

# Current Concepts of Catamenial Epilepsy

## Katamenial Epilepside Güncel Kavramlar

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### Summary

Seizures do not occur randomly. They tend to cluster in the majority of men and women with epilepsy. Seizure clusters, in turn, often show a temporal periodicity. When the periodicity of seizure exacerbation aligns itself with that of the menstrual cycle, it is designated catamenial epilepsy. The neuroactive properties of reproductive steroids and the cyclic variation in their serum concentrations are important pathophysiologic factors. There is evidence for the existence of at least 3 patterns of catamenial seizure exacerbation: perimenstrual and periovulatory in ovulatory cycles, and entire luteal phase in anovulatory cycles. A rational mathematical basis for this categorization of catamenial epilepsy has been developed. It identifies over one-third of women as having catamenial epilepsy. If seizures show hormonal sensitivity in their occurrence, they may also respond to hormonal treatment. A randomized, double-blind, placebo-controlled National Institute of Health (NIH) progesterone trial found that cyclic progesterone supplement is no better than placebo overall, but did reduce seizure frequency significantly in the subset of women with perimenstrual seizure exacerbation. There have also been successful open-label trials using depomedroxyprogesterone and depot gonadotropin-releasing hormone analogues.

Key words: Catamenial; epilepsy; hormones; progesterone; reproductive; seizures.

### Özet

Nöbetler gelişigüzel olarak oluşmazlar. Epilepsili kadın ve erkeklerin çoğunluğunda nöbetler kümelenme eğilimindedirler. Nöbet kümelenmeleri sıralı olarak, sıklıkla zamansal bir periyodite gösterirler. Nöbet alevlenme periyoditesi kendisini menstrual döngünün periyoditesi ile eşzamalı duruma getirdiği zaman katamenial epilepsiden bahsedilir. Üreme steroidlerinin nöroaktif özellikleri ve serum konsantrasyonlarındaki siklik değişimleri önemli patofizyolojik faktörlerdir. Katamenial nöbet alevlenmelerinin en az üç paterni olduğuna dair kanıtlar vardır: ovuluar döngülerde perimenstrual ve periovuluar, anovuluar döngülerde tüm luteal faz boyunca. Katamenial epilepsinin bu sınıflaması için akla uygun bir matematiksel temel geliştirilmiştir. Kadınların 1/3'ünden fazlasının katamenial epilepsili olduğu saptanmıştır. Eğer nöbetler ortaya çıkışlarında hormonal duyarlılık gösterirlerse, hormonal tedaviye de yanıt verebilirler. Randomize, çift kör, placebo kontrollü NIH Progesteron Çalışması, perimenstrual nöbet alevlenmeleri olan kadınların bir alt gurubunda siklik progesterone desteğinin bütünü ile plasebodan üstün olmadığını fakat nöbet sıklığını anlamlı olarak azalttığını bulmuştur. Depo medroksiprogesteron ve depo gonadotropin releasing hormon analoglarının kullanıldığı başarılı açık etiketli çalışmalar da vardır.

Anahtar sözcükler: Aybaşı; epilepsi; hormonlar; progesteron; üreme; nöbet.

### Definition, Patterns and Prevalence

Seizures do not occur randomly in the majority of men and women with epilepsy.<sup>[1,2]</sup> They tend to cluster in over 50% of cases.<sup>[1,2]</sup> Seizure clusters, in turn, may occur with temporal rhythmicity in a significant proportion of men (29%) and women (35%) with epilepsy.<sup>[3]</sup> When periodicity of seizure exacerbation aligns with the menstrual cycle, it is com-

monly known as catamenial epilepsy.<sup>[4]</sup> There is compelling evidence that seizure numbers and cycle days with seizure occurrence vary across the menstrual cycle. Specifically, there is an approximately 2-fold difference between highest (first day of menstrual flow, Day 1) and lowest (mid-luteal phase, Day -8) values for both seizure frequency and days with occurrence.<sup>[2]</sup> The demonstration of variation in seizure frequency and cycle days with seizure occurrence across



