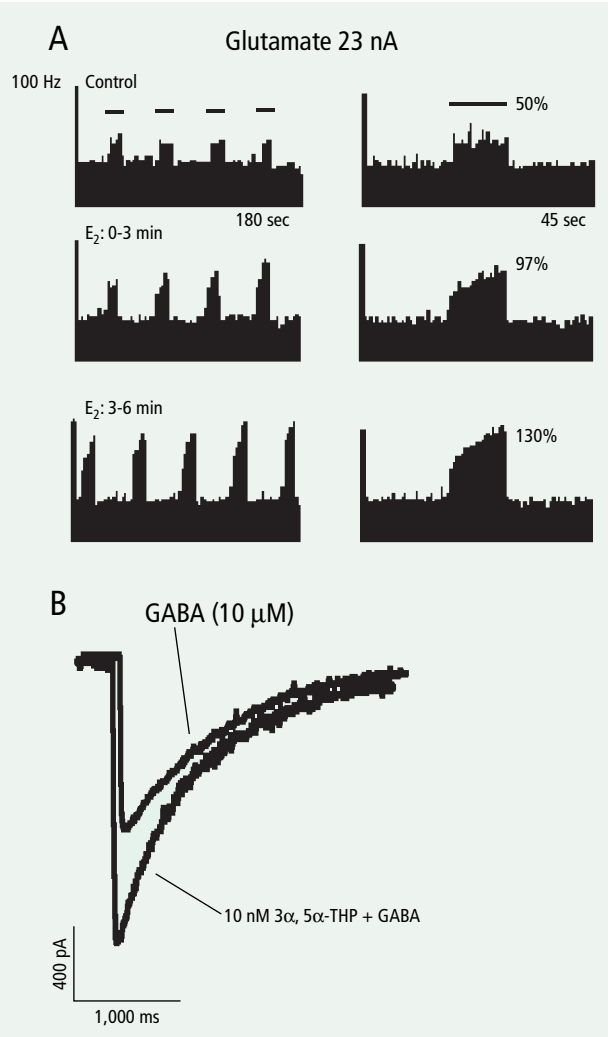

FIGURE 1. Acute application of **(A)** 17β-estradiol or **(B)** a progesterone metabolite exerts opposite effects on neuronal responses to neurotransmitters. **(A)** Local acute application of 17β-estradiol (E_2) increases cerebellar Purkinje cell responses to iontophoretically applied glutamate, an excitatory transmitter (bars above histogram). Both individual responses (left) and averaged response (right) of extracellular discharge from a representative neuron are presented. **(B)** In contrast, physiologic concentrations of the progesterone metabolite 3α-OH-5α-pregnan-one (THP) increase GABA-gated current recorded from acutely isolated CA1 hippocampal pyramidal neurons using whole cell patch-clamp recording techniques.

spines **(Figure 2)** and excitatory synapses on hippocampal neurons.[18] Notably, increases in the number or density of spines and synapses occur not only with estradiol treatment but also as hormone levels fluctuate naturally across the reproductive cycle.[18] Further anatomic analysis of axonal varicosities has shown that estradiol increases the number of vari-

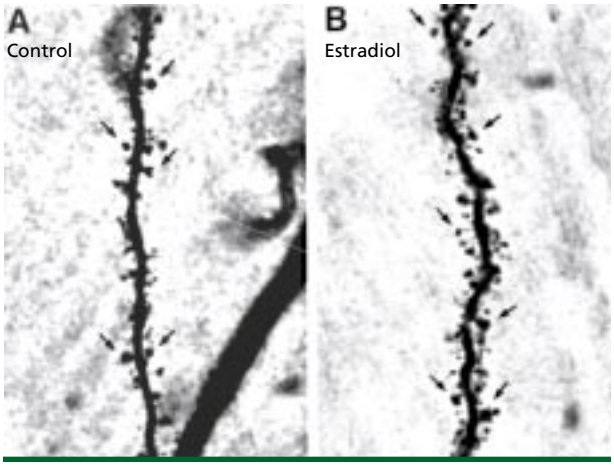

FIGURE 2. Estradiol increases dendritic spine density, as shown in these photomicrographs of representative dendrites on hippocampal neurons from **(A)** a control female rat that was ovariectomized to remove endogenous ovarian hormones and **(B)** an ovariectomized female rat treated for 3 days with estradiol. Note that the density of dendritic spines, small thornlike protrusions that are sites of excitatory synaptic contact, is greater in the estradiol-treated rat. Some dendritic spines are indicated by arrows. Reprinted, with permission, from reference 21. Copyright 1997 by the Society for Neuroscience.

cosities that make synaptic connections with multiple dendritic spines, and that these multiple spines arise from different postsynaptic neurons.[19]

Thus, anatomic studies show that estradiol not only increases the density of excitatory inputs to individual neurons in the hippocampus but also promotes divergence of pre- to postsynaptic input. This change could increase the synchronization of synaptically driven neuronal firing in the hippocampus, and therefore may be important in estradiol's proconvulsant effects on limbic seizure activity.

Because the synapses formed on dendritic spines are glutamatergic, the anatomic data described above predict that estradiol would increase neuronal sensitivity to glutamatergic synaptic input. Indeed, electrophysiologic studies show this to be the case. Interestingly, estradiol selectively increases neuronal sensitivity to synaptic input mediated by the NMDA type of glutamate receptor, while responses mediated by the AMPA receptor are not affected **(Figure 3)**.[20] This electrophysiologic result is corroborated by receptor-binding autoradiography studies showing that estradiol increases glutamate binding to NMDA, but not AMPA, receptors[21] and histologic studies indicating that estradiol increases expression of the NMDA receptor subunit that is common to all forms of the NMDA receptor.[22] Because NMDA receptors have been shown to be important in experimental models of epilepsy, this functional effect of estradiol also could contribute to its proconvulsant effects. Consistent with this prediction, estradiol has been shown to increase hippocampal seizure susceptibility in several animal models: direct measurement of electrographic seizure threshold in the hippocampus,[23] hippocampal kindling,[24] and chemically induced seizures that depend upon the hippocampus, such as kainate-induced behavioral seizures.[2]

THE BASIS OF PROGESTERONE'S DEPRESSANT EFFECTS

Another ovarian hormone, progesterone, can exert numerous effects via a classic nuclear receptor, but can also exert effects via nonnuclear receptors after it is readily metabolized via two enzymatic conversions in the brain to a neuroactive steroid, 3α-OH-5α-pregnan-one (3α,5α-THP, or allopregnanolone). The primary effect of 3α,5α-THP and its isomer, 3α,5β-THP, is to modulate the $GABA_A$ receptor,[25] which mediates most fast inhibition in the brain **(Figure 1B)**. Levels of this metabolite in the circulation parallel those of progesterone; therefore, it is increased during the luteal phase and during pregnancy.

The $GABA_A$ receptor is a pentameric structure composed of varying combinations of 5 subunits from a pool of 17 genetically distinct subunit subtypes: 6 α, 3 β, 3 γ, and 1 each of δ, ε, π, θ, and ρ.[26] Each subunit, in turn, is composed of 4 membrane-spanning α-helices, with the second transmembrane segment surrounding a central chloride channel. Generally, this receptor contains 2 α, 2 β, and 1 γ subunits, but other combinations exist. Different subunit isoforms can produce receptors with varying biophysical and pharmacologic properties.

When two molecules of GABA bind to the $GABA_A$ receptor, the central chloride channel is gated open, allowing Cl^- influx into the neuron, which hyperpolarizes most neurons of the adult CNS and results in inhibition of neuronal activity. The $GABA_A$ receptor is also the target of most known depressant sedative drugs, such as benzodiazepines, barbiturates, and anesthetics, which all bind to unique sites on the receptor, as does the steroid 3α,5α-THP. At physiologic concentrations, this steroid rapidly enhances the ability of GABA to allow Cl^- into the cell[25] by increasing the open time of the channel;[27] as a result, this steroid is more

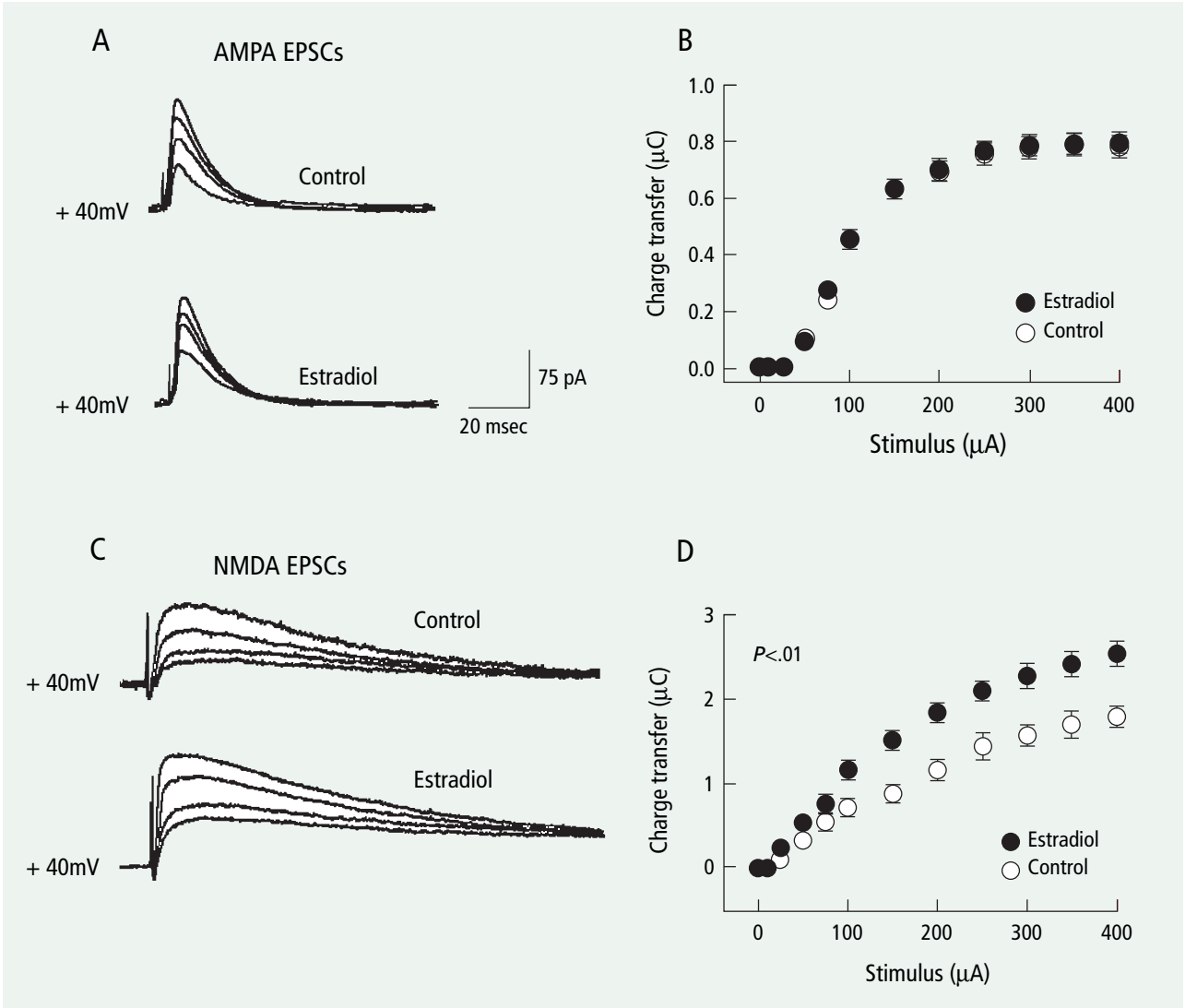

FIGURE 3. Estradiol increases neuronal sensitivity to glutamatergic synaptic input mediated by the NMDA type of glutamate receptor, with no effect on the AMPA type. Shown are electrophysiologic recordings of AMPA **(A)** and NMDA **(C)** receptor–mediated excitatory postsynaptic currents (EPSCs) in hippocampal neurons from control and estradiol-treated animals, and stimulus-response curves for AMPA **(B)** and NMDA **(D)** receptor–mediated neuronal responses. Note that estradiol treatment increases neuronal sensitivity to NMDA receptor–mediated input, with no effect on AMPA receptor–mediated responses. Hormone treatment was identical to that of Figure 1, and AMPA and NMDA responses were recorded from the same cells. Adapted, with permission, from reference 20. Copyright 2001 by the Society for Neuroscience.

potent as an anxiolytic than the benzodiazepine class of tranquilizers, and in fact can act effectively as an anxiolytic, anticonvulsant, and even anesthetic drug.

Progesterone withdrawal and CNS excitability

Across the menstrual cycle, circulating levels of this steroid are increased for 10 to 12 days before declining to low levels. It is therefore important to characterize not only acute effects but also chronic and potential withdrawal effects of the steroid on $GABA_A$ receptor function. Such withdrawal effects are seen with other sedative drugs, such as alcohol. Using a 21-day-administration paradigm in rats, withdrawal from 3α,5α-THP resulted in a behavioral excitability state characterized by increased anxiety and seizure activity triggered by $GABA_A$ channel blockers.[28–30] Across the entire time course of progesterone exposure, a more complex pattern of anxiety behavior has emerged,[31] with anxiety levels increasing after 48 to 72 hours of exposure, then

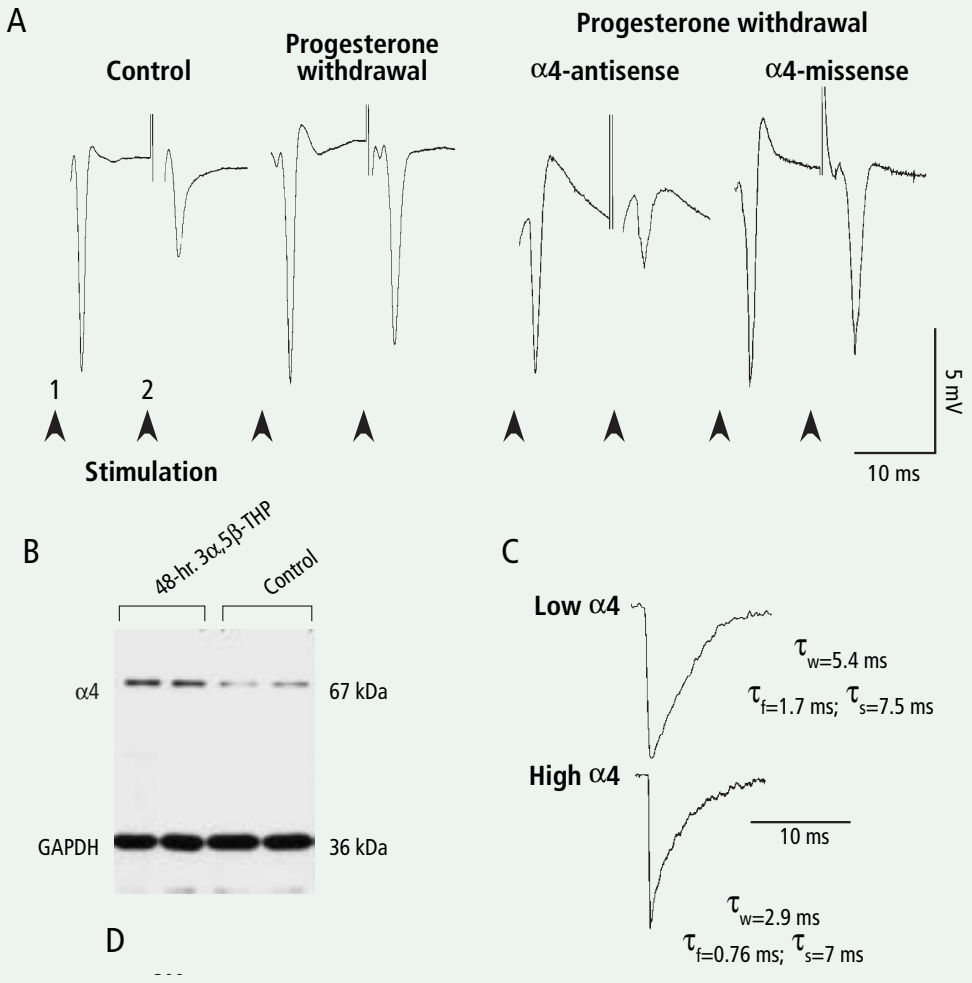

FIGURE 4. Progesterone withdrawal increases CNS excitability, an effect dependent upon $GABA_A$ receptor α4 subunit upregulation. **(A)** Paired-pulse inhibition is a model of hippocampal circuit excitability, such that response to the second of two paired stimuli ("2") is smaller than response to the first ("1"). This inhibition is reduced following progesterone withdrawal (ie, response "2" is larger). This effect was prevented when increases in α4 subunit expression were suppressed by intraventricular administration of α4 antisense oligonucleotide during withdrawal, but not altered in the missense control. Reprinted, with permission, from reference 34. **(B)** Chronic exposure to the GABA-modulatory progesterone metabolite 3α,5β-THP for 48 hours increases expression of the $GABA_A$ receptor α4 subunit similar to progesterone withdrawal (67-kDa band on the representative Western blot). **(C)** Suppression of α4 expression during 48-hour steroid treatment ("Low α4") produced inhibitory synaptic current with a slower decay than normally observed after steroid treatment ("High α4"), suggesting that increased α4 expression produces reduced inhibition. Reprinted, with permission, from reference 33. **(D)** Seizure activity produced by the Cl^- channel blocker picrotoxin is increased after progesterone withdrawal, an effect prevented when α4 expression is suppressed by antisense treatment during the withdrawal period. These results suggest that chronic treatment and withdrawal from progesterone and its 3α,5β-THP metabolite result in increased excitability, both in vitro and in vivo, because of increased expression of $GABA_A$ receptors containing the α4 subunit. Adapted, with permission, from reference 30. Copyright 1998 Nature Publishing Group.

decreasing by 5 to 7 days after exposure until withdrawal, when anxiety again increases. This bimodal pattern of anxiety response is, in fact, similar to the pattern reported in catamenial epilepsy,[8] with exacerbation of seizures reported at midcycle and again during the late luteal-phase decline in circulating levels of progestins.

A similar pattern of change is observed when the cellular characteristics of hippocampal neurons are analyzed. Both 2-day progesterone exposure and progesterone withdrawal result in GABA-gated current nearly insensitive to modulation by benzodiazepines, owing to an increase in expression of novel subtypes of $GABA_A$ receptors containing the α4 subunit,[30,31] which are uniquely insensitive to modulation by the benzodiazepine class of GABA modulators.[32]

The increase in α4 expression also leads to decreases in inhibition gated by the $GABA_A$ receptor, as suggested by several findings **(Figure 4)**. First, suppression of α4 expression using antisense technology prevents the increase in seizure susceptibility observed following progesterone withdrawal.[30] Under conditions of suppressed α4 expression, measures of reduced inhibition seen at the circuit and synaptic level following progesterone withdrawal are also prevented.[33,34] At the circuit level, inhibitory feedback triggered by paired stimuli (paired-pulse inhibition) is significantly attenuated following progesterone withdrawal.[34] At the synaptic level, unitary current recorded from the CA1 region of the hippocampus after 48-hour 3α,5α/β-THP exposure exhibits a faster decay than control. If the total integrated current is evaluated after hormone exposure, there is a reduction in the total amount of Cl^- transferred, leading to a reduction in inhibitory tone.[33] Because suppression of α4 expression prevents these effects, these findings suggest that substitution of novel α4-containing $GABA_A$ receptors for the ambient receptor population after progesterone exposure/withdrawal leads to reduced inhibition in the brain, thus permitting increased CNS excitability.

SUMMARY AND CONCLUSIONS

Across the menstrual cycle, it appears that both the acute and chronic effects of estradiol enhance excitatory input around the time of the midcycle peak. In contrast, the acute effects of the progesterone metabolite appear to enhance inhibitory responses of limbic neurons during the luteal phase, until the time of hormone decline, when altered $GABA_A$ receptors' subunit composition would reduce inhibition, leading again to increased excitability **(Figure 5)**. Thus, these diverse effects of ovarian hormones tend to exacerbate seizure activity at midcycle and during the late luteal phase, a pattern common to catamenial epilepsy.

