Progesterone therapy in women with complex partial and secondary generalized seizures

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Article abstract—This open trial assessed the effects of adjunctive progesterone therapy on seizure frequency in 25 women with catamenial exacerbation of complex partial (CPS) and secondary generalized motor (SGMS) seizures. Progesterone was well tolerated by 23 of the 25 women and had readily reversible dose-related side effects of asthenia and emotional depression in two. Eighteen women (72%) experienced a decline in seizure frequency during a 3-month treatment period compared with the 3 months prior to therapy ($p < 0.01$). Average daily CPS frequency declined by 54% ($p < 0.01$), SGMS by 58% ($p < 0.02$).

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Reproductive hormones influence neuronal excitability by specific mechanisms that alter cell metabolism and neural transmission.[1,2] Estradiol lowers many seizure thresholds, while progesterone and some of its metabolites exert antiseizure effects.[3] Seizure frequency in women may increase in relation to the menstrual cycle (catamenial epilepsy) as a result of the withdrawal of progesterone or the elevation of serum estradiol-to-progesterone ratio.[4,5] The rapid premenstrual withdrawal of the antiseizure effect of progesterone is considered to be a factor in the premenstrual exacerbation of seizures.[4] Abnormally low progesterone secretion during the luteal phase is considered to be a factor in seizure exacerbations that occupy the entire second half of the menstrual cycle.[3-6]

One-half of women with epilepsy may have some form of reproductive dysfunction: amenorrhea, oligomenorrhea, or abnormally prolonged or shortened menstrual cycle intervals.[7] These menstrual disorders are characterized by inadequate luteal phase cycles, that is, abnormally low progesterone secretion during the second half of the menstrual cycle.[3] Inadequate luteal phase cycles have abnormally elevated serum estradiol/progesterone ratios, which are associated with greater seizure frequency.[5,6] Natural progesterone is considered to be the treatment of choice for inadequate luteal phase cycles.[8] Based on evidence that progesterone and some of its metabolites exert potent antiseizure effects,[2] and on our favorable preliminary experience with natural progesterone suppository treatment of catamenially exacerbated complex partial seizures in eight women,[9] this open trial compared the effects of cyclic natural progesterone lozenge use plus the best antiseizure medication therapy versus the best antiseizure medication therapy alone, on seizure frequency in 25 women who had catamenial exacerbation of refractory complex partial (CPS) or secondary generalized motor (SGMS) seizures of temporal lobe origin.

Methods. The subjects were 25 women between 18 and 40 years of age who had clinically and electrographically documented refractory CPS or SGMS of temporal lobe origin. All the women had epileptiform discharges in temporal lobe derivations on EEG and serum antiseizure medication levels in the therapeutic range. All demonstrated a catamenial pattern of seizure exacerbation[3] perimenstrually between days 25 and 2 or during the entire luteal phase of the menstrual cycle between days 10 and 2. Specifically, seizure charts documented, during each of three cycles, a twofold-greater average daily seizure frequency during the period of catamenial exacerbation than the average daily seizure frequency during the remainder of the menstrual cycle. Fourteen women in our series had seizure exacerbation during the entire luteal phase. They all had inadequate luteal phase cycles, as documented by low serum progesterone levels of less than 5 ng/ml during the mid-luteal phase.[3] Eleven women had perimenstrual exacerbations with normal

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Table. Effects of progesterone therapy on seizures

Seizure type	Catamenial pattern	Subjects improved	Seizures*		Δ (%)	p
			Baseline	Treated		
Both	LUT + PM	18/23	0.391	0.175	–55	<0.01
Both	LUT	11/14	0.393	0.161	–59	<0.02
Both	PM	7/9	0.389	0.198	–49	<0.05
CPS	LUT + PM	18/23	0.304	0.140	–54	<0.01
CPS	LUT	11/14	0.319	0.135	–58	<0.02
CPS	PM	7/9	0.282	0.147	–48	<0.05
SGMS	LUT + PM	10/13	0.154	0.064	–58	<0.02
SGMS	LUT	5/7	0.148	0.051	–66	<0.10
SGMS	PM	5/6	0.161	0.077	–52	<0.10

* Average daily frequency/patient.
CPS Complex partial seizures.
SGMS Secondary generalized motor seizures.
LUT Entire luteal phase exacerbation.
PM Perimenstrual exacerbation.

mid-luteal phase progesterone levels. Women were excluded if they were pregnant, had amenorrhea, or had taken major tranquilizers, antidepressant medications, or reproductive hormones during the 3 months prior to entry into this investigation.

