Epilepsia, **42**(12):1584–1589, 2001
Blackwell Science, Inc.

Premature Ovarian Failure in Women with Epilepsy

Pavel Klein, Adriana Serje, and John C. Pezzullo

Department of Neurology, Georgetown University Hospital, Washington, D.C., U.S.A.

Summary: *Purpose:* Women with epilepsy (WWE) have an increased risk for several reproductive endocrine disorders that may affect their fertility. The incidence of premature ovarian failure (POF) in women with epilepsy has not been systematically studied. This study examined the incidence of POF in women with epilepsy.

Methods: Fifty consecutively evaluated cognitively normal women with epilepsy, aged 38–64 years, whose seizures began before age 41 years, were interviewed for symptoms of perimenopause and menopause. Endocrine studies, performed in women aged 45 years or younger at the time of evaluation, included serum follicle-stimulating hormone (FSH; done on menstrual cycle day 3 in menstruating women), inhibin A levels when FSH was normal, thyroid-stimulating hormone (TSH), prolactin, and, in menstruating women, menstrual cycle day 20 serum progesterone level. Nonsurgical premature menopause was defined as secondary amenorrhea of >12 months' duration with FSH levels of >14 International Units (IU) in women younger than 42 years. Premature perimenopause was defined by the presence of one or more of the following: somatic perimenopausal symptoms; change in previously regular menstrual cycles without evidence of other reproductive endocrine disturbance; and FSH level of >14 IU or inhibin A level of <7 pg/ml. Similarly aged neurologically normal women seen in the menopause and sleep clinics served as control subjects. Statistical analysis included Fisher's exact test, Kruskal–Wallis test, *t* test, and multivariate logistic regression analysis with significance set at $p < 0.05$.

Results: Seven (14%) of 50 women with epilepsy had nonsurgical premature perimenopause (six of seven) or menopause (one of seven), compared with three of 82 control ($p = 0.042$). Five of 41 women with localization-related epilepsy (LRE) had POF compared with two of nine women with primary generalized epilepsy (PGE; $p = 0.595$). Mean age of POF was 39.6 years (range, 37–42 years). Seizure duration, age at seizure onset, seizure severity and lateralization, smoking history, age of menarche, body mass index and incidence of depression was not statistically different between women with and without POF. There was no statistically significant association between POF and antiepileptic drugs (AEDs). Women with POF were more likely to have had catamenial exacerbation of their seizures than were women without POF ($p = 0.02$).

Conclusions: Women with epilepsy have an increased risk for developing POF. This finding should be considered in counseling women with epilepsy on family planning. **Key Words:** Epilepsy—Seizures—Menopause—Premature ovarian failure.

Women with epilepsy (WWE) have an increased risk for several reproductive endocrine disorders. About 35% of menstrual cycles of WWE are anovulatory (1). Women with temporal lobe epilepsy (TLE) have an ~20% risk of developing polycystic ovarian syndrome and 15% risk of developing hypothalamic hypogonadism, compared with 5% and 1.5% risk for the two respective conditions in the general population (2). These conditions may contribute to reduced fertility and birth rate among women with epilepsy, which are ~70% of the expected (3). Premature menopause or perimenopause (premature ovarian failure, POF) is another reproductive endocrine cause of infertility.

Revision accepted September 19, 2001.

Address correspondence and reprint requests to Dr. P. Klein at Georgetown University Hospital, Department of Neurology, 1st Floor Bles, 3800 Reservoir Road NW, Washington, DC 20007, U.S.A. E-mail: kleinp2@gunet.georgetown.edu

The average age of natural menopause in U.S. women is 50.5 years (4). POF has been defined variably as natural menopause or perimenopause that occurs before age 40–45 years. It affects 1% of women by age 40 years (5). The incidence of POF in WWE has not been systematically studied. In one previous study, two (4%) of 50 women with TLE had POF (2), but this group included women aged 20–40 years, and many of them were in their twenties or early thirties, before the age of onset of POF in the general population. In addition, four (8%) women in that series had low serum estradiol levels without hypothalamic hypogonadism to indicate declining ovarian function (2). In another study of menstrual irregularities in women with epilepsy, four of a group of 238 women aged 18–45 years had menopause before age 40 years (6).

This study set out to examine the incidence of POF in women with epilepsy in a more age-appropriate population group.