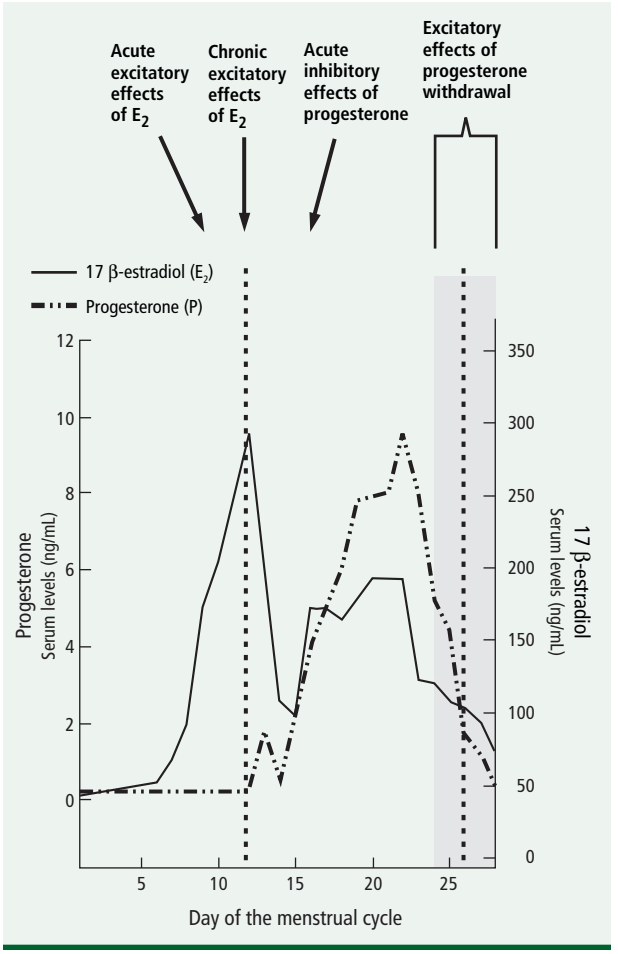

FIGURE 5. Potential time course of altered excitability by ovarian steroids across the menstrual cycle. Time course for fluctuations in circulating levels of progesterone (left axis) and 17β-estradiol (E_2, right axis) during a typical 28-day menstrual cycle. The first two arrows indicate theoretical time points when acute and chronic actions of E_2 might exert excitatory effects on the CNS via glutamate receptors and increases in excitatory synapse formation, respectively, around the midluteal peak in levels of this hormone. In contrast, potentiation of GABA-mediated inhibition by 3α,5α-THP during the progesterone-dominant luteal phase (third arrow) would produce a potentially anticonvulsant effect until the decline in steroid levels ("withdrawal," shaded area), when decreased inhibition may result as a function of lower 3α,5α-THP levels and the formation of quickly decaying α4-containing $GABA_A$ receptors. Dotted lines indicate time points for exacerbation of seizure activity associated with catamenial epilepsy.

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Hormones and seizures*

NANCY FOLDVARY-SCHAEFER, DO; CYNTHIA HARDEN, MD; ANDREW HERZOG, MD; AND TOMMASO FALCONE, MD

ABSTRACT

The opposing effects of estrogen (proconvulsant) and progesterone (anticonvulsant) on seizure threshold have been noted in animal and human studies. Levels of these hormones fluctuate throughout the menstrual cycle, and, in some women with epilepsy, these fluctuations may be related to the occurrence of seizures around the time of menses or an increase in seizures in relation to the menstrual cycle, also known as catamenial epilepsy. Variations in concentrations of antiepileptic drugs across the menstrual cycle may also contribute to increased seizure susceptibility. Diagnosis of catamenial epilepsy requires careful assessment of menstrual and seizure diaries and characterization of cycle duration and type. While there are several approaches to the treatment of catamenial epilepsy, each is based on small, unblinded studies or anecdotal reports. It is important for the physician to work closely with the patient to determine whether her seizures are indeed catamenial and to design an appropriate treatment plan.

From the Departments of Neurology (N.F.-S.) and Obstetrics and Gynecology (T.F.), The Cleveland Clinic Foundation, Cleveland, Ohio; the Weill Cornell Medical College Comprehensive Epilepsy Center, New York, N.Y. (C.H.); and the Neuroendocrine Unit at Beth Israel Deaconess Medical Center and the Department of Neurology, Harvard Medical School, Boston, Mass. (A.H.).

Address: Nancy Foldvary-Schaefer, DO, Department of Neurology, Section of Epilepsy, The Cleveland Clinic Foundation, 9500 Euclid Avenue, S51, Cleveland, OH 44195; e-mail: foldvan@ccf.org.

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The term *catamenial* is derived from the Greek word *katamenios*, meaning monthly. In ancient times, the cyclical nature of epileptic attacks was attributed to the cycles of the moon.[1] In the Middle Ages, a vapor arising from the uterus was believed to induce epileptic attacks. In 1857, Sir Charles Locock first described the relationship between epileptic seizures and the menstrual cycle.[2] Hysterical epilepsy (from the Greek *hystera*, meaning uterus) "was confined to women and observed a regularity of return connected with the menstruation." In 1881, Gowers described the first series of menstruation-related seizures, in 46 of 82 women.[3]

HORMONES AND THE MENSTRUAL CYCLE

The normal menstrual cycle is depicted in **Figure 1**.[4] The average interval between menstrual periods is 28 days during the reproductive years, increasing at either end of reproductive life. Cycles between 24 and 35 days are considered normal. By convention, day 1 of the cycle is the first day of menses, and ovulation occurs 14 days before the onset of menses in 95% of women.

The hypothalamic-pituitary-ovarian axis regulates the interactions between neurohormones, gonadotropin-releasing hormone (GnRH), pituitary gonadotropins, and the gonadal steroids through a feedback-loop mechanism **(Figure 2)**.[5] Synthesized in the medial basal hypothalamus, GnRH is secreted in a pulsatile manner from nerve terminals at the median eminence into the portal system and delivered to the anterior pituitary gland. Normal menstrual function is dependent on the pulsatile secretion of GnRH within a critical, narrow range of amplitude and frequency. In the anterior pituitary, GnRH stimulates the pulsatile secretion of follicle-stimulating hormone and luteinizing hormone. This pulsatile secretion is critical to proper follicular development, which in turn is responsible for the

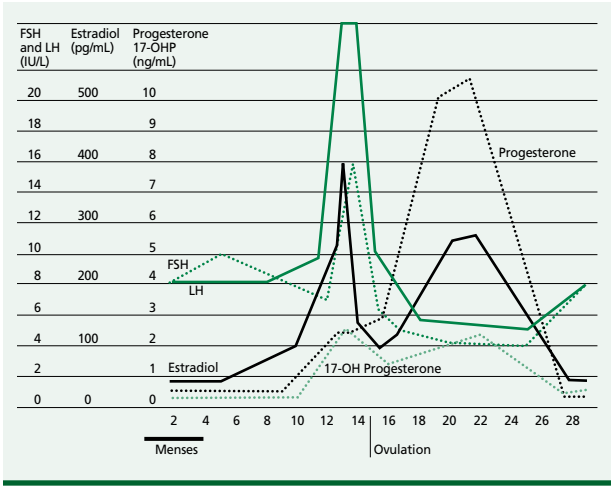

FIGURE 1. Hormone levels during the normal menstrual cycle (FSH = follicle-stimulating hormone; LH = luteinizing hormone). Reprinted, with permission, from reference 4.

luteal phase of the menstrual cycle. The pituitary gonadotropins regulate the production of the gonadal steroids estrogen and progesterone that modify release of the gonadotropins through feedback on pituitary cells. There are three biologically active estrogens: estradiol, estrone, and estriol. Estrogens are highly lipophilic, capable of crossing the blood-brain barrier.

Abnormal follicle-stimulating hormone secretion during the follicular phase results in diminished follicular development and subsequent inadequate corpus luteum formation and function, a condition known as the inadequate luteal phase (ILP).[6] In the ILP, the corpus luteum is defective in progesterone production, while the estrogen-producing function remains unimpaired. Menstrual cycle duration is variable and cycles may be unusually short or long. ILP cycles occur in more than 25% of women.

PATHOPHYSIOLOGY OF HORMONE-SENSITIVE SEIZURES

Hormonal influences

Seizures are influenced by the physiologic variation in sex hormone secretion during the menstrual cycle and throughout the reproductive life of women with epilepsy. Both estrogen and progesterone exert significant effects on seizure threshold. Estrogen has proconvulsant effects in a variety of animal models, while progesterone has the opposite effect. Several studies in humans also demonstrate the opposing effects of estrogen and progesterone on seizure susceptibility.[7–9]

Bäckström[10] was the first to systematically study the relationship between seizures and sex steroids. In six ovulatory cycles of women with epilepsy, a positive correlation between seizure frequency and the estrogen-to-progesterone ratio was observed, peaking in the premenstrual and preovulatory periods and declining during the midluteal phase. The correlation was stronger for generalized motor seizures than for focal seizures, but it was present in both. In three anovulatory cycles, seizure frequency correlated positively with estradiol levels. Other studies also suggest that luteal-phase progesterone is deficient in women with catamenial epilepsy.[11–14]

Water balance

Early observations of an association between cerebral edema and convulsions led to a series of experiments in the early 20th century investigating the effect of water ingestion on seizures. Excessive water ingestion and the antidiuretic hormone vasopressin provoked seizures in patients with epilepsy, while negative water balance produced by fluid restriction had the opposite effect.[15] These findings suggested that neuronal cell membrane permeability was defective in epilepsy and that water imbalance may underlie catamenial epilepsy. However, no significant difference in body weight, sodium metabolism, or total body water was found between women with perimenstrual seizures and healthy controls or between epileptic women with and without catamenial tendencies.[16]

Antiepileptic drug metabolism

Gonadal steroids are actively metabolized in the liver, largely by the cytochrome P450 group of oxidase enzymes, the system active in the metabolism of many of the antiepileptic drugs (AEDs). Drugs that stimulate hepatic metabolism may directly affect the serum concentration of endogenous sex steroids and vice versa. Fluctuations of AED concentrations across the menstrual cycle have been reported.[13,17–19] Women with catamenial seizures taking phenytoin or phenytoin and phenobarbital were found to have lower AED concentrations despite taking higher doses of the drugs.[13] The phenytoin concentration was significantly lower during menses in women with perimenstrual seizures compared with women who had seizures unrelated to menses,[13] and levels were lower and clearance was greater during menses than during the periovulatory period in women with perimenstrual seizures.[17,18]

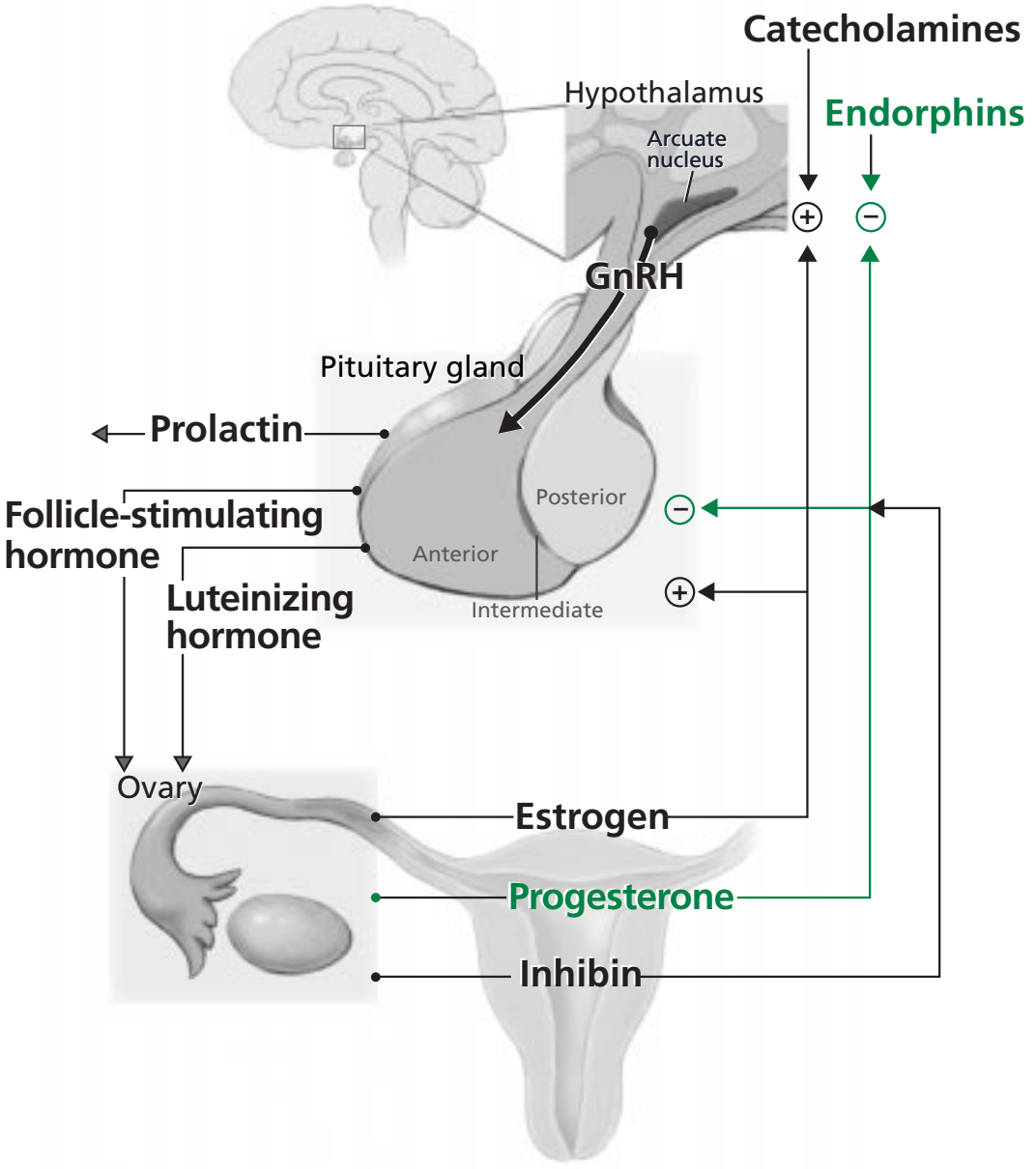

FIGURE 2. The hypothalamic-pituitary-ovarian axis regulates interactions between neurohormones, gonadotropin-releasing hormone (GnRH), pituitary gonadotropins, and the gonadal steroids through a feedback-loop mechanism. See text for detailed explanation. Reprinted, with permission, from reference 5.

CATAMENIAL EPILEPSY: CHARACTERIZATION CAN BE A CHALLENGE

Definition and incidence

The incidence of catamenial epilepsy varies from 10% to 78%, largely because of methodologic differences among studies.[3,15,20–27] Catamenial epilepsy is often vaguely defined as the occurrence of seizures around menses or an increase in seizures in relation to the menstrual cycle. Many studies rely on self-reports or seizure diaries over a single cycle or are limited to institutionalized patients or medically refractory cases. Patient perceptions of how seizures relate to menses are often inaccurate.[24,26] Duncan and colleagues[24] reported that 78% of women they studied claimed to have catamenial seizures, but

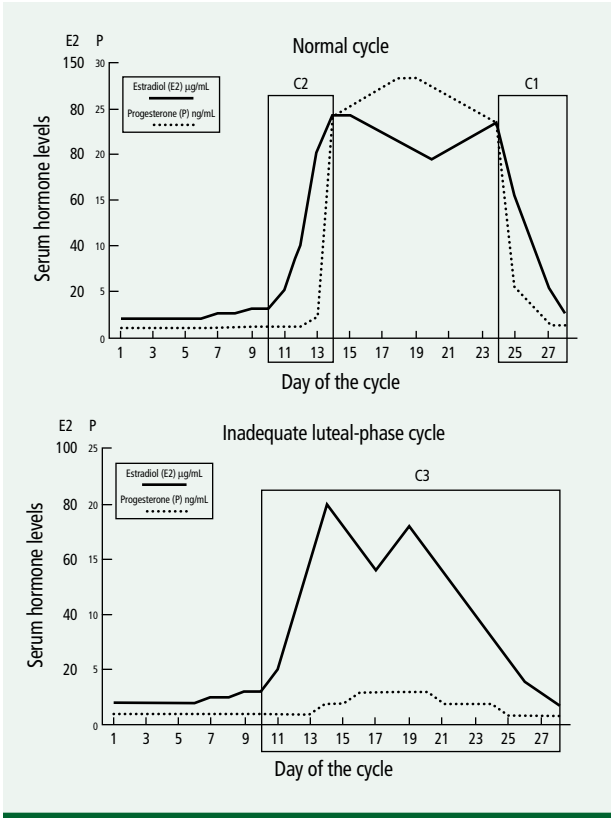

FIGURE 3. Three patterns of catamenial epilepsy. The perimenstrual pattern (C1) is defined as a greater average daily seizure frequency during the menstrual phase (day –3 to +3) compared with the midfollicular (day 4 to 9) and midluteal (day –12 to –4) phases in ovulatory cycles. The periovulatory pattern (C2) is characterized by a greater average daily seizure frequency during the ovulatory phase (day 10 to –13) compared with the midfollicular and midluteal phases in ovulatory cycles. In the C1 and C2 patterns, hormonal fluctuations result in an elevated estrogen-to-progesterone ratio. In the luteal pattern (C3), seizure frequency is greater during the ovulatory, luteal, and menstrual phases than during the midfollicular phase in women with inadequate luteal-phase cycles. Reprinted, with permission, from reference 14.

only 12.5% fulfilled the criteria by having a sixfold increase in average daily seizure frequency.

Although an increase in seizures immediately before and during menses is the most prevalent pattern, some women have cyclical seizures during other phases of the menstrual cycle. Herzog and colleagues[14] described three distinct patterns of catamenial epilepsy in 184 women with refractory temporal lobe epilepsy, as depicted in **Figure 3**. The average daily seizure frequency in women with normal cycles was significantly greater during the perimenstrual and periovulatory phases than during the midfollicular or midluteal phases. In contrast, seizures during ILP cycles occurred with a significantly lower frequency during the midfollicular phase than during any other phase. When catamenial tendencies were defined as a twofold increase in seizure frequency during a particular phase of the cycle, they were seen in approximately one third of women.

Diagnosis

The diagnosis of catamenial epilepsy is established by careful assessment of menstrual and seizure diaries and characterization of cycle type and duration. Ovulation is documented by a rise of at least 0.7 °F on basal body temperature charts. Luteinizing hormone urinary kits may also be used. More sophisticated measurements of ovulation include a serum progesterone level greater than 3 ng/mL or an endometrial biopsy showing a secretory-phase endometrium. ILP cycles can be suspected by a basal body temperature rise of less than 11 days, a midluteal progesterone level less than 5 ng/mL, or an out-of-phase endometrial biopsy of greater than 2 days. Ovulation is more difficult to document in very short (< 23 days) or very long (>35 days) cycles.

Some women with epilepsy appear to be at increased risk of ovulatory dysfunction. In a recent study, anovulatory cycles were found to be significantly more common in women with idiopathic generalized epilepsy (27%) than in those with focal epilepsy (14%) or in controls (11%).[28] Idiopathic generalized epilepsy and the use of valproic acid currently or within 3 years were predictors of ovulatory failure. However, in another investigation of 100 women with focal epilepsy, 39 had anovulatory cycles.[29] Some women have both ovulatory and anovulatory cycles,[28,30] requiring analysis of multiple cycles. Seizure frequency appears to be greater during anovulatory cycles.[12,14] Limbic system dysfunction may underlie these findings, as electrical stimulation of the amygdala and hippocampus suppresses luteinizing hormone release and ovulation in female rats.[31]

PERIMENOPAUSE AND MENOPAUSE: THE HORMONE-SEIZURE LINK MAY LINGER

Seizures may be influenced by perimenopause and menopause in women with epilepsy. Rosciszewska[32] was the first to suggest, in 1978, a relationship between menopause and a change in seizure pattern. Abbasi and colleagues[33] found that 41% of perimenopausal and menopausal women with epilepsy reported an increase in seizures during this life change.

Harden and colleagues[34] studied seizure tendencies in 39 perimenopausal women (irregular menses with or without hot flashes) and 42 menopausal women (at least 1 year without menstruation) with epilepsy. Perimenopause was associated with an increase in seizures in the majority of subjects, and a reported history of catamenial epilepsy was associated with an increase in seizures during perimenopause. The gradual decline in estrogen and progesterone during perimenopause and the elevation in the estrogen-to-progesterone ratio may underlie these findings.[35] Among menopausal women, one third of subjects reported an increase, one third reported a decrease, and one third reported no change in seizure frequency after cessation of menses. Subjects who reported a catamenial pattern during their reproductive years were significantly more likely to have a reduction in seizures during menopause, implying that the factors influencing seizure susceptibility had subsided. These findings suggest that women with catamenial epilepsy may also be affected by hormonal changes later in life.

A significant proportion of women in this study reported that taking hormone replacement therapy produced an increase in seizures,[34] although it appears that many menopausal women with epilepsy can take hormone replacement therapy without increased risk of seizures.

Earlier menopause and perimenopause?

