Treatment of Catamenial Epilepsy Is Still Up in the Air

Progesterone vs Placebo Therapy for Women with Epilepsy: A Randomized Clinical Trial.

Herzog AG, Fowler KM, Smithson SB, Kalayjian LA, Heck CN, Sperling MR, Liporace JD, Harden CL, Dworetzky BA, Pennell PB, Massaro JM. *Neurology* 201278(24):1959–1966.

OBJECTIVE: To assess progesterone treatment of intractable seizures in women with partial epilepsy. METHODS: This randomized, double-blind, placebo-controlled, phase III, multicenter, clinical trial compared the efficacy and safety of adjunctive cyclic natural progesterone therapy versus placebo treatment of intractable seizures in 294 subjects randomized 2:1 to progesterone or placebo, stratified by catamenial and noncatamenial status. It compared treatments on proportions of ≥ 50% responders and changes in seizure frequency from 3 baseline to 3 treated menstrual cycles. RESULTS: There was no significant difference in proportions of responders between progesterone and placebo in the catamenial and noncatamenial strata. Prespecified secondary analysis showed that the level of perimenstrual seizure exacerbation (C1 level) was a significant predictor of responders for progesterone but not placebo. With increasing C1 levels, responders increased from 21% to 57% with progesterone versus 19% to 20% with placebo. Reductions in seizure frequency correlated with increasing C1 levels for progesterone but not placebo, progressing from 26% to 71% for progesterone versus 25% to 26% for placebo. A prespecified clinically important separation between progesterone and placebo responders (37.8% vs 11.1%; p = 0.037) was realized among 21.4% of women who had C1 level ≥ 3. CONCLUSION: There was no difference in the primary outcome of ≥ 50% responder rates between progesterone versus placebo for catamenial or noncatamenial groups. Post hoc findings suggest that the level of perimenstrual seizure exacerbation is a significant predictor of responder rate with progesterone and that progesterone may provide clinically important benefit for a subset of women with perimenstrually exacerbated seizures. CLASSIFICATION OF EVIDENCE**:** This study provides Class III evidence that cyclic progesterone is ineffective in women with intractable partial epilepsy. Post hoc analysis identified a subset of women with higher levels of perimenstrual seizure exacerbation that were responsive to treatment.

Commentary

Seizure clustering is a common occurrence in many types of epilepsy. As with any phenomenon distributed unevenly, the human mind strives to find explanations for periods of relative quiescence interspersed with periods of prominent activity. Women with epilepsy have consistently associated seizure clustering with the menstrual cycle, so much so that there is a name for the phenomenon of women who experience exacerbation during this time: catamenial epilepsy. There has been a struggle to explicitly define catamenial epilepsy, since epilepsy occurs in so many different and complex patterns. Likely, women who have seizures in a monthly pattern will attribute it to the menstrual cycle whether or not there is a relationship. Notably, women are not alone in cycling of seizures: This phenomenon may be reported in men as well. In a questionnaire study of 141 men and women presenting to an epilepsy center, 29% reported seizure clustering, and gender was not a significant predictor of patients reporting clusters (1).

Given the fact that clustering is very common, it is quite possible that at least some clustering is indeed related to cycling of hormones and, therefore, tied to the menstrual pattern. Several different catamenial patterns have been reported, including seizures that occur perimenstrually (between days -3 to 3 of the menstrual cycle, the so-called "C1 pattern"), those that occur in the periovulatory period (Days 10–13, the "C-2 pattern"), and those that occur in anovulatory cycles (Days 10–3, the "C3 pattern") (2).

Since there is an acknowledged likely association of seizure clusters to menses, there have been numerous attempts to intervene with various therapeutic maneuvers—including acetazolamide and intermittent benzodiazepine therapy—and potentially more targeted interventions that would address hormonal surges that have been implicated in catamenial epilepsy. The most promising intervention appeared to be introduction of natural progesterone on Days 14 to 25 of the menstrual cycle. Yet, no intervention, including this one, had been subjected to a randomized controlled trial until the present study, which was a welcome attempt to finally

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prove that this intervention that was clearly well grounded in theory was also effective in practice.

The study recruited very slowly, and eventually was stopped prematurely for futility (that is, even after randomizing only about half the initially planned enrollment, it was clear that the progesterone arm would not separate from placebo). The results of the study demonstrated that progesterone therapy was ineffective in the group as a whole, which was a great disappointment. In itself, this is yet another example of why randomized controlled trials are so important; previous open trials had demonstrated a > 50 % overall reduction in seizures compared to pretreatment baseline, a result that was clearly not supported (3, 4).

Yet, there was a possible silver lining suggested by a preplanned post-hoc analysis: Apparently, women who had a very pure form of the C-1 pattern (at least 3 times as many seizures premenstrually as at other times) did improve compared to placebo. Moreover, the more pure the C1 pattern (as measured by the score from 1–10), the greater the likelihood of success. As noted in the publication, "Progesterone responder rates increased with C1 levels . . . from 24% to 64% ($r = 0.254$, $p = 0.001$). A graph included in the paper shows a systematic rise with each step higher in the C1 level.

While these results may demonstrate that there is a subset of those with catamenial epilepsy who may benefit from intermittent progesterone, there are several facts that imply that the number of women who benefit are likely to be small: The first is that the encouraging graph, showing a mounting success rate with the rising C1 level with a statistically significant improvement beginning at a C1 level of 3. On closer inspection, it becomes clear that C levels are not assessed independently; each cohort is calculated inclusive of all the levels above it. Thus, for example, the C-1 3 level (N = 63) includes all women with a C-1 level of 3 *and above,* 4 level (N = 51) is 4 *and above*, and so on. To give an analogy, one could claim that everyone over 30 had a higher risk of being in a nursing home compared with those under 30, with a higher and higher rate for those 30 and above, compared to 40 and above, compared to 50 and above because you are increasingly enriching for the true population with a higher risk (60 and above). In other words, one really cannot determine from this data whether those with a C-1 level of ≥ 3 or ≥ 4, for example, actually had a higher risk compared to placebo since they are not separated out, so you cannot tell at which "level" the response sharply increased.

Even if one accepted a level of ≥ 3 as the cutoff for an improvement, the number of women who were included in this group was very small at only 20% of the randomized group. A final concern is that if the treatment response is tied to the C-1 pattern, one must consider the heterogeneity even within a single woman. According to data from this very study, women may not demonstrate the same pattern consistently. The patterns during the 3-month baseline were assessed for the first 100 women entering the study (249 cycles in all) (2). Even in one woman, patterns changed from month to month. Many women did not experience a catamenial pattern in all cycles: 16% of cycles were anovulatory, and of the 208 ovulatory cycles, only 22.1% were pure C1, while 10.6% were C2, and a similar number was experienced in C1 and C2 patterns in the same cycle!

In conclusion, the data from this study is very important and clinically relevant. Most women will not benefit from progesterone therapy. A few select women with very consistent exacerbation of seizures in the days just before and after menstruation may benefit—but even these women may not benefit all of the time. To justify progesterone use, it would be important to document seizure relationship to menstruation in a prospective manner for several months prior to treatment initiation. Even then, the level of catamenial exacerbation that would predict benefit remains unknown.

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References

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