Hormones and seizures*

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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.

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*This article has been excerpted and adapted, with permission, from two previous review articles by these authors:

- Foldvary-Schaefer N, Falcone T. Catamenial epilepsy: pathophysiology, diagnosis, and management. *Neurology* 2003; 61(6 suppl 2):S2–S15.
- Harden CL. Menopause and bone density issues for women with epilepsy. *Neurology* 2003; 61(6 suppl 2):S16–S22.

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

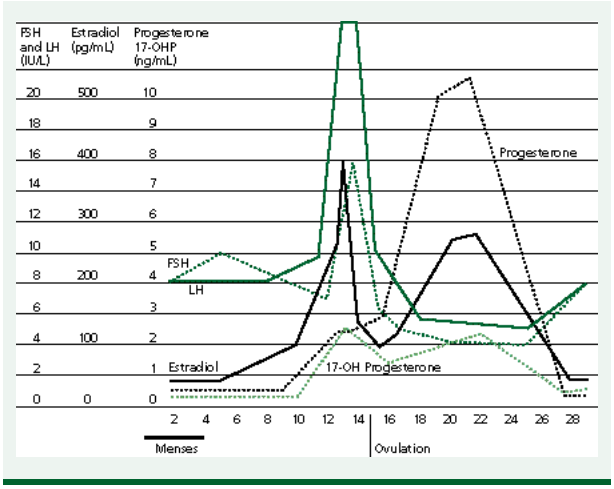

FIGURE 1. Hormone levels during the normal menstrual cycle (FSH = follicle-stimulating hormone; LH = luteinizing hormone). Reprinted, with permission, from reference 4.

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]

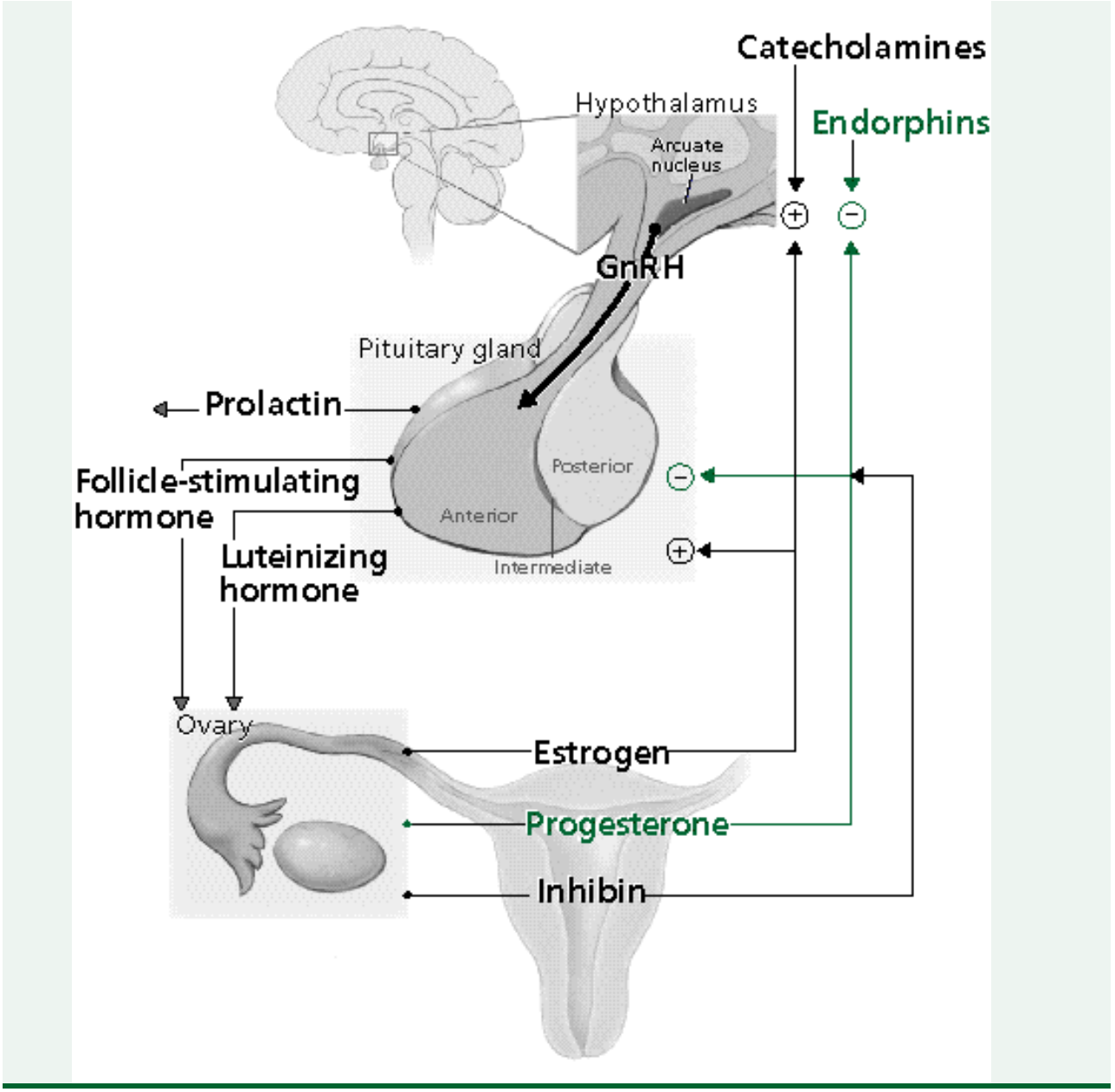

FIGURE 2. The hypothalamic-pituitary-ovarian axis regulates interactions between neurohormones, gonadotropin-releasing hormone (GnRH),pituitary gonadotropins, and the gonadal steroids through a feedback-loop mechanism.See text for detailed explanation.Reprinted, with permission,from reference 5.

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

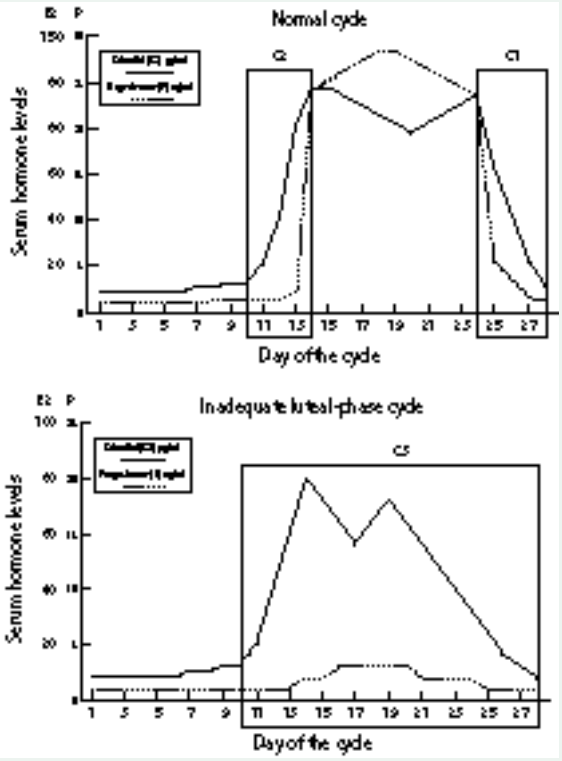

FIGURE 3. Three patterns of catamenial epilepsy. The perimenstrual pattern (C1) is defined as a greater average daily seizure frequency during the menstrual phase (day –3 to +3) compared with the midfollicular (day 4 to 9) and midluteal (day –12 to –4) phases in ovulatory cycles. The periovulatory pattern (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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