The age at menopause and perimenopause may also be influenced by epilepsy. Klein and colleagues[36] reported a significant risk of early perimenopause onset in women with primary generalized and focal epilepsy compared with controls. Another recent study[37] of the relationship between epilepsy and reproductive health in 68 menopausal women with epilepsy found a significant association between age at last menses and severity of epilepsy in terms of lifetime seizure frequency. The onset of menopause was earlier in women with monthly seizures (46.7 years), differing significantly from women with less than one seizure per month (47.7 years) and from women with fewer than 20 seizures over their lifetime (49.9 years). The number of AEDs and years of therapy had no effect on age at menopause onset. Overall, this study suggests that women with epilepsy are at risk for early menopause, with onset 3 to 4 years before the normative menopausal age of 51 years in the general population. It is unclear whether central nervous system factors, direct ovarian factors, or both are most important in the relationship between epilepsy and menopause.

MANAGEMENT OF CATAMENIAL EPILEPSY: DIVERSE BUT UNDOCUMENTED APPROACHES

A variety of approaches have been proposed for the treatment of catamenial epilepsy; however, all are based on small, unblinded series or anecdotal reports.

Acetazolamide

Acetazolamide is an unsubstituted sulfonamide and a potent inhibitor of carbonic anhydrase. On the basis of the observation that starvation, ketosis, and acidosis reduce seizures, the anticonvulsant properties of acetazolamide were initially attributed to the production of metabolic acidosis due to carbonic anhydrase inhibition. However, studies failed to demonstrate a correlation between bicarbonate levels and seizure frequency.[38] Acetazolamide produces an accumulation of carbon dioxide in the brain that is sufficient to prevent seizures in animals.[39]

Acetazolamide has been used to treat perimenstrual seizures for nearly 50 years on the basis of anecdotal reports; however, efficacy has not been clearly demonstrated.[40,41] A diuretic effect was the proposed mechanism of action; however, body weight, sodium metabolism, and total body water during menses were not different between women with and without catamenial seizures, and total body water was unchanged once seizures were controlled with the drug.[16] In a retrospective study of 20 women with catamenial seizures treated with acetazolamide, seizure frequency and severity were significantly reduced in 40% and 30% of cases, respectively.[42]

The initial dose is 4 mg/kg given in one to four divided doses for 5 to 7 days immediately before and during menses, not to exceed 1 g/day. Adverse effects include paresthesias, drowsiness, ataxia, nausea, vomiting, malaise, anorexia, fatigue, diuresis, intermittent dyspnea, depression, hyperchloremic metabolic acidosis, dysgeusia, renal calculi, and aplastic anemia. Tolerance, due to the induction of increased amounts and activity of carbonic anhydrase in glial cells, and the production of additional glial cells, may be reduced with cyclical dosing regimens.[43]

Cyclical antiepileptic drugs

Intermittent benzodiazepines have been used for years to treat women with catamenial seizures. However, only clobazam has been studied. Clobazam is the first 1,5-benzodiazepine to be marketed

TABLE 1
Adjunctive progesterone for the treatment of catamenial epilepsy*

	Study year		
	1986[49]	1995[50]	1999[51]
Formulation	Suppository	Lozenges	Lozenges
Dosage	100–200 mg TID on days 15–28 of cycle		
Treatment duration	3 months	3 months	3 years
No. subjects	8	25	15
% Improved	75	72	100
% Seizure-free	0	0	20
% Reduction in seizure frequency (from baseline)	68†	CPS, 54‡ GMS, 58†	CPS, 62‡ GMS, 74‡

* Adapted, with permission, from reference 51.
† $P < .05$
‡ $P < .01$
TID = three times daily; CPS = complex partial seizures; GMS = generalized motor seizures

(although it is not available in the United States) and is purported to have fewer adverse effects than older benzodiazepines that have a 1,4 configuration. A double-blind, crossover study compared clobazam with placebo in 24 women with perimenstrual seizures.[44] Clobazam 20 to 30 mg/day was administered for 10 days beginning 2 to 4 days before menses during one cycle and was effective in 78% of cases. The most common adverse effects were sedation and depression. Sustained efficacy was realized in 13 women over 6 to 13 months.[45] Tolerance was not observed.

The use of conventional AED therapy with adjustments during periods of seizure exacerbation has not been adequately investigated. In a single report of a woman treated with valproic acid in whom serum concentrations varied by 35%, with the lowest level occurring during the week of menses, seizures were reduced from eight per month to one per month when the dose was adjusted to correct for the variability in serum concentrations.[19] Although seemingly attractive, frequent changes in drug therapy increase the chance of error, particularly in the population with intractable disease.

Hormonal therapy

Oral contraceptives. Isolated cases of improved seizure control have been reported in women taking oral contraceptives. In the only double-blind, placebo-controlled study, the oral synthetic progestin norethisterone was ineffective in nine women with perimenstrual seizures.[46]

Medroxyprogesterone acetate (MPA) is a progesterone derivative available in oral and parenteral formulations. Depot MPA (Depo-Provera) is the most extensively studied progestin-only contraceptive. It is an appropriate contraceptive choice for women who are noncompliant or cognitively impaired and for those at risk of estrogenic side effects. Adverse effects include irregular menstrual bleeding, breast tenderness, weight gain, and depression. Long-term treatment often results in amenorrhea.

MPA has been shown to reduce seizures in small numbers of women with epilepsy.[47,48] Mattson and colleagues[48] treated 14 women with focal (n = 13) or absence (n = 1) epilepsy with oral MPA 10 mg given 2 to 4 times daily. Six women who failed to become amenorrheic were treated with depot MPA 120 to 150 mg at 6- to 12-week intervals. A 39% reduction in overall seizure frequency was achieved at a mean follow-up of 12 months. No serious adverse effects were reported. A 3- to 12-month delay in resumption of regular menses was observed following treatment with depot MPA.

Some women experience an increase in seizures during the interval between discontinuation of MPA and resumption of regular ovulatory cycles. This may be related to unopposed estrogen exposure during anovulatory cycles.

Natural progesterone. In contrast to oral synthetic progestins, which have been shown to be ineffective, Herzog has found natural progesterone to be effective in women with focal epilepsy and catamenial tendencies **(Table 1)**.[49–51] Average monthly seizure frequency declined by 54% to 68% during the 3-month treatment periods and by 62% to 74% after 3 years. Adverse effects, including transient fatigue and depression, resolved within 48 hours of dose reduction. Complex partial and generalized motor seizures were reduced to a similar degree. The reduction in seizures was greater in women with ILP cycles (59%) than in those with perimenstrual seizures (49%).[50] In a single case of absence epilepsy, seizure control deteriorated during progesterone therapy.[52] Whether the effects of sex steroids on seizure susceptibility differ in generalized and focal epilepsy is unknown.

Other hormonal agents. The antiestrogen clomiphene citrate, the synthetic androgen danazol,

and the synthetic gonadotropin agonists triptorelin and goserelin have been effective in reducing seizures in small series.[53–55] However, the utility of these agents is limited because of the potential for significant adverse effects, and consultation with a reproductive endocrinologist or gynecologist is suggested before their use.

Neurosteroids

Ganaxolone, 3α-hydroxy,3β-methyl-5α-pregnan-20-one, is a neuroactive steroid, or neurosteroid, that modulates the $GABA_A$ receptor complex. It is a synthetic analogue of allopregnanolone, a progesterone metabolite, that has been shown to possess anticonvulsant properties. A moderate improvement in seizures was achieved in two women with perimenstrual seizures treated with ganaxolone 300 mg twice daily from day 21 of the cycle through day 3 of menses.[56] Further investigation is needed to determine the role of neurosteroids in the treatment of hormone-sensitive seizures.

CONCLUSIONS

Approximately one third of women with epilepsy have hormone-sensitive seizures, and hormones continue to influence seizure susceptibility during menopause. Three distinct patterns of catamenial seizure susceptibility have been described. The pathophysiology of this disorder has not been entirely elucidated, although studies suggest that the abrupt withdrawal of neurosteroids has a role in perimenstrual seizure exacerbation. Various treatment approaches have been proposed, but none have been compared and efficacy is based on small, uncontrolled series and anecdotal observations. Further studies are required to determine the best treatment options for this important subset of women with epilepsy.

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Reproductive disturbances in patients with epilepsy

MARTHA J. MORRELL, MD, AND GEORGIA D. MONTOURIS, MD

ABSTRACT

In persons with epilepsy, both seizures and antiepileptic drugs can disturb reproductive health. For example, seizures can alter the release of hypothalamic and pituitary hormones, while some antiepileptic drugs alter concentrations of sex steroid hormones. Women with epilepsy are at increased risk for polycystic ovary syndrome and disorders of the menstrual cycle. Studies have found reduced fertility rates among men and women with epilepsy. The reasons for this reduction in fertility are likely to be both psychosocial and physiologic, and again, both epilepsy itself and antiepileptic drugs are implicated. Sexual dysfunction is common among patients with epilepsy and can have a somatic, psychological, or social basis. To provide the best care for patients with epilepsy, particularly women of reproductive age, clinicians must consider both the gender-based biology of epilepsy and the effects of antiepileptic drugs on reproductive health.

Epilepsy has wide-ranging physiologic consequences that arise from seizures and from the use of antiepileptic drugs. Women with epilepsy face a host of challenges, including reproductive health disturbances.[1,2] They also have lower birthrates and a greater risk for syndromes associated with infertility, such as hypothalamic-pituitary axis disruption, polycystic ovary–like syndrome, and anovulatory cycles. A growing body of research and heightened concern about the overall health of women with epilepsy have brought these risks to the attention of health care providers.

From the College of Physicians and Surgeons, Columbia University, and the Columbia Comprehensive Epilepsy Center, New York–Presbyterian Health System, New York, N.Y. (M.J.M.), and from Boston University School of Medicine and the Epilepsy Center of Boston University Medical Center, Boston, Mass. (G.D.M.).

Address: Martha J. Morrell, MD, Department of Neurology, The Neurological Institute, 710 W. 168th Street, New York, NY 10032.

HORMONE DISTURBANCES

Epilepsy and seizures alter hypothalamic and pituitary hormones,[3] and some antiepileptic drugs alter concentrations of sex steroid hormones produced by the ovaries and adrenal glands.

As depicted in **Figure 1**, the hypothalamus regulates secretion of anterior pituitary gonadotropins through the release of gonadotropin-releasing hormone (GnRH). GnRH is released episodically to stimulate the pulsatile release of the pituitary gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

Input to the hypothalamic-pituitary-gonadal axis from the cerebral cortex and from the amygdala and hippocampus (limbic cortex) is altered during seizures. Depending on the brain region disrupted by the epileptic discharge, the hypothalamus may be stimulated or inhibited. For example, the amygdala contains two distinct nuclear groups—the corticomedial nuclear group, which stimulates hypothalamic GnRH release, and the basolateral nuclear group, which inhibits GnRH release.[4] Depending on the nuclear group affected, excitation of the amygdala either inhibits or stimulates release of hypothalamic hormones such as GnRH, which ultimately alters release of the corresponding pituitary hormones.[5] Release of excitatory and inhibitory neurochemicals such as γ-aminobutyric acid (GABA) and glutamate during and after seizures may also influence hypothalamic and pituitary hormone release.[6]

The location of the ictal or interictal discharge also influences the specific type of input to the hypothala-

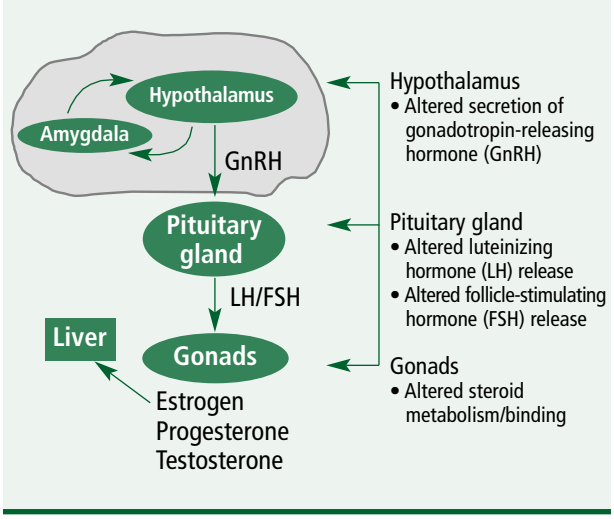

FIGURE 1. Disturbances in the hypothalamic-pituitary-gonadal axis in women with epilepsy receiving antiepileptic drugs. Input to this axis from the amygdala is altered during seizures.

mus. The laterality of limbic epileptiform discharges differentially alters hypothalamic hormone release.[7] Pulsatile secretion of LH in men with temporal lobe epilepsy has been shown to be altered interictally and with seizures.[8] Interictally, these men had lower mean LH concentrations, slower pulse rates, and higher peak amplitudes compared with nonepileptic male controls. Ictal changes were principally characterized as irregularities in secretion. These observations suggest that women with epilepsy are more likely to experience disturbances in hypothalamic hormone release, but the nature of the hormone disruption will vary depending on the focality and laterality of the epileptiform discharge and the relative frequency of ictal versus interictal epileptiform discharges.

Pituitary hormone abnormalities are observed in persons with epilepsy. LH concentration and pulsatile release are abnormal in some men and women with epilepsy,[9–11] probably because of derangement of the hypothalamic GnRH pulse generator.[12] Women with epilepsy not treated with antiepileptic drugs have a significant increase in gonadotropin basal secretion when interictal epileptiform activity is more frequent. LH release may be affected differently in different epilepsy syndromes and according to the antiepileptic drug taken. An increase in LH pulsatility was observed in one study of women with a variety of epilepsies not treated with antiepileptic drugs,[10] although another study of women with temporal lobe epilepsy treated with antiepileptic drugs found that LH pulse frequency diminished.[9]

Prolactin is also elevated interictally in some men and women with epilepsy.[13–15] Pituitary prolactin increases more than twofold after generalized convulsive seizures, most complex partial seizures, and simple partial seizures involving limbic structures, but not after nonepileptic seizures.[16–18] The increase occurs within 5 minutes, is maximal by 15 minutes, and persists for 1 hour.[19]

Sex steroid hormone levels are also abnormal in some men and women with epilepsy, as a result of antiepileptic drug–induced changes in steroid metabolism. Antiepileptic drugs that induce the hepatic microsomal enzyme system (the cytochrome P450 system) increase metabolism of gonadal and adrenal steroid hormones and induce the synthesis of sex hormone–binding globulin, a binding protein for steroid hormones. Increased protein binding decreases the free, biologically active fraction of hormone. Men and women with epilepsy who are taking drugs that induce cytochrome P450 have lower levels of sex steroid hormones.[20–25] Women taking valproate (which does not induce liver cytochrome enzymes) have higher gonadal and adrenal androgen levels.[26] These alterations in steroid hormones are associated with reproductive endocrine disorders and ovulatory dysfunction, conditions that will be discussed below.

REDUCED FERTILITY

Most studies find that fertility rates are reduced in men and women with epilepsy. Although a population-based incidence cohort of patients with epilepsy in Iceland showed no differences in live birth-rates compared with controls,[27,28] other studies have reported that fertility rates are reduced by one third[29–31] to as much as two thirds.[32]

Psychosocial and physiologic causes

This reduction in fertility rates is multifactorial. A study in Finland found that persons with epilepsy were less likely to marry and to have offspring.[33] In part, this reflects a choice. Much of that choice comes from faulty information suggesting that women with epilepsy are not fit parents, that the risk for transmission of epilepsy is high, or that the risk for birth defects in children born to mothers with epilepsy is higher than it really is. A recent survey of health care professionals likely to encounter women with epilepsy found that there is a marked lack of knowledge about pregnancy and fetal risks associated with maternal epilepsy and that many physicians would not support the decision of a

woman with epilepsy to become pregnant.[34]

Another basis for infertility is physiologic. Reproductive health disturbances in women with epilepsy include menstrual cycle abnormalities, anovulatory menstrual cycles, reproductive endocrine disorders, and sexual dysfunction. About one third of menstrual cycles in women with epilepsy are anovulatory, compared with about 10% in women without epilepsy.[35] Women with primary generalized epilepsy are more likely than women with localization-related epilepsy to have anovulatory cycles. The antiepileptic medication valproate, but not carbamazepine, gabapentin, lamotrigine, phenobarbital, or phenytoin, was significantly associated with anovulatory cycles. Women with primary generalized epilepsy receiving valproate were at highest risk. In fact, 55% of menstrual cycles were anovulatory in this group.[35]

Ovulatory failure associated with epilepsy and some antiepileptic drugs may be a result of endocrine disturbances and ovarian dysfunction. Hypothalamic-pituitary axis dysfunction is suggested by observations that pituitary release of LH in women with epilepsy is altered spontaneously and in response to GnRH.[9] Women receiving cytochrome P450 enzyme–inducing antiepileptic drugs have significant reductions in serum concentrations of estradiol, testosterone, and dihydroepiandrostenedione, as well as elevations in sex hormone–binding globulin.[20,25] Enhanced steroid metabolism and binding reduces the concentration of biologically active steroid. In contrast, adrenal and gonadal androgens are significantly elevated in women receiving the cytochrome P450 enzyme inhibitor valproate.[26] However, women with epilepsy who take gabapentin or lamotrigine, two antiepileptic drugs that do not alter cytochrome P450 enzymes, have sex steroid hormone levels that do not differ from those in nonepileptic controls not taking medications.[25]

Increased risk of polycystic ovary–like syndrome

The polycystic ovary syndrome is a gynecologic disorder affecting approximately 7% of women of reproductive age. The phenotype includes signs of excess androgen sensitivity, such as hirsutism, truncal obesity, and acne. Women with this syndrome have frequent anovulatory cycles and may have elevated androgen levels, elevated cholesterol levels with abnormal lipid profiles, an abnormal ratio of pituitary LH to FSH, elevated insulin levels, and glucose intolerance. The requirement for a diagnosis of polycystic ovary syndrome is phenotypic or serologic evidence of androgen excess, as well as anovulatory cycles. Polycystic ovaries, while often present in women with this syndrome, are not required for diagnosis. In fact, asymptomatic polycystic ovaries may be relatively common in normal women of reproductive age, occurring in 21% to 23%.[36,37] The health consequences of polycystic ovary syndrome include infertility, accelerated atherosclerosis, diabetes, and endometrial carcinoma, underscoring the importance of detection and treatment.

Women with epilepsy appear to be at risk for developing features of this syndrome, although there is no study in a cohort of women with epilepsy that is adequately designed to permit an accurate diagnosis of this syndrome. An study of 50 women with partial seizures arising from the temporal lobe found that 28 had menstrual cycle disturbances and 19 had reproductive endocrine disorders and polycystic ovaries.[11] Another assessment of 40 women with epilepsy with a variety of seizure types found reproductive endocrine disorders in 32%; the disorders were polycystic ovaries, hypothalamic amenorrhea, and luteal phase deficiency.[38] Polycystic-appearing ovaries and hyperandrogenism are reported to arise in as many as 40% of women with epilepsy receiving valproate,[26] and may be more likely to occur in women who receive valproate at puberty.[39] Polycystic ovaries were detected in 26% of a sample of 94 women with localization-related epilepsy and in 16% of nonepileptic controls. The women most likely to have multiple ovarian cysts were those with primary generalized epilepsy (41%) and those receiving valproate currently or recently (38%).[35] Polycystic ovaries in women receiving valproate may be reversible when the women are switched to other antiepileptic drugs.[35,40]

Polycystic ovary syndrome, obesity, and valproate

Obesity is associated with a higher rate of polycystic ovaries. The higher prevalence of polycystic ovaries in women receiving valproate may be related to a higher rate of obesity.[40] Valproate alters carbohydrate metabolism. Adolescent girls who gained weight after 1 year of valproic acid therapy had significantly higher insulin levels than girls who did not gain weight.[41] Postprandial insulin, C-peptide, and proinsulin levels were significantly elevated in 53 women treated for 2 or more years with valproate relative to 52 women treated for 2 or more years with carbamazepine.[42] There was no difference between the two groups in the fasting state.

Valproate is a fatty acid derivative that competes

with free fatty acids for protein binding and increases GABA-mediated inhibition. These mechanisms also increase pancreatic beta-cell regulation and insulin secretion. Glucose-stimulated increases in pancreatic secretion of insulin may be the cause of valproate-associated obesity.[43]

Impact of epilepsy vs antiepileptic drugs on reproductive health

The relative effect of epilepsy versus antiepileptic therapy on reproductive function can be considered by examining reproductive physiology in animal models of epilepsy, in nonepileptic animals treated with antiepileptic drugs, and in persons receiving antiepileptic drugs for conditions other than epilepsy.

Evidence that these reproductive health disturbances are a consequence of epilepsy as well as antiepileptic drug treatment comes from a study in female primates. Nonepileptic, regularly cycling rhesus monkeys were treated with valproate for 1 year, achieving serum concentrations of valproate similar to those of adult humans with epilepsy. Over the prospective 1-year assessment, the animals did not develop abnormalities in menstrual cycle length, ovarian morphology, or response to GnRH stimulation.[44]

A study of male gonadectomized rats with partial seizures induced by kindling or with generalized seizures induced by maximal electroshock found that partial seizures were associated with elevations in steroid hormone levels and an increase in the weight of the testes, epididymides, and prostate, whereas generalized seizures caused short-term reductions in testosterone and in the weight of the testes, epididymides, and prostate.[45] Seizures in female kindled rats arrested ovarian cyclicity and caused elevations in estradiol, prolactin, and pituitary weight and polycystic ovaries.[46] These results strongly suggest that different types of seizures cause specific types of disruptions in the hypothalamic-pituitary-gonadal axis.

