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Catamenial epilepsy: Definition, prevalence pathophysiology and treatment

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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 periodicity. When the periodicity of seizure exacerbation aligns itself with that of the menstrual cycle, it is designated as catamenial epilepsy. The neuroactive properties of reproductive steroids and the cyclic variation in their serum concentrations are important pathophysiologic factors. Recent investigations have demonstrated and confirmed the existence of at least three patterns of catamenial seizure exacerbation: perimenstrual and periovulatory in ovulatory cycles and entire luteal phase in anovulatory cycles. A rational mathematical basis for the categorization of seizure exacerbation as catamenial epilepsy has been developed. It identifies approximately one third of women as having catamenial epilepsy. If seizures show hormonal sensitivity in their occurrence, they may also respond to hormonal treatment. Successful open label trials using cyclic natural progesterone supplement, depomedroxyprogesterone and gonadotropin-releasing hormone analogues in women and using testosterone with or without aromatase inhibitor in men have been reported. Prospective, randomized, placebo-controlled, double-blind investigations are warranted and under way.

Definition, patterns and prevalence

Seizures do not occur randomly in the majority of men and women with epilepsy.[1] They tend to cluster in over 50% of cases.[1,2] Seizure clusters, in turn, may occur with temporal rhythmicity in a significant proportion of men (29%) and women (35%) with epilepsy.[3] When the periodicity of seizure exacerbation aligns with the menstrual cycle, it is commonly known as catamenial epilepsy.[4] This may be attributable to (1) the neuroactive properties of steroid hormones and (2) the cyclic variation in their serum levels.[4]

Physiological endocrine secretion during the menstrual cycle influences the occurrence of seizures (Fig. 1). In ovulatory cycles, seizure frequency shows a statistically significant positive correlation with the serum estradiol/progesterone ratio.[5] This ratio is highest during the days prior to ovulation and menstruation and is lowest during the early- and mid-luteal phase.[5] The premenstrual exacerbation of seizures has been attributed to the rapid withdrawal of the antiseizure effects of progesterone.[4,5]

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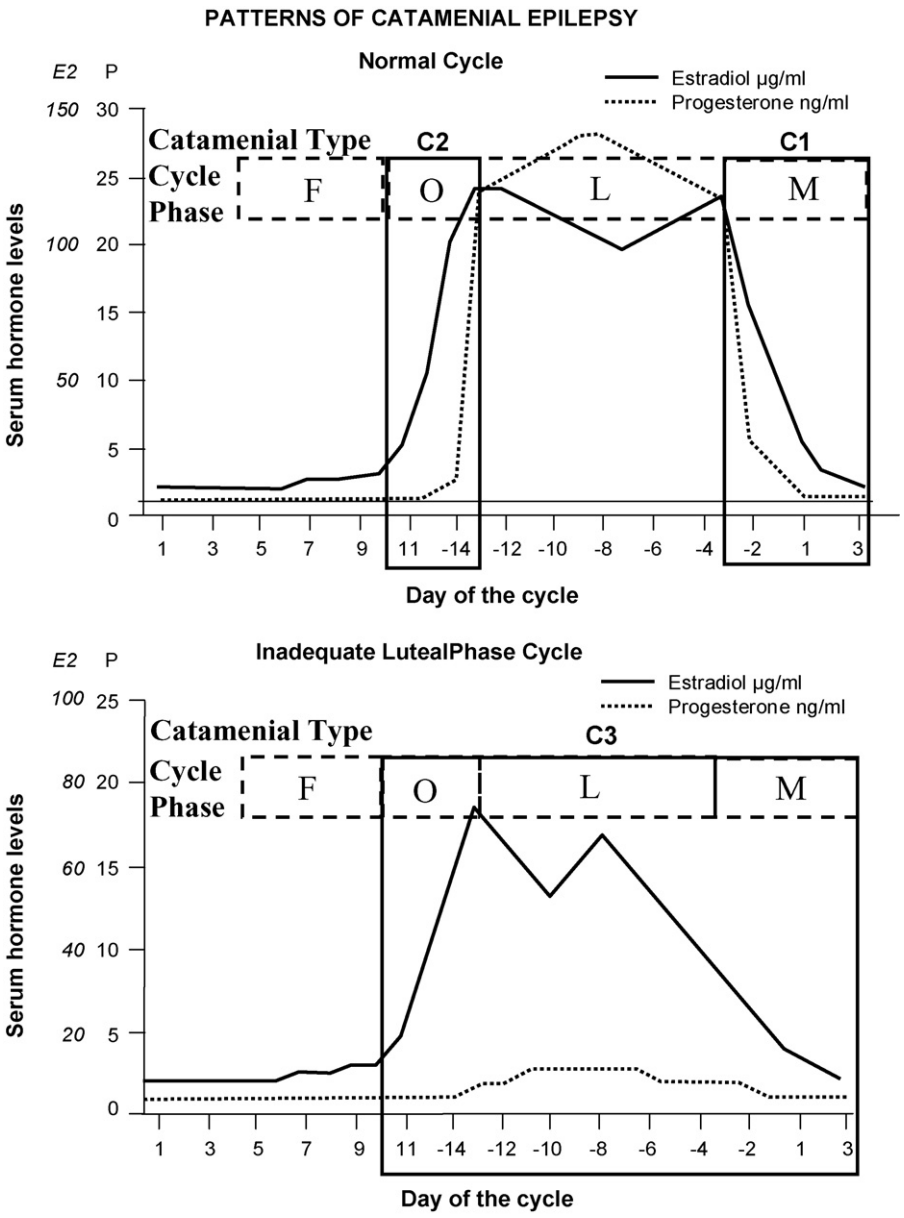