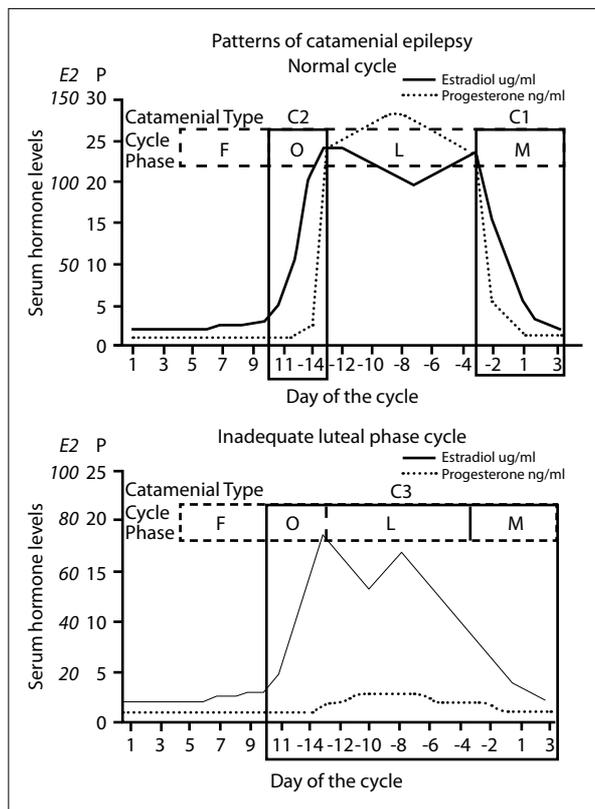
the menstrual cycle, as well as identification of specific days that have substantially higher or lower frequencies than other days, support existence of catamenial epilepsy.<sup>[2]</sup> Catamenial epilepsy is likely attributable to 1) neuroactive properties of reproductive steroid hormones, 2) cyclic variation in their serum levels, and 3) susceptibility of epileptic foci to effects of neuroactive steroids.<sup>[4]</sup>

Physiological variations of endocrine secretion during menstrual cycle influence the occurrence of seizures (Figure 1). In ovulatory cycles, seizure frequency shows a statistically significant positive correlation with serum estradiol/progesterone ratio.<sup>[5]</sup> This ratio is highest during the days prior to ovulation and menstruation, and is lowest during mid-luteal phase.<sup>[5]</sup> Premenstrual exacerbation of seizures has been attributed to the rapid withdrawal of the anti-seizure effects of

progesterone.<sup>[4,5]</sup> Mid-cycle exacerbations may be due to the pre-ovulatory surge of estrogen, unaccompanied by any rise in progesterone until ovulation occurs.<sup>[4-6]</sup> Seizures are least common during mid-luteal phase when progesterone levels are highest,<sup>[4-6]</sup> except in anovulatory cycles, during which the mid-cycle surge in estrogen still occurs -- albeit not as high as in ovulatory cycles -- but is unaccompanied by any substantial increase in progesterone levels.<sup>[4]</sup>

Herzog et al.<sup>[2,4,7]</sup> have presented statistical evidence to support the concept of catamenial epilepsy and the existence of at least 3 distinct patterns of seizure exacerbation in relation to the menstrual cycle (Figure 1): 1) perimenstrual (C1: Day -3 to 3) and 2) periovulatory (C2: Day 10 to -13) in ovulatory cycles, and 3) luteal (C3: Day 10 to 3) in anovulatory or inadequate luteal phase cycles. In these cycles, Day 1 is the first day of menstrual flow and ovulation is presumed to occur 14 days before subsequent onset of menses (Day -14). These 3 patterns can be demonstrated simply by 1) charting menses and seizures, and 2) obtaining a mid-luteal phase serum progesterone level to distinguish between normal and inadequate luteal phase cycles (<5 ng/mL).

While the precise definition of catamenial epilepsy remains arbitrary, one may maximize the efficiency of distinguishing between women whose seizure occurrence shows a high versus low degree of hormonal sensitivity by using the points of inflection of the S-shaped distribution curves that define the relationship between severity of seizure exacerbation and the number of women who have exacerbation.<sup>[4,7]</sup> These points are calculated to be in the vicinity of a 2-fold increase in average daily seizure frequency during phases of exacerbation relative to baseline comparator phases (mid-follicular [Days 4 to 9] plus mid-luteal [Days -12 to -4] phases) for all 3 types of catamenial exacerbation. We propose the use of these points of inflection values in seizure frequency for the designation of catamenial epilepsy. Using cutoffs provided by the points of inflection of the 3 reverse S-shaped curves for designation of catamenial epilepsy, the 1997 investigation found that 42.3% (78/184) of the women demonstrated at least 1 of the 3 patterns of catamenial epilepsy (ovulatory cycles C1: 35.7% and C2: 28.5%; anovulatory cycles C3: 41.4%) during their 1 observed menstrual cycle.<sup>[4]</sup> Adoption of standard, albeit arbitrary, criteria for designation of catamenial epilepsy may provide greater uniformity to study designs for the investigation of the pathogenesis and treatment of catamenial seizure exacerbation.



**Fig. 1.** Three patterns of catamenial epilepsy: perimenstrual (C1) and periovulatory (C2) exacerbations during normal ovulatory cycles, and entire second half of the cycle (C3) exacerbation during inadequate luteal phase cycles where Day 1 is the first day of menstrual flow and Day -14 is the day of ovulation. E2: Estradiol; F: Follicular; L: Luteal; M: Menstrual phase; O: Ovulatory; P: Progesterone.