Two studies have evaluated menstrual cycle regularity and ovarian morphology in women with bipolar disorder. One study found no difference in length of the menstrual cycle or appearance of polycystic ovaries in women treated with either lithium or valproate for bipolar disorder, although both groups had a high prevalence of abnormal menstrual cycle length.[47] Another study assessed women treated with valproate for bipolar disorder and reported that 47% had abnormal menstrual cycle length and 16% had polycystic ovaries, in contrast to women with bipolar disorder not receiving valproate, of whom only 13% had abnormal menstrual cycles and none had polycystic ovaries.[48] These findings are similar to those described for women with epilepsy.

Data such as these suggest that both epilepsy and some antiepileptic drugs can affect fertility and that these effects may be additive. This implies that the most sophisticated therapy for epilepsy is that which considers the effects of both the disease and its treatment on reproductive health.

SEXUAL DYSFUNCTION

Another cause of lower birthrates, and an area of clinical concern, is epilepsy-associated sexual dysfunction. Men and women with epilepsy appear to have a higher incidence of sexual dysfunction than persons with other chronic neurologic illnesses, with the dysfunction being manifested primarily as diminished sexual desire and potency. Sexual dysfunction affects 30% to 66% of men with epilepsy[49,50] and 14% to 50% of women with epilepsy.[49,51,52] Men with epilepsy have sexual complaints that include lack of spontaneous morning penile tumescence, anorgasmia, and erectile difficulties.[53,54] More than one third of women with epilepsy report dyspareunia, vaginismus, and lack of vaginal lubrication, with normal sexual desire and experience.[55]

Both men and women with localization-related epilepsy arising from the temporal lobe have been found to have significantly lower increases in genital blood flow in response to an erotic audiovisual stimulus compared with control subjects, even given normal subjective sexual arousal.[56]

Sexual dysfunction in persons with epilepsy is probably multifactorial.[57] Social development is impaired in some patients with epilepsy. Poor self-esteem as a result of having seizures may lead to feelings of sexual unattractiveness. Sexual arousal may be negatively reinforced, especially when sexual activity precipitates seizures or when sexual sensations or behaviors become identified as part of the seizure or postictal period. Realistic acceptance of the psychosomatic aspects of a chronic illness is positively correlated with sexual function, whereas poor disease acceptance is often associated with sexual dysfunction.[58] Epileptic discharges in brain regions mediating sexual behavior may also contribute to sexual dysfunction.

Alterations in pituitary and gonadal hormones are associated with sexual dysfunction. Elevated prolactin, low estrogen and progesterone, and low testosterone levels are correlated with sexual dysfunction

in women with epilepsy.[15,59,60] Impotent men with epilepsy have higher estradiol levels.[61] Some antiepileptic drugs contribute to sexual dysfunction by direct cortical effects or secondarily through alterations in the hormones supporting sexual behavior.[62,63]

Evaluating for sexual dysfunction

Sexual complaints can have a somatic, psychological, or social basis.[58] The frequency with which patients volunteer sexual complaints may depend to a great extent on the attitude of the physician. Patients with epilepsy should be questioned about precipitating factors, such as acute or chronic life stresses, seizure control, antiepileptic drugs, illnesses, or symptoms of depression. A recommended evaluation strategy includes the following:

- Thorough physical and neurologic examination
- Thyroid function tests
- Assessment of testosterone, estrogen, prolactin, and LH levels
- Complete blood cell count
- Assessment of fasting glucose level
- Urologic or gynecologic consultation.

POSSIBLE LINK TO PREMATURE MENOPAUSE?

Menopause marks the end of reproductive life. Women with epilepsy may be more likely to experience premature menopause, according to one study.[64] Seven (14%) of 50 women with epilepsy had nonsurgical premature menopause as compared with 3 (4%) of 82 nonepileptic controls. No correlation was seen between premature menopause and seizure duration, seizure severity, or age at seizure onset. Further research is needed to determine more precisely whether seizures, antiepileptic drugs, or both alter the length of the reproductive life.

Many menopausal women will be on hormone replacement therapy. The results of a study analyzing the characteristics and temporal relationship of seizures to menopause found that of 15 women taking hormone replacement therapy, the 6 who were taking progestin were significantly less likely to report a worsening of their seizures.[65] This suggests that unopposed estrogen may exacerbate seizures in menopausal women with epilepsy and that opposed estrogen replacement should be considered if hormone replacement therapy is required.

CONCLUSIONS

Epilepsy raises special concerns for women, particularly during the reproductive years. Fertility rates are reduced as a result of psychosocial pressures facing the person with epilepsy and because of disruption of physiologic systems supporting reproductive health. Ultimately, the health care provider must consider the physiologic effects of seizures and of antiepileptic drugs. The challenge is to provide the woman with epilepsy the opportunity for seizure freedom, overall good health, and enhanced well-being. This goal can be achieved when the health care provider appreciates the gender-based biology of epilepsy.

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Risks and management of pregnancy in women with epilepsy

MARK S. YERBY, MD, MPH; PETER KAPLAN, MB; AND TERESA TRAN, MD

ABSTRACT

Most women with epilepsy today can conceive and bear normal, healthy children, but their pregnancies present an increased risk for complications. Pregnancy can exacerbate seizure frequency in some women with epilepsy, and both maternal epilepsy and in utero exposure to antiepileptic drugs can increase the risk of adverse outcomes in children born to women with epilepsy. These outcomes include fetal loss and perinatal death, congenital malformations and anomalies, neonatal hemorrhage, low birth weight, developmental delay, and childhood epilepsy. After reviewing these risks, this article concludes with practical recommendations for reducing these risks and optimizing the management of pregnant women with epilepsy.

In the not-too-distant past, women with epilepsy were discouraged from childbearing and most states had laws prohibiting marriage for persons with epilepsy. Yet these attitudes have gradually given way to an atmosphere where marriage and motherhood are considered acceptable for women with epilepsy, and the management of pregnancy in women with epilepsy has gained increased attention from neurologists and other physicians.

The advent of better neurologic training, improved diagnostic techniques, and a host of effective antiepileptic drugs (AEDs) has vastly improved epilepsy management. Today, the majority of women with epilepsy can conceive and bear normal, healthy children. However, the pregnancies of women with epilepsy do present a greater risk for complications. Women with epilepsy may experience an exacerbation of their seizures during pregnancy, are more likely to have difficulties during labor, and have a higher risk of adverse pregnancy outcomes **(Table 1)**.

This article reviews the major risks that epilepsy and AEDs carry for pregnant women with epilepsy and their children. It concludes with recommendations for the management of pregnancy in women with epilepsy to minimize these risks and to avoid adverse outcomes in their offspring.

From North Pacific Epilepsy Research and Oregon Health and Science University, Portland, Ore. (M.S.Y.); Johns Hopkins University School of Medicine and Johns Hopkins Bayview Medical Center, Baltimore, Md. (P.K.); and MINCEP Epilepsy Care, Minneapolis, Minn. (T.T.).

Address: Mark S. Yerby, MD, MPH, North Pacific Epilepsy Research, 2455 NW Marshall Street, Suite 14, Portland, OR 97210; e-mail: Yerby@seizures.net.

PREGNANCY CAN INCREASE SEIZURE FREQUENCY

One quarter to one third of women with epilepsy have an increase in seizure frequency during pregnancy **(Table 2)**. This increase is unrelated to seizure type, duration of epilepsy, or seizure frequency during a previous pregnancy. While most studies have shown that the increase tends to occur toward the end of pregnancy, recent reports find that a substantial number of women (31%) experience this increase in the first trimester. In addition, of 215 prospectively studied pregnancies, 1 in 8 women (12.5%) had to be hospitalized because of complications from increased seizures during pregnancy.[1]

As pregnancy progresses, plasma concentrations, both total and unbound, of AEDs decline, even in the face of constant or, in some instances, increasing doses.[2–6] Plasma concentrations tend to rise postpartum.[7,8] Although reduction of plasma drug concentration is not always accompanied by an increase in seizure frequency, virtually all women with increased seizures in pregnancy have subtherapeutic drug levels.[9–13] The decline of AED levels during pregnancy

TABLE 1

PERMISSION NOT GRANTED FOR ONLINE REPRODUCTION

See table 3 in Yerby MS, Epilepsia 2003; 44(suppl 3):33–40.

TABLE 2

PERMISSION NOT GRANTED FOR ONLINE REPRODUCTION

Modified and updated from table 1 in Knight AH and Rhind EG, Epilepsia 1975; 16:99–110.

is largely a consequence of reduced plasma protein binding,[3,7,14] reduced albumin concentration, increased drug clearance,[2,10,15,16] and patient nonadherence. The clearance rates are greatest during the third trimester. **Table 3** summarizes select pharmacokinetic data for several AEDs when used in pregnant women.

EFFECTS OF SEIZURES DURING PREGNANCY

Seizures during pregnancy increase the risk of adverse pregnancy outcomes. Generalized tonic-clonic seizures increase the risk for hypoxia and acidosis,[17] as well as injury from blunt trauma. Canadian researchers have found that maternal seizures during gestation increase the risk of developmental delay.[18] Although rare, stillbirths have occurred following a single generalized convulsion[19,20] or series of seizures.[21] While it is uncommon, status epilepticus carries a high mortality rate for both mother and fetus. In a series of the 29 reported cases, 9 of the mothers and 14 of the fetuses died during or shortly after an episode of status epilepticus.[22] In another report, the child of a woman who had three generalized tonic-clonic seizures during her pregnancy (at 19, 28, and 32 weeks' gestation) developed an intracerebral hemorrhage in utero.[23]

Generalized seizures occurring during labor can have a profound effect on fetal heart rate.[24] The increased rate of neonatal hypoxia and low Apgar scores among infants born to epileptic mothers may

TABLE 3
Pharmacokinetic data for first-generation antiepileptic drugs when used in pregnant women

Antiepileptic drug	Decrease in total drug level by third trimester	Normal binding	Percent free fraction	
			Maternal	Neonatal
Carbamazepine	40%	22%	25%	35%
Ethosuximide	?	90%	?	?
Phenobarbital	55%	51%	58%	66%
Phenytoin	56%	9%	11%	13%
Primidone	55%	?	?	?
Derived phenobarbital	70%	75%	80%	?
Valproic acid	50%	9%	15%	19%

Data from reference 7 and from "Valproic acid disposition and protein binding in pregnancy," by Koerner M, et al, Ther Drug Monit 1989; 11:228–230.

be related to the occurrence of such seizures during labor.[25] Partial seizures do not appear to have an adverse effect on fetal heart rate.

OVERVIEW OF COMPLICATIONS IN THE OFFSPRING

The offspring of epileptic mothers are at heightened risk for a variety of adverse pregnancy outcomes, either from maternal epilepsy itself or from in utero exposure to AEDs. These complications include fetal loss and perinatal death, congenital malformations and anomalies, neonatal hemorrhage, low birth weight, developmental delay, and childhood epilepsy. The next several sections explore these risks to the children in some detail.

FETAL LOSS AND INFANT MORTALITY

Fetal death, defined as fetal loss after 20 weeks' gestation, appears to be as common and perhaps as great a problem as congenital malformations and anomalies. Studies comparing stillbirth rates found higher rates in infants of mothers with epilepsy (1.3% to 14.0%) than in infants of mothers without epilepsy (1.1% to 7.8%) **(Table 4)**.

Spontaneous abortion, defined as fetal loss prior to 20 weeks' gestation, appears to occur more commonly in infants of mothers with epilepsy.[26] Women with localization-related epilepsies appear to be at greater risk for spontaneous abortions than those with other epilepsy syndromes.[27]

Other studies have demonstrated increased rates of neonatal and perinatal death. Neonatal death rates range from 1.3% to 7.8%, compared with 1.0% to 3.9% for controls **(Table 4)**.

CONGENITAL MALFORMATIONS

Congenital fetal malformations and anomalies have been associated with in utero exposure to AEDs. *Congenital malformations* are physical defects requiring medical or surgical intervention and resulting in a major functional disturbance. *Congenital anomalies*, in contrast, are deviations from normal morphology that do not require intervention. It is uncertain whether these aberrations represent distinct entities or a spectrum of physiologic responses to insult to the developing fetus, with malformations at one end and anomalies at the other. In this review, congenital malformations and anomalies will be discussed separately.

Infants of mothers with epilepsy exposed to AEDs in utero are twice as likely to have birth defects as infants not exposed to these drugs. Whereas malformation rates in the general population range from 2% to 3%, reported malformation rates in populations of AED-exposed infants range from 1.25% to 11.5%.[16,28–33] When combined, this range of estimates for exposed infants yields a 4% to 6% risk of malformation in a pregnancy of a woman with epilepsy. Cleft lip, cleft palate, or both, along with congenital heart disease, account for many of the reported cases. Orofacial clefts constitute 30% of malformations in these infants.[29,34,35]

In one report, first-trimester seizures were associated with a 12.3% risk of congenital malformations in offspring, compared with a 4% risk among offspring exposed to maternal seizures at other times.[36]

TABLE 4
Stillbirth and neonatal death rates in infants of women with epilepsy

Investigators	Stillbirths (%)		Neonatal deaths (%)	
	Cases	Controls	Cases	Controls
Janz, 1964	12.1	7.0	1.3	—
Speidel and Meadow, 1972	1.3	1.2	2.7	1.0
Bjenkdal and Bahna, 1973	5.3	7.8	3.2	1.5
Fedrick, 1973	2.7	1.1	—	—
Higgins and Comertond, 1974	5.2	—	7.8	3.9
Knight and Rhind, 1975	2.0	—	2.9	—
Nakane, 1979	13.5	4.3	—	—
Nakane, 1980	14.0	6.7	—	—
Nelson and Ellenberg, 1982	5.1	1.9	3.5	2.7
Svigos, 1984	0	1.3	—	—
Kalen, 1986	2.2	—	2.7	—
Tanganelli and Regesta, 1992	—	—	2.2	1.4

Neural tube defects: a possible pattern of causality

A wide variety of congenital malformations have been reported, and every AED has been implicated as a cause. No AED can be considered absolutely safe in pregnancy, yet most of these drugs do not produce any specific pattern of major malformations. Possible exceptions, however, are sodium valproate and carbamazepine, which have been associated with neural tube defects (NTDs).

Robert and Guibaud[37] first made this association when, working on a birth defects registry in the Rhône-Alps region of France, they reported NTDs in infants of mothers with epilepsy exposed to valproic acid in utero. Between August 1979 and August 1982, 72 infants with lumbosacral NTDs were born in this region. Nine of the 72, or 12.5%, had been exposed to valproic acid. Two of these 9 infants had a family history of NTDs; among the others, 5 were exposed to valproate monotherapy, 1 to valproate and phenobarbital, and 1 to valproate and clonazepam.

To clarify this observation, Robert et al[38] studied another 141 pregnancies in women with epilepsy, using a combination of questionnaires and electroencephalogram registries. This unselected cohort had a malformation rate of 17.7% and 4 cases of spina bifida (all with intrauterine exposure to valproic acid, though only 1 with monotherapy).

More-recent studies have revealed an association between in utero carbamazepine exposure and NTDs.[39,40] Subsequent evaluations of these exposures identify spina bifida aperta as the specific NTD associated with the valproic acid or carbamazepine exposure.[36] Problems with methodology make frequency estimates imprecise; most published data are from case reports, case series, or very small cohorts from registries not designed to evaluate pregnancy outcomes.

The prevalence of spina bifida aperta (SBA) is approximately 1% to 2% with valproate exposure[41] and 0.5%[39,42] with carbamazepine exposure. However, a prospective study in the Netherlands[36] found that infants of mothers with epilepsy exposed to valproate had a 5.4% prevalence of SBA. The average daily valproate doses were higher in mothers of infants with SBA (1,640 ± 136 mg/day) than in mothers of unaffected infants (941 ± 48 mg/day). Other investigators have found that valproate doses of 1,000 mg/day or plasma concentrations of 70 µg/mL or less are unlikely to cause malformations.[33] Both groups recommend that the dose be reduced in cases where valproate must be used in pregnancy.[33,43] Increasing dose frequency may also help reduce high peak concentrations when valproate must be used.

Pathophysiology of neural tube defects

NTDs are uncommon, occurring in 6 in 10,000 pregnancies. Spina bifida and anencephaly, the most commonly reported NTDs, affect approximately 4,000 pregnancies annually, resulting in 2,500 to 3,000 affected births in the United States each year.[44,45] The types of NTDs associated with AED exposure are primarily myelomeningocele and anencephaly, which are the result of abnormal neural tube closure between gestational weeks 3 and 4.

A number of risk factors are associated with NTDs. A previous pregnancy resulting in offspring with an NTD carries the strongest association, with a relative risk of 10. There also are strong ethnic and geographic correlations with NTDs. Rates per 1,000 births are 0.22 for whites, 0.58 for persons of Hispanic descent, and 0.08 for persons of African descent.[46] The incidence of NTDs in offspring is 3.26 per 1,000 for women in Mexico, 1.6 per 1,000

for Mexican-born women living in California, and 0.68 per 1,000 for US-born women of Mexican descent.[46] Children born to diabetic mothers are 7.9 times as likely as the general population to have NTDs.[47] Deficiencies of glutathione, folate, vitamin C, riboflavin, zinc, cyanocobalamin, and selenium have also been associated with NTDs, as has excessive exposure to vitamin A. Elevated rates of NTDs are seen in children of farmers, cleaning women, and nurses.[48,49]

Prepregnancy weight has also been shown to be a factor. Using women weighing 50 to 59 kg as controls, Werler et al[50] found that women weighing 80 to 89 kg had a 1.9 relative risk for NTDs in their offspring and women weighing 110 kg or more had a relative risk of 4.0.

AEDs may be a necessary but not a sufficient risk factor for the development of NTDs. Therefore, it is possible that AED treatment may increase the risk in women with one or more of the other risk factors discussed above. However, the possible teratogenicity of AEDs themselves cannot be completely ruled out.

Folate deficiency as a potential mechanism of AED teratogenicity

Folate is a coenzyme necessary for the development of red and white blood cells and for proper function of the central nervous system. Normal concentrations are typically measured in the serum (normal serum folate = 6 to 20 ng/mL) and erythrocytes (normal red blood cell folate = 160 to 640 ng/mL). Folate deficiencies have been implicated in the development of birth defects. Low levels of serum folate (< 6.6 ng/mL) and red blood cell folate (< 140 ng/mL) are associated with hyperhomocystinemia, which may be associated with NTDs. Dansky et al[51] found significantly lower blood folate levels in epileptic women with abnormal pregnancy outcomes compared with those who had normal outcomes.

Eight interventional trials have shown that preconceptual folate reduces the risk of malformations, NTDs, and NTD recurrence in women with a prior affected pregnancy. Biale and Lewenthal[52] reported a 15% malformation rate in infants of epileptic mothers who received no folate supplementation, whereas no abnormalities occurred in 33 infants born to epileptic women who did receive folate supplementation. Cotreatment of mice with folic acid, with or without vitamins and amino acids, also reduced malformation rates and increased fetal weight and length in mice pups exposed to phenytoin in utero.[53]

Unfortunately, preconceptual folate supplementation may not be protective for women with epilepsy. Craig et al[54] reported a young woman whose seizures were controlled for 4 years by 2,000 mg/day of valproic acid. Although she took 4.0 mg/day of folic acid for 18 months before her pregnancy, she delivered a child with a lumbosacral NTD, a ventricular and atrial septal defect, a cleft palate, and bilateral talipes. Duncan et al[55] reported two Canadian women who delivered children with NTDs despite folate supplementation. One of the women, who took 1,250 mg of valproic acid supplemented by 3.5 mg of folic acid for 3 months before conception, aborted a child with lumbosacral spina bifida, Arnold-Chiari malformation, and hydrocephalus. The second woman, also on valproic acid, took 5 mg of folic acid but still had one spontaneous abortion of a fetus with an encephalocele and two therapeutic abortions of fetuses with lumbosacral spina bifida.

Not all research supports an association between folate deficiency and fetal malformations. Mills et al[56] found no difference in serum folate levels between mothers of children with NTDs and controls. A number of other studies have failed to demonstrate a protective effect for preconceptual folate,[57–62] but these studies are problematic because of small sample sizes, failure to document folate supplementation, or recall bias in the retrospective investigations. In addition, genetic and racial predisposition to NTDs was not accounted for.