Figure 1 Three patterns of catamenial epilepsy: perimenstrual (C1) and periovulatory (C2) exacerbations during normal ovulatory cycles and entire second half of the cycle (C3) exacerbation during inadequate luteal phase cycles where Day 1 is the first day of menstrual flow and Day 14 is the day of ovulation.

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

Herzog et al.[4,7] have presented statistical evidence to support the concept of catamenial epilepsy and the existence of at least three distinct patterns of seizure exacerbation in relation to the menstrual cycle (Fig. 1): (1) perimenstrual (C1: Days −3 to 3) and (2) periovulatory (C2: Days 10 to −13) in normal cycles, and (3) luteal (C3: Days 10−3) in 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 the subsequent onset of menses (Day −14). These three 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 the severity of seizure exacerbation and the number of women who have exacerbation.[4,7] These points are calculated to be in the vicinity of a twofold increase in average daily seizure frequency during the phases of exacerbation relative to the baseline phases for all three types of catamenial exacerbation. We propose the use of these points of inflection values in seizure frequency for the designation of catamenial epilepsy. By this criterion, approximately one third of women with intractable partial epilepsy would qualify for the designation of having catamenial epilepsy.[4,7] Adoption of a standard albeit arbitrary nomenclature may provide greater uniformity to study designs for the investigation of the pathogenesis and treatment of catamenial seizure exacerbation.

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 receptor-mediated genomically mediated (long latency) effects.[8–10]

Reproductive hormonal effects on epilepsy

Estradiol

Estradiol exerts direct excitatory effects at the neuronal membrane, where it augments *N*-methyl-D-aspartate (NMDA) mediated glutamate receptor activity.[11,12] This enhances the resting discharge rates of neurons in a number of brain areas, including the hippocampus[11–13] where estradiol increases excitability of the hippocampal CA1 pyramidal neurons and induces repetitive firing in response to Schaffer collateral stimulation.[12]

Estradiol potentiates neuronal excitability by regulating neuronal plasticity. It increases the density of spines and excitatory, NMDA receptor-containing synapses on the apical dendrites of hippocampal CA1 pyramidal neurons via a post-transcriptional mechanism.[14,15] The dendritic spine density on these neurons correlates positively with the levels of circulating estradiol during the estrous cycle of the rat and is decreased by oophorectomy.[14,15] Estradiol may thus further increase excitatory input to the CA1 neurons.