## Pathophysiology

There is considerable scientific evidence at molecular biological, neuronal, experimental animal, and clinical levels to indicate that reproductive steroids have neuroactive properties that play an important role in the pathophysiology of epilepsy and the pattern of seizure occurrence. Steroids act in the brain by direct membrane-mediated (short latency) effects as well as intracellular receptor-genomically-mediated (long latency) effects.<sup>[8–10]</sup>

## Reproductive Hormonal Effects On Epilepsy

### Estradiol

The potential importance of estradiol in regulation of temporolimbic function is highlighted by the presence of estradiol synthesizing enzymes cytochromes P45017a and P450 aromatases localized in neurons in the hippocampus, and the measurement of hippocampal estradiol levels that can surpass serum levels.<sup>[11,12]</sup> Estradiol has complex effects that vary with estradiol concentration, mode, and site of administration, blood-brain barrier, and epileptic substrate.<sup>[13]</sup> Apparently contradictory effects of estrogen in the brain are reviewed in detail by Velísková et al.<sup>[14]</sup>

Most adult animal experimental investigations have led to the prevailing opinion that estradiol has neuroexcitatory effects that can lower seizure thresholds. The thresholds of limbic seizures in female rats fluctuate during the estrus cycle inversely to estradiol levels.<sup>[15]</sup> Physiological doses of estradiol activate spike discharges<sup>[13,16–18]</sup> and lower the thresholds of seizures induced by electroshock, kindling, pentylentetrazol, kainic acid, ethyl chloride, and other agents and procedures.<sup>[13,18–22]</sup> In fact, topical brain application, as well as intravenous systemic administration, of estradiol in rabbits produces a significant increase in spontaneous, electrically recorded, paroxysmal spike discharges.<sup>[13]</sup> The increase is seen within a few seconds of application, suggesting a direct membrane, rather than genomic effect, and is more dramatic in animals with pre existent cortical lesions and estradiol priming.<sup>[13,16,18]</sup>

With regard to mechanisms of action, estradiol may act on CA1 hippocampal pyramidal neurons via convergent mechanisms that combine the effects of estradiol priming on hippocampal plasticity with subsequent direct potentiation of excitatory postsynaptic potentials (EPSPs).<sup>[16]</sup> More specifically, estradiol priming via subcutaneous estradiol

injection may act over 2 days to increase dendritic spines and excitatory synapses as well as N-methyl-D-aspartate (NMDA) binding<sup>[23,24]</sup> to increase EPSP durations and repetitive firing response to stimulation of Schaeffer collaterals.<sup>[16]</sup> Of note, estradiol priming also increases gamma-aminobutyric acid (GABA) binding.<sup>[25]</sup> Direct application of estradiol to primed CA1 hippocampal slices increases membrane-mediated EPSP response to Schaffer collateral stimulation or glutamate application within a couple of minutes.<sup>[16]</sup> The estradiol application potentiates kainate and quisqualate-mediated neurotransmission, thereby implicating non-NMDA receptors in the short-term action of estradiol.<sup>[16]</sup> It can be blocked by non-NMDA, but not NMDA, antagonists.<sup>[16]</sup> A non-NMDA mechanism of action is supported by a more recent preclinical model that suggests E2 binds ER $\beta$ R to increase glutamatergic  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA)-mediated EPSPs,<sup>[26]</sup> and binds ER $\alpha$ R to acutely suppress presynaptic GABA release and inhibitory postsynaptic potentials (IPSPs) via a metabotropic glutamate receptor 1 (mGluR1)-endocannabinoid mechanism.<sup>[27]</sup> The complex role of estrogen, however, is illustrated by evidence in some models that estradiol can raise seizure thresholds in the hippocampal region and provide neuroprotection against seizure-induced injury.<sup>[14]</sup> In summary, the combination of estradiol priming effects and direct membrane effects may converge on CA1 hippocampal neurons to exert the neuroexcitatory effects of estradiol.

Estrogen receptor-containing neurons co-localize with other neurotransmitters such as acetylcholine, and growth factors such as brain-derived neurotrophic factor (BDNF) to modulate neuronal excitability and seizure thresholds.<sup>[28,29]</sup>

Clinically, Logothetis et al.<sup>[30]</sup> showed that intravenously administered conjugated estrogen clearly activated epileptiform in 11 of 16 women and was associated with clinical seizures in 4.