The utility of folate supplementation for the general population is clearly established. Women with epilepsy, like all women of childbearing age, should take folate supplements, but it remains unclear whether this will reduce the risk of birth defects in the children of those women taking AEDs. The recommended daily allowances of folate have been raised to 400 µg/day for nonpregnant women, 600 µg/day for pregnant women, and 500 µg/day for lactating women. Increased folate catabolism during pregnancy, together with variations in requirements among individual women, has led some to call for higher folate supplementation, on the order of 500 to 600 µg/day.[63] The 400-µg/day dose recommended by the Centers for Disease Control and Prevention (CDC) may not be high enough for many women who do not metabolize folate effectively. Even with folate supplementation, women taking valproate or carbamazepine should avail themselves of prenatal diagnostic ultrasonography to rule out NTDs.

Other possible mechanisms of AED teratogenicity

Over the last 15 years, a body of evidence has accumulated supporting the following hypotheses:

- An arene oxide metabolite of phenytoin or other AEDs is the ultimate teratogen
- A genetic defect in epoxide hydrolase (the enzyme system that detoxifies arene oxides) increases the risk of fetal toxicity
- Free radicals produced by AED metabolism are cytotoxic
- A genetic defect in free radical scavenging enzyme activity increases the risk of fetal toxicity.

Epoxides. A large number of drugs and chemicals can be converted into epoxides; these reactions are catalyzed by the microsomal monoxygenase system.[64,65] Arene oxides are unstable epoxides formed by aromatic compounds. Various epoxides are electrophilic and may elicit carcinogenic, mutagenic, and other toxic effects by covalent binding to critical cell macromolecules.[66,67] Epoxides are detoxified by two types of processes: (1) conversion to dihydrodiols catalyzed by epoxide hydrolase in the cytoplasm, and (2) conjugation with glutathione in the microsomes (spontaneous or mediated by glutathione transferase). Epoxide hydrolase activity has been found in the cytosol and the microsomal subcellular fraction of adult and fetal human hepatocytes. Interestingly, epoxide hydrolase activity is much lower in fetal livers than in adult livers.[68] One third to one half of fetal circulation bypasses the liver, resulting in higher direct exposure of extrahepatic fetal organs to potential toxic metabolites.[69]

These facts cannot completely explain the teratogenicity seen with phenytoin or other AEDs. The lymphocyte cytotoxicity seen with epoxide metabolites correlates with major but not minor malformations.[51] Although dysmorphic abnormalities have been described in siblings exposed to ethotoin in utero, ethotoin is not metabolized through an arene oxide intermediate.[70] Similarly, embryopathies have been described with exposure to mephenytoin, which also does not form an arene oxide intermediate.[71] Finally, trimethadione is clearly teratogenic but has no phenyl rings and thus cannot form an arene oxide metabolite. Therefore, an alternative mechanism must exist.

Free radical intermediates of AEDs and teratogenicity. Some drugs are metabolized or bioactivated by co-oxidation during the prostaglandin synthetase–catalyzed synthesis of prostaglandins. Such drugs serve as electron donors to peroxidases, resulting in an electron-deficient drug molecule, which by definition is called a free radical. In the search for additional electrons to complete their outer ring, free radicals can covalently bind to cell macromolecules—including nucleic acids (DNA, RNA), proteins, cell membranes, and lipoproteins—to produce cytotoxicity.

SYNDROMES OF CONGENITAL ANOMALIES

In contrast to malformations, which are anatomic deformities requiring intervention to maintain functional health, anomalies are abnormalities of structure that do not constitute a threat to health. Patterns of anomalies in infants of mothers with epilepsy have been noted with exposure to certain AEDs. Five clinical syndromes have been reported in infants of mothers with epilepsy: fetal trimethadione syndrome, fetal hydantoin syndrome, primidone embryopathy, fetal valproate syndrome, and fetal carbamazepine syndrome. Dysmorphic facial features have also been described in infants of mothers taking benzodiazepines or lamotrigine. Clinically, these syndromes primarily involve dysmorphic features of the midface. Moore et al[72] suggest that learning and behavior disturbances are an important aspect of these syndromic anomalies. In an unselected cohort of 52 affected children, 77% were found to have developmental delay, 81% to have autistic behaviors, and 39% to be hyperactive.[72]

Clinical and laboratory evidence clearly supports the association of certain AEDs with teratogenic effects, particularly facial and distal digital anomalies. However, the existence of drug-specific syndromes is doubtful. Facial dysmorphism is difficult to quantify and clearly not drug-specific. Infants of epileptic mothers with similar dysmorphic features were described in the preanticonvulsant era.[16,73] Follow-up of these infants into adulthood has yet to be accomplished, so the significance of these anomalies is unclear. Gaily et al[74] followed a cohort of infants of mothers with epilepsy to 5 1/2 years of age. Compared with control children, these children had an excess of minor anomalies characteristic of fetal hydantoin syndrome, but so did their mothers relative to control mothers. Only hypertelorism and digital hypoplasia were associated with phenytoin exposure. Certain anomalies, particularly epicanthal folds, appeared to be associated with maternal epilepsy, not with AED exposure.

The hypothesized association of dysmorphic features with mental retardation[29] has not been con-

firmed. In the few cases that have been followed into early childhood, the dysmorphic features tended to disappear as the child grew older.[10] Mental deficiency was found in only 1.4% of infants of mothers with epilepsy followed to 5 1/2 years of age.[75] Exposure to AEDs below toxic concentrations or to maternal seizures did not increase the risk of lower intelligence. No association between features of fetal hydantoin syndrome and mental retardation could be demonstrated.

The primary abnormalities in these syndromes involve the midface and distal digits. In a retrospective study spanning 10 years of deliveries in Israel, hypertelorism was the only anomaly seen more often in infants of mothers with epilepsy than in controls.[76] This anomaly was associated with all AEDs except primidone. A prospective study of 172 deliveries of infants of mothers with epilepsy evaluated eight specific AEDs and other potential confounding factors and found no dose-dependent increase in the incidence of malformations with any individual AED. Furthermore, no specific defect could be associated with individual AED exposure.[77] It has been suggested that, since a variety of similar anomalies of the midface and distal digits are seen in a small proportion of children exposed to AEDs in utero, a better term for the entire group of abnormalities would be *fetal anticonvulsant syndrome* or *AED embryopathy*.[78–80]

NEONATAL HEMORRHAGE

For many years it has been reported that infants of mothers with epilepsy are at increased risk for a unique form of neonatal hemorrhage. First described by Van Creveld,[81] who suggested that vitamin K deficiency might be the cause, it was first delineated as a syndrome by Mountain et al,[82] but there have been numerous reports of in utero AED exposure associated with neonatal hemorrhage.[83–89] It was initially associated with exposure to phenobarbital or primidone but has subsequently also been described in infants exposed to phenytoin, carbamazepine, diazepam, mephobarbital, amobarbital, and ethosuximide.

It has been differentiated from other hemorrhagic disorders in infancy in that the bleeding occurs internally, during the first 24 hours of life. Accurate prevalence figures are not available.

The hemorrhage appears to result from a deficiency of vitamin K–dependent clotting factors II, VII, IX, and X. Maternal coagulation measures are invariably normal. The fetus, however, will demonstrate diminished clotting factors and prolonged prothrombin and partial thromboplastin times. A prothrombin precursor, protein induced by vitamin K absence (PIVKA), has been discovered in the serum of mothers taking anticonvulsants.[90] Assays for PIVKA may permit prenatal identification of infants at risk for hemorrhage.[91,92]

The historical demonstration of an increased risk of neonatal hemorrhage, coupled with a demonstrated deficiency of vitamin K and the PIVKA findings, led clinicians to believe that the relative lack of vitamin K and the presence of PIVKA was the cause of this particular neonatal hemorrhage. Several studies demonstrated that oral maternal supplementation increased neonatal vitamin K and reduced hemorrhage.[93–95]

This practice has been challenged, however. Kaaja et al[96] found no difference in rates of neonatal hemorrhage between 667 infants of mothers with epilepsy (0.7%) and 1,334 control infants (0.4%). No mothers in either group received vitamin K supplementation, but all infants received intramuscular vitamin K at delivery. These researchers felt that no evidence of a difference in clinical bleeding could be found, so supplementation was not recommended. Hey[97] measured cord blood from 137 infants of mothers with epilepsy taking phenobarbital, phenytoin, or carbamazepine and found that 14 of 105 had prolonged prothrombin times but none had any clinical bleeding. He concluded that the lack of clinical bleeding in his series made vitamin K supplementation inappropriate.

The problem, in part, is that there is confusion between vitamin K deficiency, laboratory evidence of abnormal coagulation measures, and clinical bleeding. Vitamin K deficiency is common, the presence of PIVKA less so, but clinical bleeding in neonatal life is rare. Shapiro et al[98] demonstrated that PIVKA presence is fairly uncommon in the general population of newborns (2.9%) and more common in premature infants. We have no good data on the prevalence of neonatal hemorrhage in infants of mothers with epilepsy, but we do have reasonably accurate case reports.

We also have reasonable causation. AEDs can act like warfarin and can inhibit vitamin K transport across the placenta. These effects can be overcome by large concentrations of the vitamin. Despite lower coagulation factor levels, the fetus is generally able to obtain enough maternal vitamin K

in utero. After birth, the infant must rely on exogenous sources of vitamin K because the newborn gut is sterile. Routine administration of vitamin K at birth is not adequate to prevent hemorrhage if any two of the coagulation factors fall below 5% of normal values.[89] Successful treatment requires fresh frozen plasma intravenously.

It is clear that vitamin K supplementation should be offered to pregnant women with epilepsy. The risk of neonatal hemorrhage, while low, clearly exists, as demonstrated by elevated PIVKA levels, particularly in women taking enzyme-inducing AEDs. There is no effective intervention once a neonate bleeds. Also, there is the possibility of small bleeds that, while not clinically detectable at birth, may have long-term effects. Moreover, vitamin K supplementation at the recommended level (10 mg/day) poses no risk. There is also a clear need for better prevalence data on the true risk of clinical bleeding in infants of mothers with epilepsy.

LOW BIRTH WEIGHT

Low birth weight (< 2,500 g) and prematurity have been described in infants of mothers with epilepsy. The average rates range from 7% to 10% for low birth weight and 4% to 11% for prematurity.[24,30,99–101] These studies do not analyze the effects of specific seizure types, seizure frequency, or AEDs on this aspect of fetal development.

DEVELOPMENTAL DELAY

Infants of mothers with epilepsy have been reported to have higher rates of mental retardation than controls; the risk is increased twofold to sevenfold, according to various authors.[102] None of these studies controlled for parental intelligence, however. Differences in Full Scale Intelligence Quotient (FSIQ) scores at age 7 between groups of children exposed (FSIQ = 91.7) or not exposed (FSIQ = 96.8) to phenytoin reach statistical significance, but the clinical significance of these differences is unknown.[103]

We have found that infants of mothers with epilepsy score lower on measures of verbal acquisition at both 2 and 3 years of age. Though there was no difference in physical growth measures between infants of mothers with epilepsy and controls, infants of mothers with epilepsy scored significantly lower on the Bayley Scale of Infant Development's mental developmental index at 2 and 3 years. They also performed significantly less well on the Bates Bretherton early language inventory ($P \leq .02$) and on the Peabody Picture Vocabulary scales of verbal reasoning ($P \leq .001$) and composite IQ ($P \leq .01$). They also demonstrated significantly shorter mean lengths of utterance ($P \leq .001$).[104]

Infants exposed to AED polytherapy performed significantly less well on neuropsychometric testing than did those exposed to monotherapy. Socioeconomic status had the strongest association with poor test scores, but maternal seizures during pregnancy were also a significant risk factor.[105]

Leonard et al[18] have partially addressed the question of whether maternal seizures or in utero exposure to AEDs is responsible for the developmental delays seen. A group of children of mothers with epilepsy followed to school age were found to have a rate of intellectual deficiency of 8.6%. The Wechsler Intelligence Scale for Children showed significantly lower scores for children exposed to seizures during gestation (100.3) than for children whose mothers' seizures were controlled (104.1) or for controls (112.9). All AEDs are clearly not created equal in this respect, and Koch et al[106] have demonstrated that primidone, particularly when used in polytherapy, is associated with lower Wechsler Intelligence Scale scores.

EPILEPSY IN THE CHILDREN OF EPILEPTIC PARENTS

The risk of epilepsy in children of parents with epilepsy is higher than that in the general population. Interestingly, this risk is higher for children of mothers with epilepsy (relative risk = 3.2).[107] Paternal epilepsy appears to have less impact on the development of seizures in children. The presence of maternal seizures during pregnancy is associated with an increased risk of seizures in the offspring (relative risk = 2.4),[108] although AED use is not. Evidence to support a genetic component for seizure development in these infants comes from kindling studies in experimental animals. If rats with experimental epilepsy are made to have generalized seizures during pregnancy, their offspring are not more susceptible to kindling than the offspring of rats with no seizures during parturition.[109]

PROFILE OF SPECIFIC EFFECTS OF NEWER AEDs IN PREGNANCY

A number of new AEDs have been marketed in the United States since 1993: gabapentin, felbamate, lamotrigine, levetiracetam, oxcarbazepine, tiaga-

bine, topiramate, and zonisamide. The number of reported pregnancies exposed to these drugs is very low, and not large enough to determine if there is an increased risk of adverse outcome with fetal exposure. We know that lamotrigine and levetiracetam concentrations decline during pregnancy and expect that this is also true for the other newer AEDs.[5,6] The paragraphs below summarize currently available data on the use of specific newer AEDs in pregnancy.

Gabapentin

A study combining retrospectively and prospectively collected cases evaluated 44 children born to 39 mothers with epilepsy taking gabapentin. Two of 44 (4.5%) had major malformations. One child exposed to gabapentin and valproic acid had hypospadias. The other, exposed to gabapentin monotherapy until the 16th week of gestation and then to phenobarbital, had only one kidney.[110]

Lamotrigine

The International Lamotrigine Pregnancy Registry has identified 334 pregnancies in women taking lamotrigine during the first trimester. Of these pregnancies, 168 were exposed to monotherapy and 166 to polytherapy. There is a difference in malformation rates when lamotrigine is used as monotherapy (1.8%), as polytherapy with valproic acid (10%), or as polytherapy without valproic acid (4.3%). The three reported malformations attributed to monotherapy in this prospective registry were esophageal malformation, cleft palate, and club foot.[111]

Lamotrigine crosses the placenta. At birth, mother and fetus have similar plasma concentrations. Elimination in infants appears to be rather slow. At 72 hours postpartum, infant plasma levels are 75% those of the mother. Median milk-to-plasma ratios are 0.61.[8]

Oxcarbazepine

The first 12 reported cases of pregnancy with oxcarbazepine resulted in 9 live births and 3 spontaneous abortions. In a prospective study of 11 pregnancies, the birth of 1 child with spina bifida exposed to oxcarbazepine as part of polytherapy was reported.[112] The only prospective series reported to date evaluated 42 oxcarbazepine-exposed pregnancies in Buenos Aires.[113] There were no malformations in the 25 monotherapy-exposed children. One child exposed to oxcarbazepine and phenobarbital had a ventricular septal defect.

Oxcarbazepine crosses the placenta, and maternal and fetal cord levels are equivalent.[114]

Topiramate

We have little information on the number of pregnancies exposed to topiramate. There is one case report of a child exposed in utero to topiramate monotherapy who developed growth deficiency, hirsutism, a third fontanelle, an upturned nasal tip, and distal digital hypoplasia. During clinical trials, 28 pregnancies were reported, with 1 malformation and 2 anomalies. The manufacturer has collected data on 139 pregnancies during postmarketing surveillance. Of these, 87 resulted in live births, 29 were lost to follow-up, and 23 were therapeutically aborted. There were 5 cases of hypospadias [personal communication at the Finnish Epilepsy Society annual meeting, 2002].

Topiramate crosses the placenta, and cord and maternal plasma levels are equivalent at delivery. Milk-to-plasma ratios average 0.86. Infant elimination appears to be substantial, with little measurable drug found in the plasma of breast-fed infants 2 to 3 weeks postpartum.[115]

Zonisamide

Twenty-six pregnancies with zonisamide exposure have been reported. Two of the 26 (7.7%) involved congenital malformations: one child was also exposed to phenytoin, and the other to both phenytoin and valproic acid.[116]

Zonisamide freely crosses the placenta, with transfer rates of 92%. Though data are available from only 2 children, milk-to-plasma ratios are 0.8 and the elimination half-life ranges from 61 to 102 hours.[117]

EFFECTS OF VAGUS NERVE STIMULATION

Vagus nerve stimulation is a technique that uses an implanted generator to produce electrical stimulation of the left vagal nerve, in the neck. The device, manufactured by Cyberonics Corp., Houston, Tex., is used to reduce the frequency and severity of seizures. Approximately 13,000 persons with epilepsy have had the device implanted. There have been 11 pregnancies in epileptic women using the device. Eight had normal children. Two women chose to have elective abortions, and one of these fetuses was malformed, arguably from the AED that the woman was also taking. One woman had a spontaneous abortion.[118]

TABLE 5
Antiepileptic drug pharmacokinetics in plasma and breast milk

Antiepileptic drug	Protein binding (%)	Half-life (hr)		Milk-to-plasma ratio
		Adult	Neonate	
Carbamazepine	75	8–25	8–28	0.4–0.6
Ethosuximide	<10	40–60	40	0.9
Felbamate	25	14–22	?	?
Gabapentin	0	5–8	?	?
Lamotrigine	55	24	?	0.4–0.7
Levetiracetam	<10	6–8	?	?
Oxcarbazepine	45	8–10	?	?
Phenobarbital	45	75–126	45–500	0.4–0.6
Phenytoin	90	12–50	15–105	0.2–0.4
Primidone	<20	?	?	0.7–0.9
Tiagabine	95	4.5–13	?	?
Topiramate	15	19–23	?	0.86
Vigabatrin	0	5–8	?	?
Zonisamide	50–60	63	?	0.8

RECOMMENDATIONS FOR MANAGING THE PREGNANT WOMAN WITH EPILEPSY

Those who care for pregnant women with epilepsy face a dilemma. Seizures must be prevented, but fetal exposure to AEDs must also be minimized. Although it might seem ideal to withdraw the patient from AEDs before conception, for most women this is not a realistic option. Women today are more likely to be employed, and the potential disruption of their lives by seizures (eg, the risk of losing one's driver's license) makes elimination of AEDs impractical. More importantly, maternal seizures increase the risk of injury, of miscarriage, and of epilepsy and developmental delay in the offspring.

By late in the first trimester, the major organ systems have formed. The posterior neuropore closes by the 27th day of gestation, and the palate by the 47th day. By the time most women realize that they are pregnant, malformations already may have developed. Epileptic women of childbearing age need to be informed of the risks associated with AED use **(Table 1)** prior to conception, if at all possible. They also need to know that seizures can be harmful to mother and fetus, and that risks can be reduced with proper care.

General recommendations for risk reduction

Even healthy parents have a 2% to 3% risk of having a child with a malformation. Given the current state of the art, the best we can do is practice risk reduction. In general, risks can be minimized by the preconceptual use of multivitamins with folate, by using AEDs in monotherapy at the lowest effective dose, and by preventing maternal seizures. Monitoring free drug levels both before and during pregnancy will permit accurate assessment of concentrations in a situation where plasma protein binding is in flux. Dose adjustment, however, should be made on a clinical basis. Plasma AED concentrations will fall in all pregnant women, but only one fourth to one third of pregnant women will have an increase in seizures. We tend to keep the dosage as low as possible during conception and organogenesis, but will often raise it during the third trimester to reduce the risk of seizures during labor.

Vitamin supplementation

Supplementation with at least 0.4 mg/day of folate is recommended by the CDC for all women of childbearing age, whether or not they have epilepsy. Recent studies have suggested that 0.5 or 0.6 mg/day might be more effective. For women with a family history of an NTD, 4.0 mg/day is the recommended dose. A number of observational and interventional studies have demonstrated a reduction in the risk of malformations in general, and of NTDs in particular, in women taking folate prior to conception.[57,59,119–121] The doses used in these studies ranged from 0.36 to 5.0 mg/day.

Vitamin K_1, at a dose of 10 mg/day, should be initiated late in the third trimester to prevent neonatal hemorrhage. We usually prescribe it during the final month of gestation.

Breast-feeding

Breast-feeding is generally safe in term infants, as they have been exposed to the mother's AED for 9 months and their hepatic microsomal enzyme systems have been induced. However, breast-feeding should be undertaken cautiously by women receiving phenobarbital or primidone because of the risk of infant sedation. The known milk-to-plasma concentration ratios of AEDs are listed in **Table 5**.

Prenatal diagnostic techniques

Pregnant women taking valproate, carbamazepine, or both should avail themselves of prenatal ultrasonography and alpha-fetoprotein measurement. Ultrasonography has become much more accurate and, in experienced hands, can identify the vast majority of structural defects. Current prenatal testing recommendations are as follows:

- Anatomic ultrasonography at 11 to 13 weeks to identify the most severe defects, such as anencephaly
- Maternal serum alpha fetoprotein
- Repeat anatomic ultrasonography at 16 weeks to identify abnormalities such as orofacial clefts, heart defects, and caudal NTDs.

