

SEIZURE AND CYCLES

Predictors of Ovulatory Failure in Women with Epilepsy

Morrell MJ, Giudice L, Flynn KL, Seale CG, Paulson AJ, Doñe S, Flaster E, Ferin M, Sauer MV

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Women with epilepsy (WWE) are at increased risk for reproductive disorders. This study was designed to evaluate whether WWE are more likely to have anovulatory cycles and to assess the relative association of the epilepsy syndrome category and antiepileptic drugs (AEDs) to ovulatory dysfunction. Subjects included women aged 18 to 40 years not receiving hormones. Women without epilepsy (23 controls) and women with localization-related epilepsy (LRE, $n = 59$) or idiopathic (primary) generalized epilepsy (IGE, $n = 35$) receiving either a cytochrome P450 enzyme (cP450)-inducing AED (carbamazepine, phenytoin, and phenobarbital), a cP450-inhibiting AED [valproate (VPA)], or an AED that does not alter cP450 enzymes (lamotrigine and gabapentin) in monotherapy for ≥ 6 months were followed up for three menstrual cycles. A transvaginal ovarian ultrasound was obtained. Endocrine and metabolic variables were measured and luteinizing hormone sampled over 8 hours on days 2 to 5 of one cycle. Anovulatory cycles occurred in 10.9% of cycles in controls, 14.3% of cycles with LRE, and 27.1% of cycles with IGE. Of women using VPA currently or within the preceding 3 years, 38.1% had at least one anovulatory cycle in contrast with 10.7% of women not using VPA within the preceding 3 years. Predictors of ovulatory failure included IGE syndrome, use of VPA currently or within 3 years, high free testosterone, and fewer numbers of luteinizing hormone pulses, but not polycystic-appearing ovaries. WWE are more likely to experience anovulatory menstrual cycles and the effects of epilepsy syndrome, and AED therapy may be additive. Women with IGE receiving VPA were at highest risk for anovulatory cycles, polycystic-appearing ovaries, elevated body mass index, and hyperandrogenism. WWE with anovulatory cycles may have no other signs of reproductive dysfunction. Therefore, clinicians must be alert to this potential complication of epilepsy.

COMMENTARY

This study by Morrell et al. is the most recent, and perhaps most comprehensive attempt to tease out the various factors that may contribute to hormonal dysfunction in women with epilepsy. The complexity of this issue derives from the fact that epilepsy syndrome, frequency of seizures, and antiepileptic drug (AED) therapy may all affect reproductive health. What makes matters even more complex is that prior as well as current AED therapy may be a factor in hormonal regulation in a given patient. In this study, current or prior valproic acid (VPA) use were both associated with a higher number of anovulatory cycles. Fifty-five percent of all cycles in this group were anovulatory. In addition, anovulatory cycles were associated with hormonal alterations including elevated total testosterone, lower levels of steroid hormone-binding globulin, and fewer numbers of luteinizing hormone (LH) pulses.

Dr. Morrell notes that a prior study done by her group, which enrolled a smaller number of patients with a relatively high seizure frequency and taking polytherapy, came up with an entirely different answer than the current study, which enrolled patients who were taking a single AED, and who for the most part had controlled seizures (1). The earlier study found that women with localization-related epilepsy of temporal origin had the highest number of anovulatory cycles. In contrast, the present study found that ovulatory failure is most common in individuals with idiopathic generalized epilepsy, and in those who currently were taking VPA or who had taken VPA within the preceding 3 years. The discrepancy between the two studies highlights how complicated these studies are, and how easy it is to arrive at an incorrect answer. Another example is that in this study, patients taking lamotrigine (LTG) appeared to have a slightly higher percentage of polycystic-appearing ovaries than did other groups. However, Dr. Morrell points out that 71% of the women receiving LTG used VPA within the past 3 years; therefore it was not possible to separate the residual effect of VPA from a current effect of LTG. That ovulatory dysfunction could potentially persist, even when AED therapy was changed, highlights how important it is to take reproductive health into account when prescribing medications.

This study points out two possible effects of epilepsy and AEDs on reproductive function. The first is the impact of epilepsy type and medication on ovarian function. The second is the impact of enzyme-inducing AEDs on the hormonal milieu. In women receiving phenytoin (PHT), a significant

decrease in estrone and dehydroepiandrosterone sulfate (DHEAS) occurred, accompanied by a significant increase in steroid hormone-binding globulin.

The present study stands out from similar studies performed previously, in that the sample size is large, prior medication history is taken into account, the patients are receiving monotherapy, and very careful hormonal evaluation was performed on every patient. Nonetheless, conflicting reports on the impact of epilepsy syndrome and AEDs on ovulatory function still are found. For example, a recent study in 50 women with epilepsy receiving monotherapy, polytherapy, and no AED found a high rate of reproductive endocrine disorder (32%), but failed to find a relation with either epilepsy syndrome or current AED use (3). In this study, prior AED use was not taken into account. Another way to reduce the variables that may affect this question is to investigate women taking VPA for conditions other than epilepsy. Early reports, which require further validation through more careful study, found a higher rate of menstrual abnormalities in women taking VPA for bipolar mood disorders, compared with those taking other medications (4). The definitive answer to the impact of AEDs on ovulation

and the hormonal milieu will not be resolved until reproductive health is measured in a randomized trial of various medications in patients with a predetermined epilepsy syndrome who are initiating medication for the first time. Such trials are often performed to obtain monotherapy approval for new AEDs (2). It is critical that such studies begin to include measures of reproductive health.

by Jaqueline A. French, M.D.

References

1. Cummings LN, Giudice L, Morrell MJ. Ovulatory function in epilepsy. *Epilepsia* 1995;36:355–359.
2. Perucca E, Tomson T. Monotherapy trials with the new antiepileptic drugs: study designs, practical relevance and ethical implications. *Epilepsy Res* 1999;33:247–262.
3. Bilo L, Meo R, Valentino R, Di Carlo C, Striano S, Nappi C. Characterization of reproductive endocrine disorders in women with epilepsy. *J Clin Endocrinol Metab* 2001;86:2950–2956.
4. O'Donovan C, Kusumakar V, Graves GR, Bird DC. Menstrual abnormalities and polycystic ovary syndrome in women taking valproate for bipolar mood disorder. *J Clin Psychiatry* 2002;63:322–330.