### Progesterone

Progesterone, and particularly some of its neuroactive metabolites, most notably allopregnanolone, exert direct membrane-mediated inhibitory effects by potentiating GABAA-mediated chloride conductance.<sup>[9,31,32]</sup> It also potentiates action of the powerful endogenous inhibitory substance adenosine.<sup>[33]</sup> Progesterone itself also substantially diminishes nicotinic acetylcholine receptor-mediated con-

ductance, which may be relevant to autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE).<sup>[34]</sup>

Progesterone may act via genomic mechanisms to influence the enzymatic activity controlling the synthesis and release of various neurotransmitters and neuromodulators produced by progesterone receptor containing neurons.<sup>[8]</sup> Progesterone binds specific cytosolic receptors not only to produce its own characteristic effects, but also to lower estrogen receptor numbers and thereby antagonize estrogen actions.<sup>[35]</sup>

Chronic progesterone decreases the number of hippocampal CA1 dendritic spines and excitatory synapses faster than the simple withdrawal of estrogen, counteracting the stimulatory effects of estradiol.<sup>[23]</sup> Progesterone and allopregnanolone (AP) have also been shown to have neuroprotective effects on hippocampal neurons in kainic acid-induced seizure models.<sup>[36]</sup>

In most adult female animal models, progesterone depresses neuronal firing,<sup>[37]</sup> and lessens spontaneous and induced epileptiform discharges.<sup>[20-22,36-38]</sup> It retards kindling and decreases seizure occurrence.<sup>[20-22,36-38]</sup>

Bäckström et al.<sup>[39]</sup> found that intravenous infusion of progesterone, sufficient to produce luteal phase serum levels, was associated with a significant decrease in interictal spike frequency in 4 of 7 women with partial epilepsy.

### Neurosteroids

Most of the membrane effect of progesterone is due to the action of its 3 $\alpha$ -hydroxylated (i.e., A-ring-reduced) metabolite, 3 $\alpha$ -hydroxy-5 $\alpha$ -pregnane-20-one (or AP).<sup>[9,32]</sup> AP and the 3,5-hydroxylated natural metabolite of the mineralocorticoid deoxycorticosterone, allotetrahydro-deoxycorticosterone (allo-THDOC), are among the most potent of a number of endogenous neuroactive steroids with a direct membrane effect on neuronal excitability.<sup>[9,31,32]</sup> AP, but not allo-THDOC, is devoid of hormonal effects and may, together with other related neuroactive steroids, be thought of as an endogenous regulator of brain excitability with anxiolytic, sedative-hypnotic, and anticonvulsant properties.<sup>[9,31,32]</sup> AP and allo-THDOC hyperpolarize hippocampal and other neurons by potentiating GABA-mediated inhibition.<sup>[9,32]</sup> At physiological (nanogram) doses, AP acts at an extrasynaptic steroid-specific site near the synaptic receptor to facilitate chloride channel opening and prolong the inhibitory action

of GABA on neurons.<sup>[9,31,32,40,41]</sup> At higher pharmacological (micromolar) concentrations, AP also has a direct effect at the synaptic GABA receptor to induce chloride currents.<sup>[9,32]</sup> AP is one of the most potent ligands of GABA receptors in the central nervous system (CNS), with affinities similar to those of the potent benzodiazepine, flunitrazepam, and approximately 1000 times higher than pentobarbital.<sup>[9,32]</sup> The parent steroid, progesterone, enhances GABA-induced chloride currents only weakly and only in high concentrations.<sup>[9,41]</sup> Plasma and brain levels of AP parallel those of progesterone in rats. In women, plasma levels of AP correlate with progesterone levels during the menstrual cycle and pregnancy.<sup>[9]</sup> However, brain activity of progesterone and AP is not dependent solely on ovarian and adrenal production, as they are both synthesized *de novo* in the brain.<sup>[42]</sup> Their synthesis is region-specific and includes the cortex and the hippocampus.<sup>[42]</sup> By contrast, allo-THDOC is only synthesized by the adrenal gland and not in the brain.<sup>[9]</sup>

AP, allo-THDOC, and a number of other endogenous and synthetic pregnane steroids have a potent anticonvulsant effect in bicuculline-, metrazol-, picrotoxin-, pentylenetetrazol (PTZ)-, pilocarpine- and kainic acid-induced seizures and against status epilepticus, but are ineffective against electroshock and strychnine-induced seizures.<sup>[31,43-45]</sup> The anticonvulsant properties of AP resemble those of the benzodiazepine clonazepam.<sup>[31,45]</sup> AP is less potent than clonazepam, but may have lower relative toxicity.<sup>[44,45]</sup> The anticonvulsant effect of AP is greater in female rats in the diestrus 1 part of the ovulatory cycle (equivalent to human mid-luteal phase when progesterone levels are high) than in estrus (equivalent to ovulation when estrogen levels are high) or in the male.<sup>[40]</sup> Enhanced mid-luteal efficacy at the GABA receptor may be related to a progesterone-induced enhanced formation of the  $\delta$  GABA receptor subtype for which AP has high affinity.<sup>[40]</sup> Rapid withdrawal of progesterone in late diestrus makes the GABA receptor insensitive to benzodiazepine, but not AP, perhaps as the result of a decrease in the benzodiazepine-sensitive synaptic GABA receptors.<sup>[46]</sup> This effect can be blocked by inhibiting the formation of the  $\alpha 4$  subunit of the GABA receptor.<sup>[40,46]</sup>

By contrast, some of the sulfated neuroactive steroids have excitatory neuronal effects. They include pregnenolone sulfate and dehydroepiandrosterone sulfate (DHEAS), the naturally occurring sulfated esters of the progesterone precursor pregnenolone and progesterone metabolite DHEA.