Estradiol may affect neuronal excitability by cytosolic neuronal estrogen receptor-mediated, genomically dependent mechanisms. Receptors are particularly abundant in the temporolimbic system, especially in the medial and cortical amygdaloid nuclei, and occur in much fewer numbers in the hippocampal pyramidal cell layer and the subiculum.[16,17] Estrogen receptor-containing neurons colocalize with other neurotransmitters, including gamma-amino-butyric acid (GABA).[18,19] By regulating the expression of genes affecting the activity, release and post-synaptic action of different neurotransmitters and neuromodulators, estrogens may act to increase the excitability of neurons, which concentrate estradiol. For instance, estradiol lessens inhibitory neurotransmission by decreasing GABA synthesis in the corticomedial amygdala by reducing the activity of glutamic acid decarboxylase,[20] and enhances brain epileptogenic muscarinic neurotransmission by increasing choline acetyl transferase and acetylcholine.[21]

In adult experimental animals, the thresholds of limbic seizures in female rats fluctuate during the estrus cycle inversely to estradiol levels.[22] Physiological doses of estradiol activate spike discharges[12,13,23,24] and lower the thresholds of seizures induced by electroshock, kindling, pentylenetetrazol, kainic acid, ethyl chloride and other agents and procedures.[23–28] 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.[24] The increase is seen within a few seconds of application to suggest a direct membrane rather than a genomic effect and is more dramatic in animals with preexistent cortical lesions.[23,24] The role of estrogen, however, may be more complex since there is also evidence in some models that estradiol can raise seizure thresholds in the hippocampal region and provide neuroprotection against seizure-induced injury.[29]

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

Progesterone

Progesterone and particularly some of its neuroactive metabolites, most notably allopregnanolone, exert direct membrane-mediated inhibitory effects by potentiating $GABA_A$-mediated chloride conduc-

tance.[9,31,32] It also potentiates the action of the powerful endogenous inhibitory substance adenosine.[33] Progesterone itself also substantially diminishes nicotinic acetylcholine receptor-mediated conductance, which may be relevant to autosomal dominant nocturnal frontal lobe epilepsy.[34]

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.[18] 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.[35]

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.[14] Progesterone and allopregnanolone have also been shown to have neuroprotective effects on hippocampal neurons in kainic acid-induced seizure models.[36]

In most adult female animal models, progesterone depresses neuronal firing,[37] and lessens spontaneous and induced epileptiform discharges.[26–28,36–38] It retards kindling and decreases seizure occurrence.[26–28,36–38]

Backstrom et al.[39] found that intravenous infusion of progesterone, sufficient to produce luteal phase serum levels, was associated with a significant decrease in interictal spike frequency in four of seven women with partial epilepsy.

Neurosteroids

Most of the membrane effect of progesterone is due to the action of its 3α-hydroxylated (i.e. A-ring-reduced) metabolite, 3α-hydroxy-5α-pregnane-20-one or allopregnanolone (AP).[9,32] AP and the 3,5-hydroxylated natural metabolite of the mineralocorticoid deoxycorticosterone, allotetrahydrodeoxycorticosterone (allo-THDOC), are among the most potent of a number of endogenous neuroactive steroids with a direct membrane effect on neuronal excitability.[9,31,32] 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.[9,31,32] AP and allo-THDOC hyperpolarize hippocampal and other neurons by potentiating $GABA_A$-mediated inhibition.[9,32] At physiological (nanogram) with an extrasynaptic steroid-specific site near the synaptic receptor to facilitate chloride channel opening and prolong the inhibitory action of GABA on neurons.[9,31,32,40,41] At higher pharmacological (micromolar) concentrations, AP also has a direct effect at the synaptic $GABA_A$ receptor to induce chloride currents.[9,32] AP is one of the most potent ligands of $GABA_A$ receptors in the CNS, with affinities similar to those of the potent benzodiazepine, flunitrazepam, and approximately a thousand times higher than pentobarbital.[9,32] The parent steroid, progesterone, enhances GABA-induced chloride currents only weakly and only in high concentrations.[9,41] 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.[9] 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.[42] Their synthesis is region-specific and includes the cortex and the hippocampus.[42] By contrast, allo-THDOC is only synthesized by the adrenal gland and not in the brain.[9]

AP, allo-THDOC and a number of other endogenous and synthetic pregnane steroids have a potent anticonvulsant effect in bicuculine-, metrazol-, picrotoxin-, pentylenetetrazol-, pilocarpine- and kainic acid-induced seizures and against status epilepticus, but are ineffective against electroshock and strychnine-induced seizures.[31,43–45] The anticonvulsant properties of allopregnanolone resemble those of the benzodiazepine and clonazepam.[19,31,45] AP is less potent than clonazepam but may have lower relative toxicity.[44,45] 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.[40] Enhanced mid-luteal efficacy at the $GABA_A$ receptor may be related to a progesterone-induced enhanced formation of the δ $GABA_A$ receptor subtype.[40] Rapid withdrawal of progesterone in late diestrus makes the $GABA_A$ receptor insensitive to benzodiazepine, but not AP, perhaps as the result of a decrease in the benzodiazepine-sensitive synaptic $GABA_A$ receptors.[46] This effect can be blocked by inhibiting the formation of the α4 subunit of the $GABA_A$ receptor.[40,46]