METHODS

Of 124 cognitively normal women with epilepsy evaluated consecutively at Georgetown University Medical Center between April 1999 and November 2000, 50 women aged 38–64 years whose seizures began before age 41 years were interviewed for symptoms of perimenopause and menopause. The age of 41 years was chosen to exclude women with later seizure onset. It was thought that seizures beginning after that age would start too close to the natural end of reproductive life to influence it. None of the women had a history of radiation, chemotherapy, or structural hypothalamic or pituitary disease. All patients had a complete history taken and physical examination performed. Endocrine studies, performed in women aged 45 years or younger at the time of evaluation, included serum follicle-stimulating hormone (FSH; done on menstrual cycle day 3 in menstruating women) and inhibin A levels when FSH was normal. Serum thyroid-stimulating hormone (TSH), prolactin, and a.m. cortisol levels, complete blood count (CBC), and fasting glucose were measured to evaluate other possible endocrine causes of menstrual irregularities and to screen for autoimmune disorders associated with POF, such as thyroiditis, B_{12} deficiency, and diabetes mellitus. In menstruating women, menstrual cycle day 20 serum progesterone was checked to determine the ovulatory (>6 ng/ml) versus anovulatory nature of menstrual cycles. Endocrine studies were not performed on women older than 45 years because after that age, perimenopausal changes would be expected in the general population. Nonsurgical premature menopause was defined as secondary amenorrhea of >12 months duration with FSH level of >14 International Units (IU) in women younger than 42 years. Premature perimenopause was defined by the presence of one or more of the following: somatic perimenopausal symptoms (hot flashes, paroxysmal sweating, otherwise unexplained change of libido, vaginal dryness, yeast infections, and facial hirsutism); change in previously regular menstrual cycles (shorter than 26, longer than 35 days) without evidence of other reproductive endocrine disturbance; and FSH level of >14 IU or inhibin A level of <7 pg/ml.

Similarly aged neurologically normal women (age range, 41–63 years) seen in the menopause and sleep clinics served as control subjects. Eighty-three women were evaluated, 82 of whom were included in the study. One woman was excluded because linguistic difficulties precluded obtaining an accurate history. Of the control women, 25 were seen in the sleep clinic (14 with perimenopausal insomnia, four with obstructive sleep apnea, five with narcolepsy, one with unexplained excessive daytime somnolence, one with restless leg syndrome). Fifty-seven women were referred from the menopause clinic for evaluation of possible neuroendocrine causes of perimenopausal headache (42), perimenopausal depression and/or anxiety (eight), chronic fatigue syndrome (three), subjective unexplained cognitive impairment (two), unexplained paraesthesieae (one), and of stroke risk factors associated with planned hormone replacement therapy (one). All women were interviewed by one of us (P.K.), with the same reproductive history taken of all subjects in both epilepsy and control groups. Women younger than 45 years with a history suggestive of perimenopause or menopause underwent the same laboratory testing as women with epilepsy. Women with hysterectomy were included in the control group analysis, similar to the epilepsy group.

Presence of other reproductive endocrine abnormalities was evaluated by history. Catamenial exacerbation of seizures ("catamenial epilepsy") was evaluated by subjective history in patients who were menopausal at the time of initial evaluation (18 of 50: 15 medical, three surgical menopause), and who had fewer than one seizure per month. In the remaining patients (19 of 50), the presence of catamenial epilepsy was determined with 3 months of prospective seizure diaries and a single midluteal serum progesterone level, in accordance with previously published criteria for catamenial epilepsy (7).

Statistical analysis included Fisher's exact test, Kruskal–Wallis test, *t* test, and multivariate logistic regression analysis with significance set at $p < 0.05$.

RESULTS

Forty-one of 50 women had localization-related epilepsy (LRE), and nine of 50, primary generalized epilepsy (PGE). Seven (14%) of 50 WWE had premature perimenopause (six of seven) or menopause (one of seven), compared with three of 82 control (Fisher's exact test, two-sided; $p = 0.042$; Fig. 1). Five of 41 women with LRE had premature perimenopause or menopause, compared with two of nine women with PGE ($p = 0.595$). Mean age at premature menopause and perimenopause was 39.6 years (range, 37–42 years). Four (8%) of 50 WWE had had hysterectomy (two each with LRE and PGE), three of four with oophorectomy. Their ages at the time of hysterectomy and reasons for hysterectomy were 48 years (uncertain, fibroids?), 41 years (endometriosis), 38 years (uncertain, ectopic pregnancy?), and 34 years (endometriosis).