<sup>[9]</sup> They increase neuronal firing when directly applied to neurons by negatively modulating the GABAA receptor<sup>[9]</sup> and by facilitating glutamate-induced excitation at the NMDA receptor.<sup>[47]</sup> In animal seizure models, pregnenolone sulfate and DHEAS have proconvulsant effect.<sup>[48]</sup> Of note, serum DHEAS levels are substantially reduced by enzyme-inducing antiepileptic drugs (AED) such as phenytoin and carbamazepine.<sup>[49,50]</sup>

## Hormonal Treatment

### Progestogen Therapy

The term "progestogen" refers to the broad class of progestational agents. These include progesterone, (i.e., naturally occurring progesterone), and progestins (i.e., synthetic progestational agents). Progestogen treatment (Tables 1 and 2) has taken 2 forms: 1) cyclic progesterone therapy that sup-

plements progesterone during luteal phase and withdraws it gradually premenstrually to avoid withdrawal seizures, and 2) suppressive therapy in which the goal is to suppress the menstrual cycle, generally accomplished using injectable progestins or depot forms of gonadotropin releasing-hormone analogues.

### Cyclic Progesterone Therapy

In contrast to the published cyclic oral progestin trials that did not result in significant reduction of seizure frequency,<sup>[51,52]</sup> 2 open-label trials of adjunctive cyclic progesterone therapy for women with catamenial epilepsy did result in clinically important and statistically significant reductions in seizure occurrence (Table 2).<sup>[53,54]</sup> In an investigation of women who had inadequate luteal phase cycles with catamenial exacerbation of intractable complex partial seizures, 6 of 8 women experienced improved seizure control with

**Table 1.** Reproductive endocrine treatments of women with epilepsy

Investigational treatments	Dosage	Potential adverse effects
Progesterone lozenges	Days 14–25: ½ – 1 lozenge tid Days 26–27: ¼ – ½ lozenge tid Day 28: ¼ lozenge tid	Sedation, depression, breast tenderness, vaginal bleeding, constipation, exacerbation of asthma, weight gain
Depomedroxyprogesterone	150–250 mg IM q 1–3 months	As above plus delay of months to 2 years in recovery of ovulatory cycles during which time seizure numbers may increase, sometimes beyond baseline
GnRH analogue	Leuprolide: 3.75 mg IM q 4 weeks 11.25 mg IM q 12 weeks	Menopausal symptoms unless concomitant estradiol and progesterone supplement is administered
Clomiphene	Days 5–9: 25–50 mg daily	Ovarian overstimulation syndrome (N.B. distention of ovaries can be very painful)

GnRH: Gonadotrophin-releasing hormone; IM: Intramuscularly; q: Once; t.i.d.: 3 times a day.

**Table 2.** Adjunctive cyclic progestogen therapy

	Medroxy-progesterone (Herzog 1983)	Progesterone Suppositories (Herzog 1986)	Progesterone Lozenges (Herzog 1995)	Progesterone Lozenges (Herzog 3-year follow-up)
Regimen	5–10 mg. q.d. days 15–28 of cycle	100–200 mg. t.i.d. days 15–28 of cycle	100–200 mg. t.i.d. days 15–28 of cycle	100–200 mg. t.i.d. days 15–28 of cycle
Assessment	@ 3 months	@ 3 months	@ 3 months	@ 3 years
Subjects	24	8	25	15 of original 25
Number (%) improved	10 (42%)	6 (75%)	18 (72%)	15 (100%/60% overall)
Seizure Frequency	-10%	-68%*	-54%** CPS -58%* SGMS	-62%** CPS -74%** SGMS

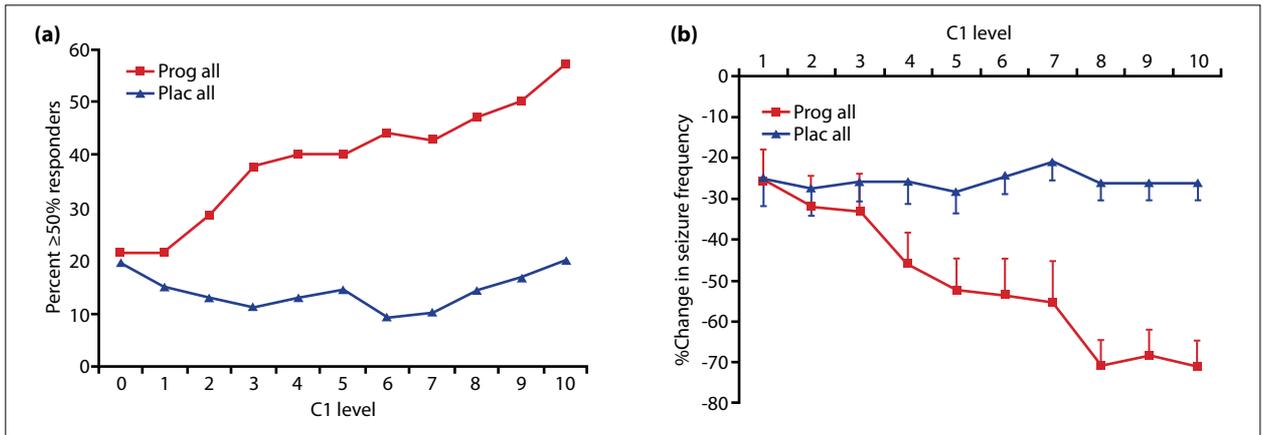
CPS: Complex partial seizure; q.d.: Each day; SGMS: Secondary generalized motor seizure; t.i.d.: Three times a day; \*= $p < .05$ ; \*\*= $p < .01$ .