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.[9] They increase neuronal firing when directly applied to neurons by negatively modulating the $GABA_A$ receptor[9] and by facilitating glutamate-induced

Table 1 Investigational sex hormone treatments of women with epilepsy

Investigational treatments	Dosage	Potential adverse effects
Progesterone lozenges	Days 14–25: 1/2–1 lozenge t.i.d. Days 26–27: 1/4–1/2 lozenge t.i.d. Day 28: 1/4 lozenge t.i.d.	Sedation, depression, breast tenderness, vaginal bleeding, constipation, exacerbation of asthma, weight gain
Depomedroxyprogesterone	150–250 mg I.M. 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 I.M. q 4 weeks 11.25 mg I.M. 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)

excitation at the NMDA receptor.[47] In animal seizure models, pregnenolone sulfate and DHEAS have proconvulsant effect.[48] Of note, serum DHEAS levels are substantially reduced by enzyme-inducing antiepileptic drugs such as phenytoin and carbamazepine.[49,50]

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 two forms: (1) cyclic progesterone therapy that supplements progesterone during the luteal phase and withdraws it gradually premenstrually and (2) suppressive therapy in which the goal is to suppress the menstrual cycle which is generally accomplished using injectable progestins or gonadotropin-releasing hormone analogues.

Cyclic progesterone therapy

In contrast to published cyclic oral progestin investigations that did not result in significant reduction of seizure frequency,[51,52] two open label trials of adjunctive progesterone therapy for women with catamenial epilepsy did result in clinically important and statistically significant reductions in seizure occurrence (Table 2).[53,54] In one investigation of women who had inadequate luteal phase cycles with catamenial exacerbation of intractable complex partial seizures, six of eight women experienced improved seizure control with a 68% decline in average monthly seizure frequency over 3 months for the whole group.[53] In a subsequent open 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 cycles and perimenstrual seizure exacerbation), 19 (72%) experienced fewer seizures with an overall average monthly decline of 54% for complex partial and 58% for secondary generalized seizures over 3 months.[54] Progesterone was more efficacious when administered during the entire

Table 2 Adjunctive cyclic progestogen therapy

	Medroxy-progesterone (Herzog, 1983)[55]	Progesterone suppositories[53]	Progesterone lozenges[54]	Progesterone lozenges (Herzog 3-year follow-up)[55]
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	at 3 months	at 3 months	at 3 months	at 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

* $p < .05$.
** $p < .01$.

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.[54] Failure to taper gradually premenstrually can result in rebound seizure exacerbation. At 3 years, the average daily seizure frequency per patient showed that the 15 women who remained on cyclic progesterone therapy and their original antiepileptic drugs continued to show improved seizure control in comparison to their own baseline (Table 2, 3-year follow-up).[55] Three women were entirely seizure-free. Four had total seizure reductions of 75—99%. Eight had reductions of 50—74%. Complex partial seizures in these 15 were lower by a statistically significant 62% (baseline: 0.328, 3-year follow-up: 0.125; $p < .01$); secondary generalized motor seizures, by 74% (baseline: 0.148, 3-year follow-up: 0.038; $p < .01$). Antiepileptic drug serum levels continued to show no significant change. The three 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 antiepileptic drugs.

By way of critique, the weakness of these preliminary progesterone investigations is that they were not placebo-controlled or blinded. The favorable 3-year follow-up results are biased by analysis of only 15 of the original 25 subjects. These 15 who remained on the original treatment regimen are more likely to represent those who had the most favorable response. There are reasons, however, to consider that the results of the present investigation may represent more than placebo effects: (1) few placebo studies, including our own progestin trial that used a similar methodology, and could be used, therefore, as a retrospective control, show favorable response in more than 50% of subjects; (2) few placebo treatments have resulted in greater than 50% seizure reduction; (3) while placebo effects generally wear off over a few months, substantial and statistically significant improvements in the present investigation persisted after 3 years in the majority of subjects.[55] Another argument against the placebo explanation is that the beneficial effect of progesterone can be eliminated by the concomitant use of a reductase inhibitor that presumably blocks the reduction of progesterone to its potent GABAergic metabolite allopregnanolone.[56] Finally, there is transcranial magnetic stimulation evidence that progesterone may increase inhibition in the brain premenstrually.[57] A prospective multicenter, randomized, double-blind, placebo-controlled investigation of cyclic, adjunctive progesterone therapy in the management of women with catamenially exacerbated, intractable localization-related epilepsy is now under way.[2,7]