Eighteen of 50 patients were menopausal at the time of the initial evaluation (15 medical menopause, including two with premature menopause, three with surgical menopause). Mean age at menopause for the whole group of WWE could not be determined because not all women included in the study had reached menopause at the time of the study.

In addition, one of the entire population of 124 WWE had hypergonadatropic amenorrhea secondary to prema-

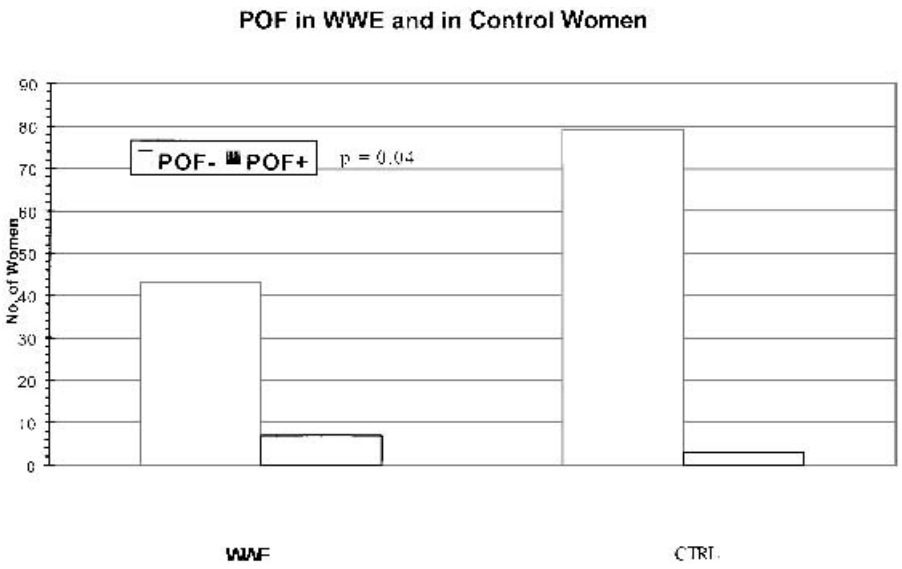

FIG. 1. Premature perimenopause and menopause in women with epilepsy and control women.

ture ovarian failure at the age of 18 years. This patient was 29 years old at the time of evaluation. Because her age was outside of the chosen age range for the population studied, she was excluded from the statistical analyses. However, the details of her clinical and laboratory findings are included in the table of clinical characteristics of women with POF (Table 1).

None of the women with POF had any other endocrine abnormalities. They all had normal prolactin and a.m. cortisol levels. One woman had an upper range of normal TSH value of 4.6 with normal remaining thyroid function tests while taking carbamazepine (CBZ); repeated TSH without CBZ was 2.4.

Among the control group, in addition to the three women with unexplained POF, one woman had POF with a history of chemotherapy, and another woman had premature Depo-provera–induced amenorrhea as part of treatment for endometriosis. Endocrine workup of the three women with POF was unremarkable. Thirteen of 82 of the control women had hysterectomy compared with four of 50 of WWE (χ^2 $p = 0.299$), including eight women with hysterectomy performed after the age of 45 years. Hysterectomy indications included fibroids (seven), endometriosis (three), ectopic pregnancy (one), cervical carcinoma (one), and cervical carcinoma in situ (one).

Five of seven women with POF had TLE, three left-sided, one right-sided, and one bitemporal. Two of five women with LRE and POF had posttraumatic epilepsy, whereas three of five had cryptogenic epilepsy (Table 1). Seizure duration, age at seizure onset, seizure severity, and body mass index (BMI) did not differ between WWE with and without POF (Kruskal–Wallis, $p = 0.717$, 0.746, 0.286, and 0.787, respectively; Table 2). Smoking history and incidence of depression likewise did not differ significantly between the two groups (Fisher's exact test, $p = 0.370$ and 0.231, respectively; Table 2).

Delayed menarche (at 17 years) was observed in one patient with POF. However, the mean age at menarche was not significantly different between WWE and POF and WWE without POF (13.38 vs. 12.56; *t* test, $p = 0.207$; Table 2).