a 68% decline in average monthly seizure frequency over 3 treatment cycles as compared to 3 baseline cycles.<sup>[53]</sup> In a subsequent open-label trial of adjunctive cyclic progesterone versus the optimal antiseizure medication alone in 25 women (14 with inadequate luteal phase or anovulatory cycles, and 11 with normal ovulatory cycles and perimenstrual seizure exacerbation), 18 (72%) experienced fewer seizures with an overall average monthly decline of 54% for complex partial and 58% for secondary generalized seizures over 3 months.<sup>[54]</sup> Efficacy was greater when progesterone was administered during the entire second half of the cycle, rather than just premenstrually, and then tapered and discontinued gradually over 3 or 4 days at the end of the cycle.<sup>[54]</sup> Failure to taper gradually premenstrually can result in rebound seizure exacerbation. At 3 years, the 15 women who remained on cyclic progesterone therapy and their original AED continued to show significantly lower average daily seizure frequency in comparison to their original baseline (Table 2).<sup>[55]</sup> Three women were entirely seizure-free. Four had total seizure reductions of 75–99% and 8 had reductions of 50–74%. Complex partial seizures (CPS) in these 15 women were lower by a statistically significant 62% (baseline: 0.328, 3-year follow-up: 0.125;  $p < .01$ ) and secondary generalized motor seizures (SGMS) by 74% (baseline: 0.148, 3-year follow-up: 0.038;  $p < .01$ ). AED serum levels continued to show no significant change. The 3 remaining women who continued on progesterone therapy had 10–50% improvement at the end of the original investigation at 3 months and were not considered further because they changed AED.

The NIH progesterone trial was a randomized, placebo-controlled, double-blind, clinical trial of progesterone versus placebo therapy in the treatment of intractable seizures in women with epilepsy.<sup>[56]</sup> The principal outcomes were the proportion of  $\geq 50\%$  responders, and the change in seizure frequency between the 3-month baseline and 3-month treatment phases. Sample size of 640 was determined as the enrollment requirement to show a significant difference ( $p \leq .05$ ) between treatments for  $\geq 50\%$  responders with 80% power for 35% progesterone vs 15% placebo responders in the catamenial stratum. The large sample size was required since only about one-third of the women were expected to show a catamenial pattern of seizure exacerbation. Catamenial designation was based on the demonstration of catameniality in 2 of 3 baseline cycles using the 1997 Herzog et al.<sup>[4]</sup> points of inflection cutoffs for designation of C1, 2 and 3 patterns. The trial enrolled only 462 women and random-

ized the 294 subjects who completed the baseline phase. Randomization was carried out separately for catamenial and non-catamenial strata, 2:1 to progesterone or matching placebo treatment. Treatment regimen consisted of baseline optimal AED treatment plus adjunctive progesterone 200 mg. lozenges or matching placebo. A whole lozenge was taken 3 times daily on Days 14–25, half lozenge 3 times daily on Days 26–27, one-quarter lozenge taken 3 times daily on Day 28, and then no lozenges until the next Day 14. The findings of the NIH trial showed that cyclic progesterone supplement did not differ significantly from placebo in treatment of intractable seizures in women with partial epilepsy.<sup>[56]</sup> A pre-specified secondary analysis, however, did identify a subset of women, specifically women with perimenstrual seizure exacerbation, who were significantly more responsive to progesterone treatment. This post-hoc predictor analysis using binary logistic regression analysis (dependent variable being  $\geq 50\%$  progesterone responder: yes or no) found that the level of perimenstrual catameniality (C1 level) is a predictor of efficacy of progesterone treatment. There was a significant interaction between C1 level and treatment. With increasing C1 levels, responder rates increased progressively from 21.3% to 57.1% for progesterone versus only 19.6% to 20.0% with placebo (Figure 2a). Changes in average daily seizure frequency progressed from -25.5 to -71.0% for progesterone versus only -25.0 to -26.3% for placebo (Figure 2b). There was also significant interaction between C1 level and progesterone treatment for the more selective analyses of just the most severe seizure type, secondary generalized tonic-clonic seizures, and CPS, but not simple partial seizures (SPS). The separation between  $\geq 50\%$  responder rates for all seizures combined for progesterone (27.3%) versus placebo (14.3%) treatments was not significant at C1 level  $\geq 1.69$ , the C1 cutoff level selected for designation to the catamenial stratum. The separation did achieve statistical significance at C1 level  $\geq 2$  (28.6% versus 12.9%) and at C1 level  $\geq 3$ , the separation (37.8% versus 11.1%) was both statistically significant ( $p = .0372$ ) and achieved the anticipated clinically important separation goal of the trial, i.e.,  $\geq 35\%$  responder rate for progesterone versus  $\leq 15\%$  responder rate for placebo.