Natural progesterone is available as an extract of yams or soy in lozenge form in variable dosages ranging from 25 to 200 mg and should be administered three times daily because of its brief half-life of about 4—6 h.[53—55] The daily regimen to achieve physiological luteal range serum levels measured 4 h after administration ranges from 50 to 200 mg, taken three times daily, with the usual optimal daily dose ranging from 300 to 600 mg.[53—55] The maintenance dosage and regimen should be individualized and based on a combination of clinical response and serum progesterone levels between 20 and 40 ng/ml. Progesterone is also available in micronized form in an oral capsule preparation that may also exert similar antiseizure effects although formal investigations to this effect are lacking. Theoretically, it is possible that first pass through the liver using the oral micronized form may result in the delivery of different concentrations of progesterone and its neuroactive metabolite to the brain.

Adverse effects occur with overdosage and include sedation, emotional depression and asthenia.[53—55] Progesterone use may also occasionally be associated with breast tenderness, weight gain, and irregular vaginal bleeding and sometimes constipation. The vehicle used to dissolve progesterone for suppository use may rarely be responsible for the development of an allergic rash. Discontinuation of the hormone or lowering of the dosage resolves these side effects.[53—55]

Drug interactions are an important consideration. Higher progesterone dosages may be required to achieve luteal range levels in women who take antiseizure medications because carbamazepine, phenytoin and barbiturates are known to enhance the hepatic metabolism of gonadal and adrenal steroid hormones as well as to increase hormonal binding to serum proteins.[56] Progesterone use has been associated with changes in antiseizure medication levels in some cases but this effect has been sporadic and not in a predictable direction. Therefore, total and possibly free serum antiseizure medication levels should be checked regularly during concomitant hormonal therapy.

Progestin therapy

Parenteral depomedroxyprogesterone may lower seizure frequency when it is given in sufficient dosage to induce amenorrhea.[52,58] In one open label study of 14 women with refractory partial seizures and normal ovulatory cycles, parenteral depomedroxyprogesterone administration in doses large enough to induce amenorrhea (i.e. 120—150 mg every 6—12 weeks) resulted in a 39% seizure reduc-

tion.[52] It was unclear whether the effect was due to direct anticonvulsant activity of medroxyprogesterone or to the hormonal consequences of the induced amenorrhea. One patient who had absence rather than partial seizures did not improve. 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—12 months in the return of regular ovulatory cycles.[52] 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[51,52] although individual successes with continuous daily oral use of norethistrone and combination pills have been reported.[59]

Gonadotrophin-releasing hormone analogue therapy

Bauer et al.[60] 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 the period of treatment with triptorelin. They reported that three patients became seizure-free; four showed a decrease in seizure frequency of up to 50%. In one the duration of seizures was shortened; two had no therapeutic effect. These results were attained within the first 2 months of starting triptorelin. The study was not a controlled study and longer term follow-up was not available for some of the patients. Serum LH and estrogen were measured in one patient before and during the second month of triptorelin treatment; and as expected showed marked inhibition of LH and estrogen production. All the women became amenorrheic. Eight of the ten patients experienced hot flushes, headache or weight gain.

Haider and Barnett[61] 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 which also did not respond to levonorgestrel/ethinyl estradiol. They reported a decrease in frequency from 10 admissions for status to three 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[62] suggested the addition of medroxyprogesterone acetate and conjugated estrogens to goserelin to prevent this while still abolishing most of the cyclical fluctuations of ovarian hormones. Finkelstein et al.[63] recently discussed the use of parathyroid hormone to prevent bone loss in women treated with GnRH analogues. Although neither Bauer et al.[61] nor Haider and Barrett[62] reported exacerbation of seizures with GnRH analogues, Herzog[64] 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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