Create a plan based on gestational age

When a pregnant women with epilepsy initially presents to her neurologist, the gestational age of the fetus must be established with reasonable accuracy. One cannot rely on the last menstrual period alone; an early ultrasonogram should be obtained to date the pregnancy. Once gestational age is established, a calendar can be planned, with dates determined ahead of time for monthly AED level checks, prenatal testing, and initiating vitamin K supplementation.

Managing more than just seizures

The management of pregnant women with epilepsy presents unique challenges. Confirmation of the diagnosis of epilepsy and verification of the most appropriate AED for the individual are the starting points. With effective patient education and careful and consistent management—which includes coordinated treatment planning by both neurologist and obstetrician—these patients can and do have successful pregnancies and healthy offspring.

NTDs are serious malformations for which there are no effective therapeutic interventions. Their risk can be reduced by careful management and theoretically may be eliminated by prenatal diagnosis and therapeutic abortion. In our role as advisors, clinicians need to recognize that all patients may not share our value systems or even begin to perceive what it really means to care for a child with an NTD. We must be sensitive to our patients' anxieties and be prepared to manage both their seizures and their emotional concerns.

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Neurodevelopmental outcomes of children born to mothers with epilepsy

KIMFORD J. MEADOR, MD, AND MARY L. ZUPANC, MD

ABSTRACT

Most children born to women with epilepsy are normal, but there is an increased risk of abnormal functional neurodevelopment in these children. Although there are many contributing factors, antiepileptic drugs (AEDs) may play a role. Most women with epilepsy must take AEDs during pregnancy because the potential for injury from seizures to both mother and fetus is a greater risk. AEDs are also used to treat other disorders, including depression and pain. Thus, an understanding of the effects of AEDs on the unborn child is relevant to physicians who treat nonepileptic mothers as well. This review discusses animal and human studies of the neurodevelopmental effects of AEDs and briefly reviews the possible mechanisms underlying these effects. Flaws in the methodology of some studies of these effects require that the results be interpreted cautiously and highlight the need for well-designed studies to explore this issue further.

The majority of children born to mothers with epilepsy are anatomically and functionally normal, but the risk for adverse outcomes is increased in these children. Both somatic malformations and abnormal functional neurodevelopment occur with increased frequency in these children.[1,2] A variety of factors contribute to the cognitive disabilities in children of mothers with epilepsy, and antiepileptic drugs (AEDs) may be an important factor.[1,2] For example, the risk of neurodevelopmental defects is increased in the children of women with epilepsy but not the children of fathers with epilepsy. However, the large majority of women with epilepsy cannot choose to avoid AEDs because of the risks that seizures pose to the mother and her unborn child. Trauma is the leading cause of nonobstetric deaths in pregnant women with epilepsy, and the risks of maternal seizures to the fetus include intracranial hemorrhage, suppression of fetal heart rate, premature delivery, and miscarriage.

From the Department of Neurology, Georgetown University Hospital, Washington, D.C. (K.J.M.), and the Department of Neurology, Medical College of Wisconsin, Milwaukee (M.L.Z.).

Address: Kimford J. Meador, MD, Department of Neurology, Georgetown University Hospital, 1st Floor Bles, 3800 Reservoir Rd., NW, Washington, DC 20007; e-mail: kjm32@georgetown.edu.

IN UTERO EXPOSURE TO AEDs IS WIDESPREAD

Epilepsy affects 0.6% to 1.0% of the population.[3] If the lower estimate of epilepsy prevalence is used, about 24,000 children are born to women with epilepsy each year in the United States alone. Because about 95% of women with epilepsy take AEDs, approximately 22,800 children each year are exposed in utero to AEDs taken by mothers with epilepsy. Given that AEDs are also used to treat other disorders, including depression and pain, and that fewer than half of all prescriptions for AEDs are for epilepsy or seizures, the total number of US children exposed in utero to AEDs each year is probably at least 45,000. This is why understanding the effects of AEDs on the unborn child is important. Nevertheless, consensus guidelines have not been able to determine which of the AEDs is the most teratogenic.[4,5]

BEHAVIORAL TERATOGENICITY: THE EVIDENCE BASE

Animal studies

In utero AED exposure can produce behavioral deficits in animals, and this occurs at blood levels similar to therapeutic levels in humans.[6,7] Phenobarbital can cause neuronal deficits, reduced brain weight, and impairment of behavioral development.[8–10] Phenytoin can affect genetic expression

and delay neurodevelopment.[11–13] Prenatal phenytoin has been associated with hyperexcitability in monkeys, producing a syndrome similar to attention-deficit/hyperactivity disorder.[14] Behavioral impairments have been seen as a result of in utero exposure to primidone, trimethadione, or valproate.[12,15] Animal studies suggest that in utero exposure to AEDs can produce neurobehavioral deficits at dosages lower than those required to produce anatomic malformations, but direct extrapolation of these results to humans may be misleading.

Human studies

Children of mothers with epilepsy have an increased risk of developmental delay and cognitive impairments.[1,2] AEDs appear to play a role, although the exact mechanisms remain uncertain. Like anatomic defects, cognitive impairments are increased in children of mothers with epilepsy, but not in children of fathers with epilepsy.[16] In addition, children of women with epilepsy who do not take an AED during pregnancy have no behavioral deficits compared with children of matched controls.[17]

Because children exposed in utero to AEDs in mothers without epilepsy appear to have the same risks for somatic malformations as children exposed in utero to AEDs in mothers with epilepsy,[18] they are probably at similar risk for behavioral deficits, but no data are available in these children. Differential behavioral effects of in utero AED exposure are uncertain, and methodologic disparities across studies have led to inconsistent results.[1,2,19] Several studies are described below because they either raise concerns of potential risks or highlight research design flaws.

In two studies from Denmark, men exposed in utero to phenobarbital had lower verbal IQ scores than predicted (by approximately 7 IQ points, or half a standard deviation in IQ score).[20] The deficit rose to 20 IQ points if these men also were born as the result of an unwanted pregnancy and were of lower socioeconomic status. Although retrospective and not definitive, these results suggest that prenatal phenobarbital exposure in humans can produce cognitive deficits lasting into adulthood. Further, the increased deficit seen in those men with multiple risk factors is consistent with other research on mental retardation.

In a study attempting to reduce the risk of intracranial hemorrhage in their children, pregnant mothers at risk for premature delivery were randomized to receive placebo plus vitamin K or phenobarbital plus vitamin K.[21] Behavioral outcomes were assessed at 2 years in 121 of the original 353 children. Children exposed to phenobarbital had a lower Bayley Mental Developmental Index score (104 ± 21 SD) compared with the placebo group (113 ± 22 SD). Although the results are consistent with the Danish studies' findings, their validity remains in doubt because only 32% of the total group of randomized children were tested at the 2-year follow-up.

In another study, 20 children exposed in utero to phenytoin had lower IQ scores (109 ± 11 SD) at 4 to 8 years of age compared with 98 controls (118 ± 12 SD).[22] However, failure to control for parental IQ limits its confidence in the interpretation of these results.

The adverse effects of phenobarbital are further supported by the preliminary report of a comparative study.[23] Children 6 to 16 years of age exposed in utero to carbamazepine, phenobarbital, or phenytoin were evaluated along with matched controls. Phenobarbital- and carbamazepine-exposed children had lower Full Scale IQ scores compared with matched controls, but the phenytoin group did not differ from its controls. Further details and replication are needed.

A prospective study comparing carbamazepine and phenytoin reported greater adverse effects with phenytoin.[24] However, the results are inconclusive because a greater proportion of the pregnant women taking carbamazepine were nonepileptic, the relative AED dose was lower for carbamazepine, and maternal IQ scores were not used in the analyses even though they were available. Comparison of child-mother IQ differences suggests that the carbamazepine-exposed and phenytoin-exposed children did not differ.[25]

A recent retrospective study assessed the relative risk of additional educational needs in 594 school-age children exposed in utero to AEDs.[26] Special education needs across groups were as follows:

- No drug, 11%
- Monotherapy with valproate, 30%
- Monotherapy with carbamazepine, 3%
- Other AED monotherapy, 6%
- Polytherapy with valproate, 24%
- Polytherapy without valproate, 16%.

The results suggest that the risk of special educational needs may be elevated with valproate use, but replication is needed to rule out selection bias. A preliminary report from the same research group, based on a retrospective study of 251 children, noted that the mean IQ score for children exposed to valproate was 82 compared with 95 for children exposed to carbamazepine and 92 for children not

exposed to AEDs.[27]

Preliminary results from a prospective study support the observation of poorer outcomes with valproate.[28] The investigators tested 60% of 299 children of mothers with epilepsy and 50% of 277 children of healthy control mothers who had been followed since birth. The mean IQ score following in utero exposure to valproate was 83 compared with 95 for the rest of the epilepsy group. This difference was significant even after controlling for age, education, and polytherapy. However, a weakness of the study is that the valproate monotherapy group consisted of only 11 children. Thus, additional studies are needed to confirm this finding.

POSSIBLE MECHANISMS OF AED EFFECTS ON NEURODEVELOPMENT

The mechanisms underlying the teratogenicity of AEDs are uncertain, and it is unclear whether functional and anatomic defects involve the same factors. Mechanisms hypothesized to underlie the teratogenic effects of AEDs include neuronal suppression, folate-related mechanisms, *N*-methyl-D-aspartate/γ-aminobutyric acid (NMDA/GABA)-related mechanisms, ischemia/hypoxia, and reactive intermediates (eg, epoxides and free radicals).

Neuronal suppression

AEDs suppress neuronal irritability, and thus may impair neuronal excitation, in turn altering synaptic growth and connectivity. There is no experimental proof of this hypothesis, but these effects could potentially lead to long-term deficits in cognition and behavior, especially in the rapidly developing brain of a fetus, infant, or child.

Folate-related mechanisms

Folate is important for DNA and RNA synthesis. Phenobarbital, phenytoin, primidone, and valproate can interfere with folate metabolism,[21] and folate requirements are increased during pregnancy. Blood folate concentrations are reported to be lower in women with epilepsy who have abnormal pregnancy outcomes,[29] but no controlled trial has been conducted. The effects of folate on malformation rates in mice exposed to phenytoin in utero are controversial.[30,31]

NMDA/GABA-related mechanisms

An animal model of fetal alcohol syndrome has shown that cognitive deficits from in utero ethanol exposure are due to the combined effects of NMDA glutamate receptor blockade and $GABA_A$ receptor activation.[32] The effect of alcohol is greatest in the third trimester, resulting in widespread apoptotic neurodegeneration, reduced brain mass, and neurobehavioral deficits. A recent study in neonatal rats demonstrated that several AEDs can produce neuronal apoptosis.[33]

Ischemia/hypoxia

AEDs may affect cardiac function. Phenytoin-induced congenital defects in animals resemble the effects of ischemia, and hyperbaric oxygen can reduce phenytoin malformations.[34] The similarity of the effects of ischemia and phenytoin may be due to free radical formation. No studies have been conducted in humans to confirm or refute this hypothesis.

Reactive intermediates

AED teratogenicity may not be mediated by the parent compound but may be the result of toxic intermediary metabolites, which can bind protein, lipids, and nucleic acid, causing cellular damage.

Epoxides. Some AEDs are metabolized to highly reactive arene oxide intermediates called epoxides. Arene oxides can be detoxified by epoxide hydrolase, and inhibition of this enzyme leads to an increase in malformations in animals.[35] Further, children exposed to phenytoin are more likely to have dysmorphic features if they have low epoxide hydrolase activity in their amniocytes.[36] However, it is unclear whether this is a viable hypothesis because the P450 enzymes that convert an AED to an epoxide are not expressed in embryonic tissues.[37] It seems unlikely that an epoxide formed by maternal enzymes would reach the fetus before binding to maternal tissues.

Free radicals. Prostaglandin H synthetase and lipoxygenases are active in the fetus and can bioactivate AEDs to free radical–reactive intermediates.[38] These reactive oxygen species can bind to DNA, protein, or lipids, leading to teratogenesis in the fetus. Consistent with this hypothesis, prostaglandin H synthetase inhibitors, free radical–trapping agents, antioxidants (eg, vitamin E), and antioxidative enzymes (eg, superoxide dismutase) can reduce phenytoin-induced teratogenic defects in animals.[39,40] Studies in humans are needed to confirm this hypothesis.

CONCLUSIONS

Children born to women with epilepsy are at increased risk for somatic malformations and behavioral impairments. AEDs probably contribute to this risk, but the potential for injury from seizures to both the mother and the unborn child is a greater risk. Thus, most women with epilepsy must take AEDs

during pregnancy. The above risks should be balanced with the knowledge that the majority of children born to women with epilepsy are normal. Design flaws in human studies preclude firm conclusions as to the incidence and magnitude of AED effects in humans. Most important, it is unknown whether there are different effects among the AEDs. Further, the mechanisms underlying these effects need to be delineated. Ultimately, a well-controlled prospective study will be required to resolve this important issue. The results of such a study would directly affect the management of women with epilepsy.

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Bone disease associated with antiepileptic drugs

ALISON M. PACK, MD; BARRY GIDAL, PharmD; and BLANCA VAZQUEZ, MD

ABSTRACT

Antiepileptic drugs (AEDs) are associated with bone disease. Early reports found rickets in children and osteomalacia in adults, but those reports were primarily in institutionalized persons. Studies in ambulatory adults and children taking AEDs do not reveal rickets or osteomalacia but do report abnormalities in biochemical indexes of bone mineral metabolism and density. In addition, fracture rates are increased in AED-treated patients. AEDs that induce the cytochrome P450 enzyme system are most commonly associated with abnormalities in bone. Emerging data suggest that valproate, an enzyme inhibitor, may also affect bone, and there is limited information on the newer AEDs. Several theories on the mechanism of AED-associated bone disease have been proposed, but no single one explains all the reported findings. Identifying AED-treated patients who are at risk for or have bone disease is important, as multiple therapies are available.

Antiepileptic drugs (AEDs) can adversely affect bone health in children, adolescents, and adults. The reported effects of AEDs on bone include rickets, osteomalacia, osteoporosis, and fractures. A number of theories have been proposed to explain why AEDs affect bone, but none explains all the reported effects. This article reviews the manifestations of bone disease in AED-treated patients, identifies the AEDs most commonly associated with bone abnormalities, explores the proposed mechanisms of AED-related bone disease, and surveys treatments available for bone disease in AED-treated patients. We conclude with general recommendations for identifying AED-treated patients at risk for bone disease. Identifying these patients is important, given that seizures can put patients at particular risk for falls and fractures.

From the Neurological Institute, Columbia Presbyterian Medical Center, New York, N.Y. (A.M.P.); the University of Wisconsin, Madison, Wisc. (B.G.); and New York University School of Medicine, New York, N.Y. (B.V.).

Address: Alison M. Pack, MD, The Neurological Institute, Columbia Presbyterian Medical Center, 710 W. 168th Street, New York, NY 10032; e-mail: ap390@columbia.edu.

BONE HEALTH IS A PROCESS

Maintenance of bone density and bone health is a dynamic process. Bone mass is determined by a balance of bone resorption and bone formation. In children and adolescents, although the rate of bone resorption is high, the rate of bone formation is even higher. After bone mineral density (BMD) peaks in the third decade of life, bone resorption is greater than bone formation, resulting in loss of bone mass. Along with absolute bone mass, the quality of bone is an important component of bone health.

MANIFESTATIONS OF BONE DISEASE IN PERSONS TREATED WITH AEDs

Rickets and osteomalacia

Rickets is a disorder of mineralization of the bone matrix in growing bone, and thus is a pathologic process seen in children.[1] Both the growth plate and newly formed trabecular and cortical bone are affected. Rickets occurs secondary to deficiencies in active vitamin D, calcium, or phosphorus. Clinical manifestations include hypotonia, muscle weakness, and, in severe cases, tetany. Weight bearing produces a bowing deformity of the long bones.

Bone biopsy is the most sensitive method of diagnosis. The biopsy reveals accumulation of unmineralized bone. Biochemical findings include low levels of calcium, phosphorus, and vitamin D metabolites

(25-hydroxyvitamin D and 1,25-dihydroxyvitamin D) and elevated levels of alkaline phosphatase.

Rickets has been reported in children treated with AEDs.[2] However, most of the subjects were institutionalized, and recent reports in ambulatory children have not found evidence of rickets.[3–6]

Osteomalacia, which literally means softening of bone, results from a reduction in bone matrix mineralization.[7] In contrast to rickets, osteomalacia occurs after cessation of growth and involves only the bone and not the growth plate. Drug-induced osteomalacia occurs secondary to either deficiencies in calcium, phosphate, and active vitamin D or interference with their deposition or action in bone.

As with rickets, bone biopsies of patients with AED-induced osteomalacia are histologically characterized by an increase in osteoid or unmineralized bone and reveal a mineralization defect that produces prolonged mineralization lag time. Low calcium, phosphate, and active vitamin D levels are found in serologic studies. Clinically, diffuse muscle pain is the most common presentation, and persons with osteomalacia have an increased risk of fracture.

Early reports described osteomalacia in patients treated with AEDs.[8,9] However, these reports primarily involved institutionalized patients in whom lack of nutrition and lack of sunlight probably influenced outcomes. Evidence of osteomalacia is rarely found in ambulatory persons.[10,11]

Osteoporosis

Osteoporosis is defined by a reduction in bone mass leading to an increased risk of fracture. It is the major cause of vertebral and hip fractures in the United States. Osteoporosis occurs when there is failure to achieve peak bone mass, increased bone resorption, or inadequate bone formation. Multiple risk factors contribute to the development of osteoporosis **(Table 1)**.

The diagnosis of osteoporosis currently depends on the measurement of BMD. The present criterion standard for obtaining BMD measurements is dual-energy x-ray absorptiometry (DXA).[12] DXA can measure bone mineral content at multiple sites and can detect a 5% decrement in BMD. The most frequently studied site is the lumbar spine, while others include the proximal femur and the radius. Whole-body measurements of both bone mineral content and body composition may be performed.

DXA results are given as absolute BMD, T score (standard deviation after comparison with a sex- and race-matched population), and Z score (standard deviation after comparison with an age-, sex-, and race-matched population). The World Health Organization uses the T score to define osteopenia and osteoporosis, as follows:

- Normal BMD: T score greater than –1
- Osteopenia: T score between –1 and –2.5
- Osteoporosis: T score less than –2.5.

In clinical practice, osteopenia and osteoporosis define the risk for having a fracture, as prospective studies have found that for each standard deviation below 0, the relative risk of fracture increases 1.5-fold to 3-fold.[13,14]

Markers of bone turnover may be increased in osteoporosis. Bone turnover is determined by bone formation and bone resorption, and both can be affected in osteoporosis. Osteoporosis is usually associated with a net increase in resorption over formation. **Table 2** outlines markers of bone turnover. Markers of resorption are markers of bone degradation and reflect the activity of osteoclasts, cells responsible for bone breakdown. Measurements of bone resorption are in the urine or serum. Markers of bone formation include procollagen markers, bone-specific alkaline phosphatase, and osteocalcin (or bone Gla protein). These markers assess the activity of osteoblasts, cells that form bone.

Two classes of osteoporosis exist: primary and secondary. Primary osteoporosis is the reduction in bone mass and occurrence of fractures in menopausal women or older men and women. Secondary osteoporosis occurs in the setting of a specific pathogenic mechanism.

AEDs are a recognized factor that can contribute to secondary osteoporosis.[15] Several studies have used DXA to measure BMD in adults receiving AEDs, finding significantly reduced BMD at the ribs and spine, femoral neck, and total hip.[16,17] A

TABLE 1
Risk factors for osteoporosis

- Increased age
- Race/ethnicity (white or Asian)
- Family history of osteoporosis
- Small frame
- Menopause
- Poor nutrition
- History of smoking
- Alcohol use
- History of an eating disorder
- Hyperthyroidism
- Hyperparathyroidism
- Liver disease
- Medication use: antiepileptic drugs, glucocorticoids, heparin

TABLE 2
Markers of bone turnover

Markers of bone formation
• Alkaline phosphatase (bone-specific alkaline phosphatase)
• Osteocalcin
• Carboxy-terminal propeptide of type I collagen
Markers of bone resorption
• Hydroxyproline
• N-telopeptide of collagen cross-links
• Cross-linked C-telopeptide of type I collagen

prospective study quantified ongoing bone loss in men receiving AEDs, with the highest rate of bone loss in the youngest men.[17] Use of AEDs is associated with reduced BMD in children as well; reports have described reduced axial, appendicular, and whole-body bone mass.[3–6]

In addition, markers of bone resorption are elevated in patients with epilepsy receiving long-term treatment with AEDs[18] and after recent initiation of therapy.[19,20] Markers of bone formation have also been assessed in patients receiving AEDs. Increases in alkaline phosphatase have been seen in both children and adults receiving AEDs, and in reports that measured the isoenzymes, the increase in total alkaline phosphatase was due mainly to the bone fraction.[21,22] High serum levels of osteocalcin are described with AED treatment, and significant elevations in the C-terminal extension peptide of type I procollagen have been reported in patients taking AEDs.[18–20]

Fracture

The most important clinical sequelae of bone disease are fractures. The consequences of fractures include hospitalization, loss of independence, and death. Both osteoporosis and osteomalacia increase the risk for fracture. In the United States, more than 1 million fractures occur as a result of osteoporosis each year.[23] Vertebral and hip fractures are associated with the most significant morbidity and mortality.[24] Identifying patients with epilepsy who are at risk for fracture is clearly important, particularly when seizure control is inadequate and the patient may be at especially high risk for sustaining a fracture during a seizure.