In the trial,<sup>[56]</sup> 38.1% of the subjects had C1 level  $\geq 1.69$ , 34.4% had C1 level  $\geq 2$ , and 21.4% had C1 level  $\geq 3$  levels of perimenstrual exacerbation (Table 3). Of note, 12.2% had C1 level  $\geq 6$ , which is almost identical to the 12.4% found in the Duncan study (Table 3).<sup>[57]</sup> The findings suggest that 21.4%



**Fig. 2.** (a) Percent ≥50% responders in relation to C1 level: Progesterone vs placebo. This is a plot of ≥50% responders versus the level of perimenstrual seizure exacerbation (C1 level). C1 levels were determined during baseline and are expressed as multiples of the combined mid-follicular and mid-luteal seizure frequencies. Each level includes all women who had seizure exacerbation greater than or equal to that specific level of catameniality. With increasing C1 levels, the rate of ≥50% responders increased from 21.3% to 57.1% with progesterone treatment as compared to an increase of only 19.6% to 20.0% with placebo treatment. The anticipated primary outcome that 35% of catamenial progesterone treated versus 15% of placebo treated women would show a ≥50% reduction in seizure frequency is realized at C1 level ≥3 where 37.8% of progesterone treated as compared to 11.1% of placebo treated women were ≥50% responders ( $p = .0372$ ). In comparison to the responder rate of the combined placebo group, the progesterone responder rates are significantly greater at each C1 level ≥3. (b) Percent change in average daily seizure frequency in relation to C1 level: Progesterone vs placebo. With increasing C1 levels from 1-10, the percent reduction in ADSF (mean±SEM) progressed from 25.5% to 71.0% for progesterone as compared to 25.0 to 26.2% for placebo. Separation between the treatments reached significance at C1 levels ≥4. In comparison to change in ADSF in the combined placebo group, the changes in ADSF in progesterone treated subjects are significant at each C1 level ≥3. C1: Perimenstrual seizure exacerbation; Plac: Placebo; Prog: Progesterone.

of women with intractable seizures, i.e., the percentage that had C1 level ≥3 baseline, might be considered candidates for cyclic progesterone supplement.

A tertiary outcome of the trial was to determine whether AP may mediate seizure reduction in progesterone-treated women with epilepsy.<sup>[58]</sup> AP levels were significantly greater than in baseline cycles for women treated with progesterone but not placebo, regardless of catamenial designation. There was a significant inverse correlation between changes in seizure frequency and changes in AP levels for the subset of subjects who showed a significantly greater responder rate in post hoc analysis of the trial; i.e., subjects who had a 3-fold or greater increase in average daily seizure frequency perimenstrually as compared to the mid-follicular and mid-luteal phases ( $C1 \geq 3$ ):  $r = -0.442$ ,  $p = .013$  and specifically for  $C1 \geq 3$  progesterone-treated patients ( $r = -0.452$ ,  $p = .035$ ), but not other groups ( $C1 \geq 3$  placebo:  $r = -0.318$ ,  $C1 < 3$  progesterone:  $r = 0.099$ ,  $C1 < 3$  placebo:  $r = 0.131$ ;  $p = NS$ ). The findings support AP as a mediator of seizure reduction in progesterone-treated women who have a substantial level of perimenstrually exacerbated seizures.

Failure of the trial to prove the principal hypothesis may relate to the design that attempted to treat 3 patterns of catamenial epilepsy that likely differ in pathophysiology with a single treatment regimen.<sup>[4,56,59]</sup> Specifically, cyclic

**Table 3.** Percentage of women who have various levels of perimenstrual seizure exacerbation

C1 level	# WWE	% WWE
≥0	294	100.00
≥1	196	66.67
≥1.69	112	38.10
≥2	101	34.35
≥3	63	21.43
≥4	51	17.35
≥5	44	14.97
≥6	36	12.24
≥7	31	10.54
≥8	24	8.16
≥9	22	7.48
≥10	19	6.46

C1 level: Level of perimenstrual seizure exacerbation; WWE: Women with epilepsy.

