

## WOMEN WITH EPILEPSY: CAN THE TREATMENT BE WORSE THAN THE DISEASE?

### Long-term Reproductive Endocrine Health in Young Women with Epilepsy During Puberty

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**OBJECTIVE:** To evaluate the outcome of epilepsy and later reproductive endocrine health in girls who had epilepsy during puberty, by using a population-based controlled study.

**METHODS:** Sixty-nine (88%) patients and 51 (94%) control subjects of previously identified cohorts of 78 girls with epilepsy and 54 healthy control girls participated in this study (initial age, 8–18.5 years, at follow-up, 12.5–25.8 years). Thirty-five of the patients were initially taking valproate (VPA), 17, carbamazepine, and 17, oxcarbazepine as monotherapy. Most of the patients (61%) were off medication. All the subjects were examined clinically; the medical and menstrual histories were obtained; ovarian ultrasonography was examined; and serum reproductive hormone concentrations were analyzed.

**RESULTS:** No significant differences were found in laboratory or clinical findings between the patients off medication and the control subjects. Postpubertal patients taking

medication had higher serum testosterone (1.9 nmol/L; SD, 0.7 nmol/L) and androstenedione (18.8 nmol/L; SD, 15.2 nmol/L) levels than patients off medication (1.4 nmol/L; SD, 0.5 nmol/L; and 9.5 nmol/L; SD, 2.6 nmol/L) or control subjects (1.4 nmol/L; SD, 0.5 nmol/L; and 10.2 nmol/L; SD, 3.2 nmol/L; all comparisons,  $P < 0.02$ ). All patients still taking VPA had elevated serum androstenedione levels. Polycystic ovary syndrome was more common in patients on medication (38%; in 63% on VPA, in 25% on other medication) than in patients off medication (6%) or in controls (11%) ( $P = 0.005$ ).

**CONCLUSIONS:** Epilepsy during pubertal maturation does not affect reproductive endocrine health in female subjects who discontinue the medication before adulthood. However, an increased prevalence of endocrine disorders is detected if the patients remain on antiepileptic drugs, especially VPA, until adulthood.

### COMMENTARY

When planning any pharmacotherapy for seizure disorders, clinicians must consider those antiepileptic drugs (AEDs) that are likely to render the patient seizure free with the least number of adverse events. In the case of women with epilepsy, careful attention must be paid to the impact that AEDs may have on reproductive endocrine disorders, for both the short and the long term. This point is clearly illustrated in the article by Mikkonen and colleagues. The most common reproductive endocrine disorders in women with epilepsy include polycystic ovarian syndrome (PCOS), hypothalamic amenorrhea, premature menopause, and hyperprolactinemia (1).

Reproductive endocrine disturbances are not only the expression of an iatrogenic effect but also may result from a direct impact of the epileptic disorder on endocrine control centers in the brain, particularly the hypothalamic–pituitary axis (1,2). For example, Herzog and colleagues associated partial seizures of left temporal origin with the development of PCOS in women

with epilepsy (3), while Morrell and colleagues identified primary generalized epilepsy as a risk factor for ovulatory failure (4). The prevalence of PCOS in women with epilepsy is higher than that of the general population, even for women not being administered AEDs (3).

Iatrogenic effects of AEDs on reproductive endocrine functions may be mediated through abnormal hormonal secretion by peripheral endocrine glands—by altering the protein binding and metabolism of sex hormones or by causing weight gain that can result in insulin resistance (1–4). The clinician, therefore, must assume that an additive effect exists between endogenous (i.e., epilepsy-related) and iatrogenic risk factors. Clearly, before the start of pharmacotherapy, the clinician's challenge resides in identifying any endogenous or genetic predisposition to developing a reproductive endocrine disorder and in making a careful assessment of which AEDs might be likely to facilitate their occurrence. Cautious selection of an AED is particularly relevant in the case of PCOS, as the condition can eventually

result in serious long-term medical complications, including type II diabetes mellitus, infertility, endometrial cancer, and mood disorders (5,6).

A review of the literature of PCOS in women with epilepsy illustrates the complex interaction between endogenous and iatrogenic factors leading to the development of this disorder. Between 4% and 6% of women in the general population have PCOS. Yet Herzog and colleagues found a prevalence rate of 20% among 50 women with epilepsy, the majority of whom were not taking any AED (3). This rate was comparable to the 15% rate reported in the study of Mikkonen et al. As in the study by Mikkonen and colleagues, several other studies have identified valproic acid (VPA) as the AED more likely to be associated with the development of PCOS, with prevalence rates ranging from 11% to 60% (3,7–10). In contrast, the prevalence rates of PCOS among women with epilepsy taking AEDs other than VPA ranged from 6% to 15%, which are similar to the rates of women with epilepsy who are not being administered AEDs.

The mechanisms by which VPA causes reproductive endocrine disturbances continue to be the source of debate. Weight gain is one possible mechanism; it can result in insulin resistance that, in turn, leads to high insulin concentrations, which are known to stimulate ovarian androgen synthesis (5,6). Hyperandrogenism also has been identified in VPA-treated women who are lean, however. Increased serum testosterone and androstenedione were found during the first 3 months of therapy with VPA in 50% of women with new-onset epilepsy (11). No association was found between an increase of these sex hormones and weight gain. Finally, it is important to note that the increased risk of PCOS in women taking VPA was not restricted to those with epilepsy, but also was identified in women with bipolar disease (12).

Other AEDs also can have a negative impact on sex hormones. AEDs such as carbamazepine, phenytoin, or phenobarbital that induce hepatic enzymes decrease the free fraction (and hence the bioactivity) of estradiol by increasing serum levels of sex hormone-binding globulin (SHBG). Such changes can lead to menstrual disturbances (8). Theoretically, new AEDs without enzyme-inhibiting or -inducing properties (e.g., lamotrigine, levetiracetam, tiagabine, and gabapentin) should have minimal or no impact on reproductive endocrine functions. The data are still lacking, and controlled studies should be carried out to establish the lack of iatrogenic effects with respect to reproductive endocrine functions. For example, are new AEDs, such as gabapentin and pregabalin, that cause weight gain as likely to increase the risk of PCOS as are those that do not induce weight gain?

Should VPA be avoided in women with epilepsy of child-bearing age? It is reasonable to suggest that VPA should not be the first AED for consideration in this patient population.

Before it is prescribed, clinicians must carefully investigate the presence of any risk factors of PCOS, such as irregular menstrual cycles, increased body mass index, evidence of hyperandrogenism, diabetes mellitus, and a family history of PCOS. In addition, women should be asked to keep careful diaries of their menstrual cycles and monitor any weight changes. Serial measurement of serum androstenedione and testosterone as well as ultrasonography studies of the ovaries are usually not performed in women with epilepsy taking VPA, but they should be considered in women at higher risk. Fortunately, the impact of VPA on reproductive endocrine disorders appears to be reversible. In a 1-year follow-up study of women with epilepsy and a reproductive endocrine disorder that had been attributed to VPA, replacement of VPA by other non-enzyme-inducing AEDs, such as lamotrigine, has been found to lead to the normalization of endocrine functions (13). The study of Mikkonen et al. demonstrated that discontinuation of VPA before adulthood reduces the prevalence rates of reproductive endocrine disorders to that of controls. However, the final decision to discontinue VPA will have to be weighed against the risk of worsening of seizures.

*by Andres M Kanner, Ph.D.*

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