Progesterone lozenges, 200 mg tid, were administered in relation to the pattern of seizure exacerbation. They were provided for days 23 to 25 of each menstrual cycle for perimenstrual exacerbation, and for days 15 to 25 of each menstrual cycle for entire luteal phase exacerbation, with subsequent tapering and discontinuation by day 28 for both. Progesterone dosage was adjusted if necessary to produce physiologic luteal range progesterone serum levels between 5 and 25 ng/ml 4 hours after taking a lozenge. This was documented each month in each case. Antiseizure medication levels were monitored randomly at least once each month during the 3 months prior to treatment and randomly at least once each month during progesterone treatment. All levels remained in the therapeutic range without dosage adjustment. The nonparametric Wilcoxon matched-pairs test was used to compare the average daily seizure frequency between a 3-month treatment period and the 3 months prior to therapy. The nonparametric sign test for correlated samples was used to compare antiseizure medication levels before and during treatment.

Results. Eighteen women (72%) experienced a decline in average daily seizure frequency ($p < 0.01$) during a 3-month treatment period compared with the 3 months prior to therapy (table). Two women did not tolerate progesterone because of asthenia and emotional depression. These symptoms resolved in both cases within 1 day upon discontinuation of therapy. Seizure frequency did not decline in five women. None, however, experienced a 10% or more increase. Average daily seizure frequency per patient declined by 55%, from 0.391 to 0.175 ($p < 0.01$), based on data from the 23 women who tolerated progesterone therapy at the time of entry into the investigation. In this group, average daily CPS frequency per patient declined by 54%, from 0.304 to 0.140 ($p < 0.01$). Among the 13 treated women with generalized seizures, average daily SGMS frequency per patient decreased by 58%, from 0.154 to 0.064 ($p < 0.02$). The 14 women with entire luteal phase catamenial exacerbation of seizures and 2 weeks of progesterone therapy showed a greater response than the nine with perimenstrual exacerbation and 6 days of therapy (59% versus 49% overall; 58% versus 48% for CPS and 66% versus 52% for SGMS). Antiseizure medication levels during treatment did not differ significantly from pretreatment values for the group.

Discussion. The data suggest that natural progesterone therapy benefits most women with catamenially exacerbated, intractable CPS or SGMS of temporal lobe origin. Moreover, this treatment has been generally well tolerated. None of the women experienced a significant increase in seizures or any serious or lasting side effects.

In the absence of an adequate response to classic antiseizure medication therapy, treatment may be considered in women with catamenial epilepsy who have documented inadequate luteal phase cycles, that is, cycles with low progesterone levels during the mid-luteal phase. More than one-third of women with epilepsy have reproductive endocrine disorders that are characterized by inadequate luteal phase cycles.[7,10] Such cycles are associated with greater seizure frequency.[5,6] This group commonly shows seizure exacerbation during the entire luteal phase of the cycle.[3] Natural progesterone is considered by some to be the treatment of choice for inadequate luteal phase and is commonly used to help induce fertility in this setting.[8]

Treatment may also be considered in women with catamenial epilepsy who have no demonstrable reproductive endocrine abnormality. This group most commonly experiences worsening of seizures perimenstrually, presumably in relation to the withdrawal of the antiseizure effects of progesterone[4] or to an actual premenstrual decline in

serum antiseizure medication levels.[11,12] Progesterone therapy premenstrually lessened seizure frequency significantly, but not as much as entire luteal phase therapy (59% versus 49%).

Synthetic progestin therapy has also benefited some women with epilepsy.[13,14] Parenteral depomedroxyprogesterone significantly lessens seizure frequency when it is given in sufficient dosage to induce amenorrhea.[13,14] A regimen of approximately 120 to 150 mg given intramuscularly every 6 to 12 weeks generally achieves this goal.[14] Side effects include those encountered with natural progesterone. Depot administration, however, is also commonly associated with hot flashes, irregular breakthrough vaginal bleeding, and occasionally a lengthy delay of 6 to 12 months in the return of regular ovulatory cycles.[14] Long-term hypoestrogenic effects on cardiovascular status need to be considered with chronic use. Oral synthetic progestins administered cyclically or continuously have not been effective in clinical investigations,[14,15] although there are reports of individual successes with continuous daily oral use of norethindrone and combination pills.[16]

The results suggest a need for a formal placebo-controlled, double-blind, crossover investigation with comparisons of free anticonvulsant and EEG findings as well as seizure frequency and severity before and during hormonal therapy to firmly establish the role of progesterone in the comprehensive management of women with epilepsy.

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