progesterone supplement may have greater efficacy where progesterone withdrawal (C1 pattern), rather than estrogen surge (C2) or high luteal phase estradiol/progesterone serum level ratios (C3 pattern), are causally implicated. The design also assumed that the mathematically determined cutoff for catamenial designation would match the cutoff for a significant progesterone response. The absence of a significant difference between progesterone and placebo responders at the C1 cutoff level of  $\geq 1.69$  and finding of a significant difference at a clinically important level at C1 level  $\geq 3$  may suggest that there is a difference between the catamenial level that mathematically best distinguishes hormonally sensitive seizures and the level that distinguishes progesterone responders at a statistically significant and clinically important level. Actual enrollment of a larger sample size might have achieved a significant difference, i.e., 234 progesterone and 117 placebo-treated subjects might show the demonstrated C1  $\geq 1.69$  progesterone responder rate of 27.3% versus placebo rate of 14.2% with  $p \leq .05$  and power of 0.80. Even with these larger numbers, however, the responder rate would still not achieve what we considered to be a clinically important responder level of  $\geq 35\%$ .

### Progestin Therapy

Parenteral depomedroxyprogesterone may lower seizure frequency when given in sufficient dosage to induce amenorrhea.<sup>[52,60]</sup> In an open-label study of 14 women with refractory seizures (13 with partial seizures and 1 with absence seizures) and normal ovulatory cycles, parenteral depomedroxyprogesterone administration, 120–150 mg intramuscularly every 6–12 weeks, resulted in a favorable response in 7 women and an overall 39% reduction in seizure frequency.<sup>[52]</sup> The woman with absence seizures did not benefit. It was unclear whether the effect was due to direct anticonvulsant activity of medroxyprogesterone or to hormonal consequences of the induced amenorrhea. Side effects included those encountered with natural progesterone. Depot administration, however, is also commonly associated with hot flashes, irregular breakthrough vaginal bleeding, and a lengthy delay of 6 to 12 months or more in return of regular ovulatory cycles.<sup>[52]</sup> Long-term hypoestrogenic effects on cardiovascular and emotional status need to be considered with chronic use. Bone density is only partially maintained.

Oral synthetic progestins administered cyclically or continuously have not proven to be an effective therapy for seizures in clinical investigations<sup>[51,52]</sup> although individual

successes with continuous daily oral use of norethistrone and combination pills have been reported.<sup>[61]</sup> One possible factor might be that synthetic progestins lower serum and cerebral cortical levels of AP and produced anxiety-like behavior in female rat model.<sup>[62]</sup>

### Gonadotrophin-Releasing Hormone Analogue Therapy

Bauer et al.<sup>[63]</sup> used triptorelin, a synthetic gonadotrophin-releasing hormone (GnRH) analogue (3.75 mg) in a controlled release depot form intramuscularly every 4 weeks for an average of 11.8 months in 10 women (aged 20–50) with catamenial seizures intractable to high therapeutic doses of carbamazepine, diphenylhydantoin, phenobarbital, and valproic acid in monotherapy or combined. They remained on a stable dose of the anticonvulsant throughout period of treatment with triptorelin. They reported that 3 patients became seizure-free and 4 showed decrease in seizure frequency of up to 50%. In 1, duration of seizures was shortened; 2 had no therapeutic effect. These results were attained within the first 2 months of starting triptorelin. The study was not a controlled study and long-term follow-up was not available for some patients. Serum luteinizing hormone (LH) and estrogen were measured in 1 patient before and during the second month of triptorelin treatment, and as expected, showed marked inhibition of LH and estrogen production. All of the women became amenorrheic. Eight of the 10 patients experienced hot flashes, headache, or weight gain.

Haider and Barnett<sup>[64]</sup> reported on their use of goserelin 3.6 mg subcutaneously every 4 weeks in a 41-year-old woman who had had frequent catamenial status epilepticus despite therapeutic anticonvulsant drug levels that did not respond to levonorgestrel/ethinyl estradiol. They reported a decrease in frequency from 10 admissions for status to 3 over a similar period.

GnRH analogues basically create a medical oophorectomy. Common side effects are flushing, vaginal dryness, and dyspareunia. Serious long-term risks include osteoporosis and cardiovascular disease. Reid and Gangar<sup>[65]</sup> suggested addition of medroxyprogesterone acetate (MPA) and conjugated estrogens to goserelin to prevent this while still abolishing most of the cyclical fluctuations of ovarian hormones. Finkelstein et al.<sup>[66]</sup> recently discussed use of parathyroid hormone to prevent bone loss in women treated with GnRH analogues. Although neither Bauer et al.<sup>[63]</sup> nor Haider and

Barnett<sup>[64]</sup> reported exacerbation of seizures with GnRH analogues, Herzog<sup>[67]</sup> found that during the first 3 weeks, when there is an initial stimulation of estrogen before its production is inhibited, some women experienced such a marked exacerbation of their seizures and auras that they could not tolerate further use of GnRH analogue.

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