Increased fracture rates have been described in patients with epilepsy.[25–29] Although some studies have found this increased risk to be related to seizures, AED use may be independently associated with fracture risk. One study in postmenopausal women found that those treated with AEDs had double the rate of hip fracture that controls did.[26] A recent meta-analysis identified AED use as a risk factor with a high-strength association with fracture.[29]

BONE HEALTH IN ADULTS TREATED WITH AEDs

Early reports identified AED use as a risk factor contributing to abnormalities in bone mineral metabolism and BMD in institutionalized adults. Pathologic and serologic findings were often consistent with osteomalacia. It is difficult to clearly understand the effects of AEDs on bone in institutionalized patients, as many confounding factors may compromise these patients' bone health, including inadequate sunlight, nutrition, and exercise. More recent studies in ambulatory outpatients have not found definitive evidence of osteomalacia but have found biochemical abnormalities and reduced BMD.[16–18,30,31]

Reduced BMD has been found in adults receiving long-term AED therapy.[16–18,30,31] The sites of reduced BMD include the lumbar spine and hip. Some reports have identified treatment duration as being correlated with low BMD,[16,17] but this is not a consistent finding.[31,32] Bone loss over 1 year was prospectively identified in one study.[17]

Biochemical abnormalities in adults receiving AEDs include hypocalcemia, hypophosphatemia, reduced levels of active vitamin D metabolites, elevated parathyroid hormone (PTH) levels, and elevated markers of bone resorption and formation.[9,16,18,22,30,33–41] In contrast, one study of patients taking valproate found hypercalcemia.[30] The elevated serum calcium was postulated to reflect increased bone resorption. Although significant reductions in levels of vitamin D metabolites were reported in early studies, more recent reports have not found abnormalities of vitamin D.[16,18,31]

BONE HEALTH IN CHILDREN RECEIVING AEDs

Understanding the effects of AEDs in children is important, as it is during childhood and adolescence that peak BMD is obtained. The first studies describing bone abnormalities in children receiving AEDs found evidence of rickets.[42] Like the early adult studies, these were primarily in institutionalized children. Studies in ambulatory children have not found rickets[3–6] but have found other biochemical abnormalities and decreased BMD relative to

children not treated with AEDs.

Pediatric studies reveal findings consistent with both increased and decreased bone turnover. Elevated markers of bone formation and resorption have been reported.[19,20,43,44] As in recent adult studies, these elevations have been independent of reduced levels of vitamin D metabolites.[11,19,20] In addition, PTH levels are not elevated in some studies in which increased markers of bone turnover are seen.[19,20] Decreased markers of bone formation and resorption have also been described in several pediatric studies.[5,6]

Compared with children not receiving AEDs, children who receive AEDs may have reduced BMD.[3–6] The clinical significance of these findings is not clear, as there are no pediatric BMD reference databases. Further longitudinal studies are needed to understand the long-term effects of AEDs on developing bone.

WHICH AEDs ARE LINKED WITH BONE DISEASE?

AEDs that induce the cytochrome P450 enzyme system (phenobarbital, phenytoin, and carbamazepine) are most commonly associated with abnormalities in bone. Most of the published studies and evidence involve patients receiving these medications.[3,4,18–20,36,41]

Valproate is an inhibitor of the cytochrome P450 enzyme system, and emerging data suggest that it also negatively affects bone. Although early reports evaluating indexes of bone metabolism in patients taking valproate found no significant abnormalities, a recent study of 40 adults receiving long-term valproate monotherapy found increased serum concentrations of calcium, low levels of vitamin D metabolites, increased markers of bone resorption and formation, and decreased BMD.[30] A few small pediatric studies have evaluated bone mass in children taking valproate, finding both reduced BMD[4,5,45] and normal BMD.[46]

Multiple new AEDs have been approved over the past 10 years. Few studies have evaluated the effect of these newer medications on bone mineral metabolism and BMD.[5,31,32] One study in adults looked at the effect of some of the new drugs (gabapentin, lamotrigine, topiramate, and vigabatrin) on bone mineral metabolism and BMD, and found no significant abnormalities.[32] In children, short stature, low bone mass, and reduced bone formation were described in boys and girls treated with lamotrigine either alone or in combination with valproate.[5] Certainly, more studies are needed to determine whether any of these AEDs cause abnormalities in bone.

TABLE 3
Proposed mechanisms of AED-related bone disease

- Reduced levels of vitamin D metabolites secondary to induction of the cytochrome P450 enzyme system
- Reduced calcium absorption
- Impaired response to parathyroid hormone
- Hyperparathyroidism
- Impaired bone formation
- Impaired bone resorption
- Vitamin K deficiency
- Calcitonin deficiency

AED polytherapy has been shown to be associated with a higher risk of bone metabolism abnormalities than monotherapy.[16,35,41] No particular combination has emerged as more likely to cause bone disease, but in all of the studies identifying polytherapy as an independent risk factor, treatment included an enzyme-inducing AED as one of the agents.

MECHANISMS OF AED-ASSOCIATED BONE DISEASE

Several theories have been proposed to explain the link between AEDs and bone disease **(Table 3)**.[47] No single theory explains all the reported findings, and there may be multiple mechanisms.

Increased catabolism of vitamin D, resulting from hepatic induction of the cytochrome P450 enzyme system, is the principal mechanism reported. However, it does not explain the findings described in patients receiving other medications, such as valproate (an inhibitor of the cytochrome P450 enzyme system), or the recent evidence of increased bone turnover independent of vitamin D deficiency.

Levels of active vitamin D metabolites may be reduced in persons taking enzyme-inducing AEDs, suggesting that induction of hepatic cytochrome P450 enzymes partially explains the findings in bone.[33,37,41] The AEDs that induce cytochrome P450 enzymes may cause increased conversion of vitamin D to polar inactive metabolites in the liver microsomes, reducing levels of bioavailable vitamin D.[41,48] Reduced levels of biologically active vitamin D lead to decreased absorption of calcium in the gut, resulting in hypocalcemia and an increase in circulating PTH. PTH then increases the mobilization of bone calcium stores and subsequent bone turnover.

Impairment of calcium absorption is another postulated mechanism, as AEDs may interfere with

intestinal absorption of calcium. Impaired absorption would lead to hypocalcemia and feedback hypersecretion of PTH. Markedly decreased calcium absorption was found in rats treated with phenytoin but not in those treated with phenobarbital,[49] suggesting that impaired calcium absorption may play a role in patients treated with phenytoin.

Impaired bone resorption and formation may contribute to AED-associated bone disease. Significant bone resorption was found in neonatal mouse calvaria treated with phenytoin and one of its metabolites (5-[4-hydroxyphenyl]-5-phenylhydantoin).[50] Those calvarias treated with phenytoin and its metabolite had increased bone resorption, as demonstrated by significantly increased calcium in the medium, compared with controls. Proliferation of human osteoblast-like cells was inhibited by treatment with phenytoin and carbamazepine at concentrations equivalent to therapeutic doses for the treatment of epilepsy.[51] These results suggest that both bone resorption and formation may be affected by AEDs.

Inhibition of the cellular response to PTH also may have a role. Fetal rats treated with phenytoin or phenobarbital demonstrated an impaired response to PTH.[42] Inhibition of the bone resorptive response to PTH could lead to hypocalcemia, a frequent finding in patients taking AEDs.

Hyperparathyroidism, as demonstrated in clinical studies, is another possible mechanism. Both male patients with normal vitamin D status[18] and subjects who were vitamin D–repleted[11] have shown evidence of hyperparathyroidism. Hyperparathyroidism can primarily activate bone resorption and, through a coupling phenomenon, secondarily activate bone formation. Increased bone turnover in the setting of hyperparathyroidism is consistent with this theory. However, one study found increased bone turnover and normal levels of PTH.[19,20]

Poor vitamin K status may be an independent risk factor for postmenopausal bone loss, as suggested by accumulating evidence.[52] Vitamin K is a cofactor in the posttranslational carboxylation of several bone proteins, most markedly osteocalcin, a marker of bone formation. Rats treated with phenytoin had more bone loss over a 5-week period than did rats treated with phenytoin and vitamin K_2 (menatetrenone).[53] These findings suggest that insufficiency of vitamin K may contribute to bone loss secondary to phenytoin exposure.

Calcitonin deficiency is a final postulated mechanism, having been associated with AED treatment both in vitro and in vivo.[42,54] Calcitonin, a hormone produced by the thyroid gland, inhibits osteoclast-mediated bone resorption. A deficiency of calcitonin may therefore accelerate bone turnover.

TREATMENT OF AED-ASSOCIATED BONE DISEASE

Multiple therapies for bone disease are available, but vitamin D supplementation is the only modality studied specifically for the treatment of bone disease in persons taking AEDs.[55,56] Other approved therapies for bone loss include calcium supplementation, bisphosphonates, hormone replacement therapy (HRT), selective estrogen receptor modulators, and calcitonin. Although not approved by the US Food and Drug Administration (FDA), vitamin K supplementation is being studied as a potential treatment for bone loss.

High-dose vitamin D supplementation normalized 25-hydroxyvitamin D levels in one study of AED recipients[55] and improved biochemical indexes of bone mineral metabolism and BMD in another.[56] The dosages ranged from 400 to 4,000 IU/day. The recommended daily allowance is 400 to 800 IU.

Calcium supplementation can slow the rate of bone loss in elderly women not taking AEDs who have inadequate dietary calcium intake.[24] The recommended daily allowance varies according to age, sex, and reproductive status (1,000 mg to 1,500 mg). Because most people do not achieve adequate calcium intake from their diet, supplementation is usually necessary.

Bisphosphonates are potent inhibitors of bone resorption. Given the findings of increased bone resorption associated with AEDs, bisphosphonates may be an effective treatment for bone disease in patients receiving AEDs.[24] Alendronate and risedronate are two FDA-approved bisphosphonates. For treatment of osteoporosis, the dosage of alendronate is 10 mg/day or 70 mg/week; for prevention of osteoporosis, the dosage is 5 mg/day or 35 mg/week. Risedronate is given at a dosage of 5 mg/day.

Hormone replacement therapy. Data also support the efficacy of HRT in stopping bone loss in postmenopausal women.[24] However, HRT has multiple reported side effects, including increased risk for breast cancer, cardiovascular events, and venous thromboembolism,[57] and women with epilepsy should be aware that HRT may increase seizure activity.[58]

Selective estrogen receptor modulators. Raloxifene is an FDA-approved selective estrogen receptor modulator that acts as a partial agonist in bone.

In postmenopausal women not taking AEDs, raloxifene increases bone mass and reduces the risk of vertebral fracture by 40% to 50%.[59,60] Its side effects include an increased risk of deep venous thrombosis and an increase in hot flashes. Raloxifene is given at a dosage of 60 mg/day.

Calcitonin may be an effective treatment in persons with bone disease receiving AEDs, since studies have associated reduced calcitonin levels with AED use. In a study of postmenopausal women not taking AEDs, intranasal salmon calcitonin at a dosage of 200 IU/day reduced the rate of vertebral fracture but not of peripheral fracture.[61]

Vitamin K supplementation. Interventional studies have shown retardation of bone loss with increased vitamin K intake (via vitamin K_1 and vitamin K_2 supplement formulations) in postmenopausal women.[52,62] Similarly, growing rats treated with phenytoin and menatetrenone (vitamin K_2) had higher BMD than did animals treated with phenytoin alone.[53] Vitamin K_2 may therefore have a therapeutic benefit in AED-induced bone loss.

IMPLICATIONS AND RECOMMENDATIONS

Few physicians are aware of the long-term effects of AEDs on bone. A recent survey of US board-certified or board-eligible pediatric and adult neurologists highlights this lack of awareness.[63] Although the length of time needed for AEDs to affect bone is not known, several prospective studies have found changes in markers of both bone turnover and BMD after 1 year of treatment.[17,19,20]

We recommend evaluating bone by quantifying BMD as measured by DXA after 5 years of AED treatment and before AED treatment in postmenopausal women. We recommend proceeding as follows:

- If the T score is greater than –1, encourage calcium and vitamin D supplementation and weight-bearing exercise.
- If the T score is between –1 and –2, also encourage supplementation and weight-bearing exercise, and repeat the study in 1 to 2 years.
- If the T score is less than –2, further intervention may be required and the treating neurologist may wish to refer the patient to an internist or an endocrinologist.

Vitamin D supplementation in high doses has been shown to improve biochemical indexes of bone mineral metabolism and BMD in patients taking AEDs. In addition, other therapeutic options are available for the treatment of bone loss and may be effective for AED-associated bone disease.

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Recommendations for the care of women with epilepsy

PATRICIA E. PENOVICH, MD; KAREN E. ECK, MS, FNP; AND VASILIKI V. ECONOMOU, MD

ABSTRACT

The clinical care of women with epilepsy entails special considerations over the life span. Endogenous depression is more prevalent in persons with epilepsy than in the general population and may be unrecognized. Seizure frequency may be influenced by hormonal fluctuations, as reflected by catamenial patterns in up to 25% of women and by changes at menopause. Fertility is lower in women with epilepsy. These women should be evaluated for anovulatory cycles and particularly for polycystic ovary syndrome, with its attendant health risks. It is important to provide folate supplementation during the childbearing years and to evaluate bone health throughout life, providing calcium and vitamin D supplementation when indicated. Particular consideration is indicated before conception and during pregnancy to minimize both potential teratogenicity secondary to antiepileptic drugs (AEDs) and the risks that seizures pose to fetus and mother. At delivery, vitamin K is indicated. Some infants may need to be monitored for AED withdrawal, while others may require a perinatal team if malformations are identified in utero. Breast-feeding is possible, with sedation rarely being a problem. Recognition, evaluation, and management of these issues will minimize the negative impact of epilepsy and improve lifelong quality of life.

From the Minnesota Epilepsy Group, P.A., St. Paul, Minn. (P.E.P.); the Columbia University Neurological Institute, New York, N.Y. (K.E.E.); and Neurological and Epilepsy Consultants, Hayward, Calif. (V.V.E.).

Address: Patricia E. Penovich, MD, Minnesota Epilepsy Group, P.A., 310 Smith Avenue N., Suite 300, St. Paul, MN 55102–2383; e-mail: pep@mnepilepsy.net.

The practical care of women with epilepsy should incorporate the science discussed earlier in this supplement with the art of caring for patients. Special considerations regarding treatment decisions and alterations occur at various stages of a woman's life and reproductive cycle. Some treatment decisions have long-term or lifelong consequences beyond the immediate therapeutic period **(Table 1)**. Building on the previous detailed reviews in this supplement, this article offers general recommendations on the management of women with epilepsy throughout the life span.

PSYCHOLOGICAL HEALTH

Depression has a lifetime prevalence of 40% to 60% in persons with epilepsy,[1] making it the most common psychiatric disorder in this population. Depression in persons with epilepsy appears to be primarily endogenous. Compared with their nonepileptic counterparts, epileptic persons with depression tend to exhibit fewer neurotic traits and more psychotic symptoms, such as delusions, paranoia, and persecutory auditory hallucinations.[2] Behavioral effects, including depression, anxiety, aggression, and psychosis, can be a consequence of:

- Seizure-related factors (eg, complex partial seizures of temporal lobe origin)
- Psychosocial factors, such as the stigma of epilepsy, decreased sexuality, fear of teratogenesis, and restriction of activities
- Adverse effects of antiepileptic drugs (AEDs)
- Other contributing risk factors, which may include genetic, endocrinologic, metabolic, or environmental factors.

The psychological status of women with epilepsy should be evaluated throughout their lives so that early treatment may be initiated and a psychological disorder will not further impair function and quality

TABLE 1
Long-term consequences of antiepileptic drugs

Consequences	Drugs implicated
Cosmetic consequences	
• Gingival hyperplasia	Phenytoin
• Hirsutism	Phenytoin
• Hair loss	Valproate
Connective tissue changes	Phenobarbital, phenytoin
Reduced bone density	Carbamazepine,* phenobarbital, phenytoin, primidone, valproate*
Weight gain	Carbamazepine, gabapentin, valproate

*Ongoing trials are evaluating this trend.

of life. Psychiatric comorbidity can be efficiently screened for with tools such as the Beck Depression Inventory, Profile of Mood States, and Cornell Dysthymia Scale. The many components of quality of life may be evaluated and measured by interview and by a shortened quality-of-life screening tool such as the 31-item Quality of Life in Epilepsy Inventory. Treatment approaches may include evaluation of AED choice; use of antidepressant, antianxiety, or other psychotropic medications; and referral for counseling or psychotherapy when appropriate.

PREPREGNANCY ISSUES

Assessment for catamenial epilepsy. During premenarche and menarche, a differentiation of seizure pattern associated with the menstrual cycle may become apparent for nearly 25% of women with epilepsy. Catamenial epilepsy is defined as a doubling of the baseline seizure frequency during hormonal changes in the menstrual cycle. Specific catamenial seizure patterns have been identified,[3] with an increase in seizure frequency at the following times:

- During perimenstrual days (pattern C1)
- At ovulation (pattern C2)
- In the setting of anovulation when the luteal phase is inadequate (pattern C3).

Every woman with epilepsy should be objectively assessed for a catamenial pattern through the use of a monthly calendar recording both seizure occurrence and menstrual flow. Although there is no well-controlled, double-blind trial of any therapeutic modality to improve seizure control for women with catamenial epilepsy, several modalities have been reported to be useful for women with C1 and C2 patterns **(Table 2)**.[4–7]

TABLE 2
Management strategies for women with C1 or C2 patterns of catamenial epilepsy[6,7]*

1. Check total and free antiepileptic drug (AED) levels before and at the time of breakthrough. If they are decreased, give a bolus dose of the AED at the C1 or C2 period.
2. Give acetazolamide up to 1 g/day in divided doses as a burst at C1 or C2 period, replacing K^+ as necessary. (Panel† recommends discontinuing acetazolamide between menses to prevent rebound effects.)
3. Administer a benzodiazepine burst at C1 or C2 period[4,5]
4. Give oral contraceptives
   a. Depot medroxyprogesterone acetate (Depo-Provera), combined oral pill
   b. Progesterone lozenges[6,7]
      • Days 14–25: 100–200 mg three times daily
      • Days 26–27: 50–100 mg three times daily
      • Day 28: 50 mg three times daily
   c. Natural progesterone (Prometrium) 100–400 mg daily

* See also the article by Foldvary-Schaefer and colleagues in this supplement (pages S11–S18).

† At an experts roundtable meeting, "Epilepsy in Women: The Biological Basis for the Female Experience," New York, N.Y.; February 28, 2003.

Infertility and altered hormone cycling. Fertility is two to three times lower in women with epilepsy than in the general population, and these women are only one third as likely as their female siblings to become pregnant (see the article by Morrell and Montouris in this supplement). The causes may be multifactorial, as discussed by others[8–11] (see also the article by Foldvary-Schaefer and colleagues in this supplement).

The monthly diary described above may be useful in defining anovulatory cycles. Ovulation is normally characterized by a midluteal progesterone level of more than 3 to 5 ng/mL and/or by a morning body temperature elevation of more than 0.7°F in midcycle. Anovulatory cycles typically are irregular. Cycles that are shorter than 23 days or longer than 35 days, missed menses, or midcycle bleeding can be indicative of anovulation. Coordinating care with an obstetrician-gynecologist or endocrinologist is indicated if menstrual irregularity is noted.

Clinicians should be sensitive to any evidence of altered hormone cycling that suggests polycystic

TABLE 3
Polycystic ovaries vs polycystic ovary syndrome

Polycystic ovaries
8 to 10 cysts that are 4 to 10 mm in diameter in a peripheral distribution around the ovary

Polycystic ovary syndrome
- No requirement for presence of ovarian cysts
- Menstrual dysfunction:
  —Fewer than 6 to 9 menses per year
  —Cycles of < 23 days' or > 35 days' duration
- Hyperandrogenism: increased testosterone, hirsutism, acne, androgenic alopecia
- Obesity in truncal distribution
- Impaired glucose tolerance with insulin resistance
- Abnormal lipid profile

ovaries or polycystic ovary syndrome (PCOS) **(Table 3)**.[12] Women presenting with the PCOS phenotype **(Table 3)** should undergo further evaluation to minimize the long-term health risks through hormone therapy, diet, and exercise. Direct questioning about hair patterns is crucial, as many women use hair-removal and hair-growth products for cosmetic reasons and the androgenic alopecia or hirsutism that is often characteristic of PCOS may not be evident during the interview.