Two of seven women with POF had a history of other reproductive endocrine disorders, infertility in both cases, compared with nine of 34 women without POF (Fisher's exact test, $p = 1.000$).

Five of seven women with POF had a history of catamenial exacerbation of seizures, significantly more than the ten of 43 women without POF ($p = 0.020$). In one of seven of women with POF, the catamenial seizure exacerbation began only during the perimenopausal transition.

There was no association between POF and antiepileptic drugs (AEDs). Five of seven women with POF in this series were receiving CBZ at the time of evaluation, and six of seven women had received CBZ at some point during their epilepsy. Of the other common AEDs, five of seven women had had exposure to barbiturates in the past (three at the time of evaluation), four to phenytoin (PHT; three in the past, one at the time of evaluation), three to valproic acid (VPA; two at the time of evaluation, one in the past) and two to lamotrigine (LTG), both at the time of evaluation. Possibly because of the small sample, there was no significant association between treatment with any of the AEDs at the time of evaluation of the AEDs and POF using multiple stepwise regression analysis. Information on past AED treatments and on duration of exposure to different AEDs for the whole group studied was not sufficient to evaluate the effect of

TABLE 1. *Characteristics of women with epilepsy with and without POF*

	Patients with POF (n = 7)	Patients without POF (n = 43)	Significance
Age at seizure onset (yr)	16 ± 2.3[a]	18.8 ± 1.7[a]	NS[b]
Seizure duration (yr)	26.6 ± 2.7[a]	25.2 ± 1.8[a]	NS[b]
Seizure frequency (mo)	2.5 ± 1.4[a]	5 ± 2.9[a]	NS[b]
Body mass index	25 ± 5.5[a]	24.7 ± 5.3[a]	NS[c]
Age at menarche (yr)	13.4 ± 0.71[a]	12.6 ± 0.28[a]	NS[c]
Depression	1/7	15/43	0.406 (NS)[d]
Smoking	2/7	7/43	NS[d]
Other reproductive abnormalities	2/7	31/43	NS[d]
Catamenial seizure exacerbation	5/7	10/43	0.020[d]

POF, premature ovarian failure.
[a] Values expressed as mean ± SEM.
[b] Kruskal–Wallis test.
[c] *t* Test.
[d] Fisher's exact test.

past treatments and duration of treatment with different AEDs on POF.

DISCUSSION

These results show that WWE have an increased risk of developing POF compared with the control population. There was no difference between LRE and PGE.

Menopause occurs at an average age of 50 years (4) as a result of depletion of ovarian follicles. In premature ovarian failure, amenorrhea or anovulation with sex steroid deficiency and elevated gonadotropins occurs early. Declining follicular function results in reduced ovarian estrogen, progesterone, and inhibin production and in elevated serum gonadotropin [i.e., FSH and luteinizing hormone (LH)] concentrations. POF affects 1% of the female population before age 40 years (5,8). In the present study, the risk of nonsurgical POF in WWE was 14%, with 42 years as the defined age of POF. Four (8%) of 50 women in the present series became symptomatic by age 40 years. We included in the analysis women who had had hysterectomy, to estimate the incidence of nonsurgical POF in all women with epilepsy. Three of the women with hysterectomy underwent the procedure before age 42 years. If these women were excluded, the incidence of POF in our population would be 15%.

This study does not answer possible pathophysiologic mechanism(s) of POF in WWE. There was no association between POF and smoking, reduced body mass index, or treated depression, three factors that have been associated with advancement of the age of menopause (9,10). The women with POF had no other endocrinopathy to explain their menstrual irregularities.

POF may result from several different mechanisms. In POF, the ovaries become depleted of ova early. Premature exhaustion of ova may result from a reduced initial pool of ova, for instance in Turner syndrome, or from accelerated oocyte loss after viral infections such as mumps oophoritis, chemotherapy, or radiation. POF also

TABLE 2. *Epilepsy features and reproductive endocrine features of women with epilepsy and POF*

