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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### Commentary

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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.

by Jacqueline A. French, MD

References
Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.
   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.
   This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (DGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

   Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

   For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships
   Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.
American Epilepsy Society

Epilepsy Currents Journal
Disclosure of Potential Conflicts of Interest

Section #1 Identifying Information

1. Today’s Date: 4/30/2013

2. First Name Jacqueline  Last Name French  Degree MD

3. Are you the Main Assigned Author? ☒ Yes  ☐ No

If no, enter your name as co-author:

4. Manuscript/Article Title: Treatment of Catamenial Epilepsy Is Still Up in the Air

5. Journal Issue you are submitting for: 13.2

Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
<thead>
<tr>
<th>Type</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
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<td>1. Grant</td>
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<td>JAZZ, Upsher-Smith</td>
<td>TESC (Consortium) received funding for work performed</td>
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* This means money that your institution received for your efforts on this study.

** Use this section to provide any needed explanation.
**Section #3  Relevant financial activities outside the submitted work.**
Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

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<td>13. Other (err on the side of full disclosure)</td>
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* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

**Section #4  Other relationships**
Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- No other relationships/conditions/circumstances that present a potential conflict of interest.
- Yes, the following relationships/conditions/circumstances are present:

I receive 25% salary support for my work for the Consortium, but this is from work performed for 10 companies, not just the two listed which have projects related to benzodiazepines.

Thank you for your assistance.