Folic acid supplementation. From preadolescence to menopause, women with epilepsy should be advised to take supplemental folic acid. Although no double-blind controlled trial has been done to document definitively a cause-and-effect relation between maternal folic acid deficiency and neural tube defects, the incidence of neural tube defects in the general US population has declined since mandatory folic acid fortification of enriched grain products went into effect.[13] For women with epilepsy taking drugs other than valproate, the dosage of supplemental folic acid is not clearly determined, but 2 to 4 mg/day is recommended. For women with epilepsy taking valproate, 4 mg/day is recommended.

Folic acid supplementation should begin at least 1 month before a planned conception. However, more than half of all pregnancies are unplanned, and women often do not realize that they are pregnant until the 6th week of pregnancy. Therefore, primary care physicians and/or neurologists should provide this critical preventive measure to all women with epilepsy who are of childbearing age (see the article by Yerby and colleagues in this supplement).

TABLE 4
Effect of antiepileptic drugs (AEDs) on hormonal contraceptive agents[14]

Enzyme-inducing AEDs	Enzyme-inhibiting AEDs	AEDs with no effect
Barbiturates	Felbamate	Ethosuximide
Carbamazepine	Valproate	Gabapentin
Oxcarbazepine		Lamotrigine
Phenytoin		Levetiracetam
Topiramate >200 mg/day		Tiagabine
		Zonisamide

Contraceptive efficacy. Birth control is an important part of the social and medical concerns of our patients with epilepsy. The efficacy of nonhormonal methods of contraception is not affected by AEDs or by epilepsy itself. Hormonal methods of contraception may be affected by AEDs, depending on the metabolic pathways involved in the breakdown of the birth control hormone (combined oral pill or progestin-only formulations given by injection or subcutaneous implant) **(Table 4)**. The AEDs that induce the hepatic cytochrome P450 system have been shown to induce the metabolism of the hormonal agents and may thereby increase the contraceptive failure rate of these agents.[14] It has been typically recommended that barrier methods of contraception be used concomitantly or that a higher estrogenic content (at least 50 µg of estradiol per pill) be prescribed. There is no definitive prospective study that clarifies this issue. The perceived increased overall health risk of formulations with a higher estrogen content may be "false" in that the estrogen is metabolized more quickly to a lower effective dose, thus avoiding the potential complications of high-dose estrogen therapy.

PREGNANCY

Pregnant women with epilepsy may be at greater risk for complications, difficult labor, and adverse outcomes than the general population, as discussed previously in this supplement. Prenatal counseling by the neurologist and the primary care physician in conjunction with the obstetrician-gynecologist can reassure the patient that 90% of women with epilepsy have successful pregnancies with healthy outcomes.

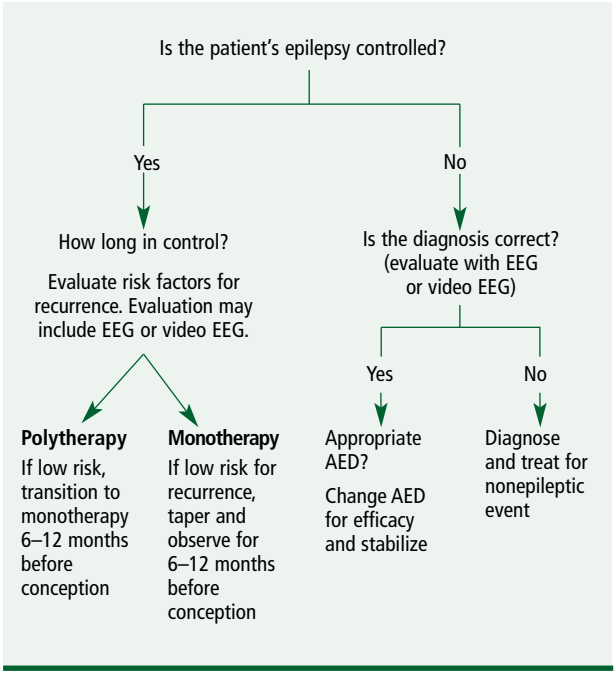

FIGURE 1. Prepregnancy evaluation for the use of antiepileptic drugs (AEDs).

Pregnancy is not the time to make a major medication change or discontinue a medication. For women with epilepsy who have plans of childbearing, recommendations for AED use should be addressed and any changes made in anticipation of the pregnancy. The primary care physician may wish to consult with the neurologist in this complex decision tree **(Figure 1)**. AED selection is a complicated decision based on seizure classification, epilepsy syndrome, and known or estimated teratogenic risk of the AED **(Table 5)**.[15,16] Other factors that may affect the outcome of the patient's pregnancy should be evaluated as well. These include maternal age, other medications that the woman is taking (including over-the-counter and herbal medications), smoking, alcohol use, nutritional habits, exercise, social support systems, and access to health care.

Seizure control is the goal. The primary goal is to maintain good seizure control throughout pregnancy, particularly for tonic-clonic seizures, which can injure the mother and the fetus via hypoxia, acidosis, and blunt trauma. These factors place the fetus at greater risk for developmental problems, stillbirth, or spontaneous abortion, and they outweigh the risk of AED exposure. Medication compliance should be stressed, and free (when appropriate and available) and total drug levels should be monitored monthly and maintained at levels that provided optimum control for the patient before pregnancy. If a seizure occurs, is self-limited, and is typical for the patient, an evaluation of provocative factors (sleep deprivation, illness, drug level) may suffice. If the seizure is atypical for the patient (eg, a new seizure type), prolonged, or secondarily generalized, a reevaluation may be indicated that includes imaging. In the event of a generalized seizure, preeclampsia must be ruled out through serial blood pressure readings and urinalysis for glucose and ketones.

Seizures during labor. If a seizure occurs during labor or delivery, eclampsia must be ruled out as causative. Only 1% to 2% of women with epilepsy have a seizure during labor.[17] AEDs should be continued throughout labor; however, absorption may be delayed and intravenous administration may be called for if it is feasible. If a parenteral form of the patient's AED is not available, a buccal or intravenous benzodiazepine, intravenous fosphenytoin, or intravenous valproate may be used emergently. Emergency intravenous therapy with a benzodiazepine, fosphenytoin, or valproate, according to standard protocols, may be used for a prolonged seizure or status epilepticus. Fetal bradycardia and increased uterine contractility have been demonstrated during a single partial seizure with secondary generalization.[18] Lorazepam used for seizures during labor and delivery has been anecdotally reported to reduce fetal heart rate, although this decrease may have been due to the seizure itself.[17]

Monitoring fetal status. The patient's neurologist, primary care physician, and obstetrician should be in consultation throughout the pregnancy. The fetal status should be monitored regularly. Most obstetricians perform early ultrasonography at 12 weeks and measure maternal serum alpha fetoprotein at 16 weeks. High-level anatomic ultrasonography should be performed at 16 to 18 weeks to detect neural tube defects as well as skeletal, cardiac, and facial abnormalities. Repeated high-definition ultrasonography may be necessary at or before 22 weeks to fully evaluate the fetus for facial and cardiac deformities. Despite advances in diagnostic resolution, parents must be counseled that no prenatal testing is 100% accurate for detecting fetal anomalies. If there are specific indications, such as metabolic or chromosomal concerns, amniocentesis or other special studies may be performed. Subsequent ultrasonographic examinations for fetal growth and condition may be performed as the obstetrician deems necessary.

TABLE 5
Teratogenic profile of antiepileptic drugs[15,16]

Antiepileptic drug	Use (seizure types)	Major malformations	FDA pregnancy category	Panel opinion*
Carbamazepine	Partial, tonic-clonic	Facial, spina bifida, cardiac	D	Caution
Ethosuximide	Absence	No specific	C	Safe
Felbamate	Partial, tonic-clonic, absence, myoclonic	Unknown	C	Unknown
Gabapentin	Partial, tonic-clonic	Unknown	C	Unknown†
Lamotrigine	Partial, tonic-clonic, absence, myoclonic, atonic	Unknown	C	Safe?‡
Levetiracetam	Partial, tonic-clonic, ?absence, myoclonic	Unknown	C	Unknown
Oxcarbazepine	Partial, tonic-clonic	Unknown	C	Unknown†
Phenobarbital	Partial, tonic-clonic, ?myoclonic	Cleft palate, heart	D	Caution
Phenytoin	Partial, tonic-clonic	Cleft palate, heart	D	Caution
Tiagabine	Partial, tonic-clonic	Unknown	C	Unknown
Topiramate	Partial, tonic-clonic, myoclonic, atonic	Unknown	C	Unknown†
Valproate	Partial, tonic-clonic, absence, myoclonic, atonic	Spina bifida	D	Caution
Zonisamide	Partial, tonic-clonic, myoclonic, ?absence, atonic	Unknown	C	Unknown†

* At an experts roundtable meeting, "Epilepsy in Women: The Biological Basis for the Female Experience," New York, N.Y.; February 28, 2003. Panel opinion is based on clinical experience and does not imply results from a scientific controlled study, which is unavailable at this time.

† Sufficient data not yet available. See discussion by Yerby and colleagues on page S33 of this supplement.

‡ See discussion on pages S54–S55 of this article.

Vitamin K supplementation. In infants whose mothers take enzyme-inducing AEDs, a hemorrhagic syndrome resulting from a deficiency of the vitamin K–dependent clotting factors II, VII, IX, and X may occur with bleeding internally, intracranially, and in subcutaneous tissues[17] (see also the article by Yerby and colleagues in this supplement). Despite normal maternal coagulation measures, the infant cannot absorb orally administered vitamin K at birth because of the sterile environment in the gut. The fetus relies on vitamin K transported across the placenta to protect against hemorrhage associated with labor and delivery. Giving the mother supplemental vitamin K, 10 mg/day, during the last month of pregnancy, beginning at week 36, permits adequate transplacental supplementation for the infant. Although this syndrome is not known to occur with use of the newer, non-enzyme-inducing AEDs, it is prudent to give every woman with epilepsy supplemental vitamin K for the final 4 weeks of pregnancy. Intravenous vitamin K can be given to the neonate at birth if the mother has not received vitamin K. The infant must receive fresh frozen plasma intravenously in the event of any hemorrhage, which can have a catastrophic outcome.

AED withdrawal in the infant. The infant has been exposed to the mother's AEDs throughout the pregnancy. Fetal metabolism of AEDs is limited. After birth, the infant's AED level will decrease according to the infant's serum level and metabolism (neonatal serum AED levels are comparable to the maternal free or unbound level). There may be a withdrawal syndrome, with lethargy, irritability, and feeding difficulties, particularly when the infant has been exposed to phenobarbital, phenytoin, benzodiazepines, or narcotic anesthetics. A severe withdrawal syndrome may require treatment with sedation or intensive care nursery observation.

Breast-feeding and postnatal AED kinetics. Breast-feeding is recommended for infants of women with epilepsy. AEDs are excreted in breast milk in inverse proportion to their protein binding **(Table 6)**. Sedation beyond that normally seen with feeding is rare except with phenobarbital. A suggestion to feed

TABLE 6
Pharmacokinetic profile of antiepileptic drugs*

Antiepileptic drug	Half-life (hr)	Protein binding (%)	Serum level (μg/mL)	Free level available?
Carbamazepine	5–12	75	6–12	Yes†
Ethosuximide	25–60	0	50–100	
Felbamate	13–30	25	30–100	
Gabapentin	5–7	0	4–16	
Lamotrigine	15–29–60‡	55	4–20	
Levetiracetam	7–8	0	< 40?	
Oxcarbazepine	8–10§	40	10–35	
Phenobarbital	70–90	45–60	15–40	
Phenytoin	7–42	90	10–20	Yes
Tiagabine	5–9	96	—¶	
Topiramate	20–24	10	2–25	
Valproate	8–12	85–95	50–150	Yes
Zonisamide	60	40–60	10–40	

* Data compiled and adapted from references 15 and 16.
† Measure carbamazepine epoxide also.
‡ Polytherapy vs monotherapy vs with valproate.
§ Used as monotherapy.
¶ Not clinically meaningful.

by breast for half of each feeding and then feed by formula has been useful; this still supplies the infant with the maternal immunoglobulins and preserves the important mother-infant bonding experience.

For most AEDs, the pharmacokinetics in the mother will return to prepregnancy levels within 10 to 14 days after delivery. This will require a downward titration of AEDs if they were increased during the pregnancy. AED levels should be measured 1 and 3 days and 2 weeks postpartum. Toxicity will result if doses are not reduced. Dosages may need to be decreased because of the emergence of side effects and toxic symptoms, especially with the new-generation AEDs, for which determination of drug levels sometimes requires up to a week of laboratory processing. Lamotrigine has recently been observed, on the basis of clinical symptomatology, to return to prepregnancy kinetics within the first 3 postpartum days (oral communication from G.D. Montouris, February 28, 2003).

TABLE 7
Tips for new mothers who have epilepsy

- Routines are disrupted. That's normal, but *take your medication*.
- Nap when the baby naps.
- Have someone else bring the baby to you for night feedings if breast-feeding; if bottle-feeding, have someone else do the night feedings to minimize sleep deprivation.
- The baby should not sleep in bed with you, in case of seizure.
- Change diapers with the baby in a safe position, eg, strapped onto a sturdy changing table, on a wide bed, in the crib, or on the floor. Have diaper stations on each floor of the house.
- Bathe the baby only when someone else is there to help.
- Strap the baby in a stroller when transporting, to prevent drop injuries or falling on top of the baby.

Advice for new mothers. Some practical counseling for the epileptic woman who will soon have a newborn infant is important. Like any new mother, she will be stressed and sleep-deprived. These factors may predispose her to seizure exacerbation. Caring for the infant at this time may be of even more concern. Some practical guidance is outlined in **Table 7**.

TERATOGENICITY AND DEVELOPMENTAL EFFECTS

To date, there is no prospective, controlled, comparative trial that indicates which AED is safest during pregnancy. Overall, infants of women with epilepsy have a reported rate of congenital major malformation between 4% and 6%, about twice that of the general population. This increased risk is especially high for women who require AED polytherapy, have refractory epilepsy, or require high serum drug levels for seizure control. This suggests that optimal maternal seizure control, monotherapy, and avoiding high peak serum levels (ie, dividing the total daily dose into multiple smaller doses with lower postabsorptive peaks) would be safer for infants. Reports from the North American Pregnancy Registry suggest a higher risk of congenital abnormality with phenobarbital and valproate use[17] (see also the article by Yerby and colleagues in this supplement).

The new AEDs marketed since 1992 have not had enough reported outcomes to yield sufficient

TABLE 8
Recommendations for the use of antiepileptic drugs (AEDs) in pregnancy

- Use monotherapy with an AED chosen for the syndrome or seizure type.
- Use the lowest dose or drug level needed for optimal control.
- Avoid high peak levels by spreading out the total daily dose into multiple smaller doses.
- There is some evidence that extended-release preparations may be safer in pregancy.[23]
- Take total and free levels (if available) of the drug monthly at trough times.

TABLE 9
Risk factors for early osteopenia and secondary osteoporosis[24]

- Inadequate nutrition, especially deficient calcium intake
- Weight < 127 lb
- Inadequate weight-bearing exercise
- Neuromuscular impairment
- Institutionalized or wheelchair/bed-bound status
- Treatment with phenobarbital, primidone, phenytoin, carbamazepine*, or valproate*
- Smoking
- Excessive alcohol intake
- Prolonged steroid therapy
- Menopause
- Fair complexion, or Asian or northern European ancestry

* Studies are being completed.

data for safety in pregnancy. However, the prospective Lamotrigine Pregnancy Registry has registered 337 first-trimester exposures to lamotrigine monotherapy. There were 293 live births, with a 2.4% incidence of major malformation among the live births. In order to detect a twofold to threefold increase in the incidence of major birth defects over the general population, 300 monotherapy exposures are needed. The registry reports 212 births with polytherapy use and 12 major defects (5.6%), with the highest incidence of defects (7 of 41 live births) being among infants exposed to valproate as part of the polytherapy.[19] This suggests that polytherapy with lamotrigine and valproate should be avoided, if possible. While other newer AEDs have fewer reported pregnancy exposures, data on the use of some other newer AEDs in pregnancy are starting to accumulate, as detailed in the article by Yerby and colleagues in this supplement.

The effect of AEDs on infant neurodevelopment has not been well studied, as discussed by Meador and Zupanc in this supplement. Most children of women with epilepsy are born normal. The incidence and magnitude of AED effects on infant cognitive development in humans are not clearly known.[20]

General recommendations for AED use in pregnancy are outlined in **Table 8**.

EPILEPSY IN MENOPAUSE

Seizure frequency in menopause is not predictable for any one individual.[21] Although most women report no change and some may experience a reduction in seizure frequency, the frequency may worsen in 30% to 40%. As metabolism changes with age, attention must be given to hepatic and renal function and to medications added by other physicians that may alter the levels of AEDs or affect the seizure threshold. Hormone replacement therapy can be given to most women with epilepsy without a change in their epilepsy. For all women with epilepsy, attention should be given to bone health throughout the life span, as addressed below.

BONE HEALTH

Maintaining bone health is a concern throughout life for all women. Up to 10% of women with epilepsy experience premature bone demineralization, particularly if they take AEDs that induce the hepatic cytochrome P450 enzyme system. Our understanding of this system continues to evolve, as does the complex nature of the interactions[22] (see also the article by Pack and colleagues in this supplement).

Women with epilepsy and their physicians should be alert to risk factors that may make them more susceptible to secondary osteoporosis even at an early age **(Table 9)**. Screening with dual-energy x-ray absorptiometry (DXA) scans of the spine or hip should be obtained in at-risk women and be repeated every 2 years or if a fracture occurs. Women should be counseled about adequate calcium intake, and a dietary history should be obtained. Supplementation with calcium and vitamin D

TABLE 10
Daily calcium requirements for women*†

Age or other relevant factors	Daily mg calcium‡ (in divided doses)
Adolescent	1,300
20–50 years	1,000
Lactating mother	1,200–1,500
Premenopausal or menopausal not on HRT	1,200–1,500
Premenopausal or menopausal on HRT	1,000
>65 years	1,200–1,500

* Data adapted from reference 24.
† Daily intake of 400 IU vitamin D is also required.
‡ 8 oz of milk provides 300 mg calcium.
HRT = hormone replacement therapy.

TABLE 11
Medical causes of secondary osteoporosis[24]

Medications	Endocrine disorders	Other diseases
• Glucocorticoids • Antiepileptic drugs • Thyroxine • GnRH agonists • Immuno-suppressants • Heparin	• Hyperparathyroidism • Hyperthyroidism • Cushing's syndrome • Diabetes mellitus type 1	• Muliple myeloma • Chronic renal failure • Mastocytosis

GnRH = gonadotropin-releasing hormone

TABLE 12
Treatments for osteoporosis*

Calcium plus vitamin D
Bisphosphonates: alendronate and risedronate
Estrogen
Selective estrogen receptor modulators: raloxifene
Calcitonin

* Treatment beyond calcium and vitamin D supplementation is not usually given unless there are vertebral fractures or dual energy x-ray absorptiometry T scores less than –2.5.

should be prescribed to meet daily needs, and the daily requirement should be taken as two or three divided doses to ensure optimal absorption and utilization **(Table 10)**. Prevention, early detection, and aggressive treatment are important for preventing secondary complications that can reduce both quality of life and the overall life span. Women who have abnormal DXA scans should be evaluated for other diseases **(Table 11)** by their primary care physician or endocrinologist, as this may warrant additional treatment **(Table 12)**.

CONCLUSIONS

Care of the woman with epilepsy should involve a comprehensive assessment of overall health to identify any impairment of physiologic function that may be an effect of the epilepsy itself or its treatment. Thorough patient interviews are helpful in identifying symptoms that may warrant further investigation. These interviews should also include life goals and family planning. Patients should be counseled about appropriate birth control and planned conception, high-risk obstetric care, and risks to mother and child relative to seizure type and medications.

Throughout the life span, the woman with epilepsy is at risk for altered endocrine functioning that may present as irregular hormone cycling, infertility, decreased bone density, or altered glucose metabolism. Research is under way to identify the pathophysiology of the clinical manifestations observed in many women with epilepsy. Unfortunately, as with many disease processes, there is a cascade of negative effects that may occur as a result of the initial disease-related disturbance. Thorough evaluation, early identification, and appropriate treatment throughout a woman's life span are imperative to minimize the negative impact on overall health and to optimize quality of life.

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