Patient age (yr)	M/PM	Symptom onset (yr)	Sz type	Sz duration	Sz locus	Sz cause	Refractory Szs	AEDs (past)	Age at menarche	Catamenial szs	Other reprod prob	BMI	FSH[b]	Inhi[c]	E2	Prog[d]
62	M	38	Cp/gtc	26	LT	Cryptogenic	+	CBZ, PM	13	+	–	26	–	–	–	–
42	PM	41	Cp/gtc	32	RT	Cryptogenic	+	CBZ, LM (DPH Tiag, Gabap)	12	–	–	34	6.2	–	52	3.1
29[a]	M	18	Cp/gtc	1	RT	Cryptogenic (prematurity)	+	CBZ, VPA	14	–	–	40	56.3	–	<10	–
42	PM	40	Sp/Cp	22	LT	Trauma	+	CBZ, PB (DPH, VPA, TPM, Tiag)	17	+	Infertility, Endometriosis	20	7.3	1.9	?	21
45	PM	41	Cp/gtc	20	BT	Trauma	+	OCBZ, LVT (DPH, PB, CBZ)	14	–	–	25	62	–	52	0.6
44	PM	42	Cp/gtc	17	LT	Cryptogenic	–	CBZ	14	+	Infertility	20	6	<7	<15	–
50	PM	37	GTC	22	Gen	PGE	–	VPA, DPH, CBZ, Mebaral	10	+	–	21	–	–	–	–
39	PM	38	GTC	32	Gen	PGE	–	LM (VPA, PB, Ethosux)	13	–	–	20	18	–	34	2.5

[a] Excluded from statistical analysis of results because of age.
[b] Normal premenopausal value, <15 IU.
[c] Normal premenopausal values, >7.8 U/L.
[d] Normal luteal premenopausal values, >50 pg/ml.
[e] Normal midluteal premenopausal value, >6 ng/ml.
CBZ, carbamazepine; VPA, valproic acid; TPM, topiramate; PB, phenobarbital; OCBZ, oxcarbazepine; LM, lamotrigine; DPH, phenytoin; LVT, levetiracetam; PM, primidone (mysoline).

may result from premature ovarian follicular dysfunction. Autoimmune oophoritis, either cellularly or humorally mediated, is the commonest form of such dysfunction (8). It is associated with other autoimmune diseases, most notably endocrine diseases such as Hashimoto thyroiditis, Grave disease, insulin-dependent diabetes mellitus and Addison disease (11), but also with nonendocrine autoimmune diseases such as pernicious anemia and myesthenia gravis (12–14). None of the women with POF in this series had clinical or biochemical evidence for any of these conditions as a possible cause of the POF, although we did not check for autoantibodies.

Oocyte atresia may be accelerated by chronic excessive gonadotropic stimulation of follicular growth (13,15). Follicular growth is dependent on the pulsatile secretion by the pituitary of FSH and LH, which, in turn, is coupled to the pulsatile secretion of the gonadotropin-releasing hormone (GnRH) in the basomedial hypothalamus, chiefly, in primates, in the arcuate nucleus. Pulsatile secretion of LH has been found to be altered in patients with both generalized epilepsy (16) and with LRE (17–19). Women with PGE have increased LH pulsatile frequency (19). Among women with LRE, women with left-sided TLE focus may have increased LH pulse frequency, whereas women with right-sided TLE may have reduced LH pulse frequency (17,18). It has been suggested that this may be due to alteration of amygdaloid input to the hypothalamic GnRh-containing neurons by temporolimbic interictal or ictal epileptiform discharges. Recently, interictal temporolimbic epileptiform discharges have been shown to acutely disrupt pulsatile LH release (20). In patients with epilepsy and POF, it is possible that chronically increased LH and FSH pulse frequency could result in an increase in ovarian stimulation, recruitment of oocytes into immature follicles, and follicular atresia, leading to premature depletion of follicles and premature menopause.

AEDs have been implicated in the pathophysiology of reproductive endocrine disorders in WWE. Valproic acid has been associated with increased incidence of polycystic ovarian syndrome in WWE (6). Hepatic enzyme-inducing AEDs such as CBZ, PHT, and barbiturates may cause hyposexuality in men and women with epilepsy (21). Possibly because of the small sample studied, we did not find a statistically significant association between treatment with different AEDs at the time of evaluation and POF. Because we had incomplete information on past treatments for women without POF and duration of treatment with different AEDs for the whole group, we could not draw any conclusions about possible relations between past AED treatments and POF or duration of treatment with different AEDs and POF. Thus we cannot rule out the possibility that our finding of increased incidence of POF among WWE could be due to AED treatment instead of, or in addition to, epilepsy itself.

POF was not associated with increased risk of other reproductive endocrine disorders. Women with POF were more likely to have had catamenial exacerbation of seizures. This suggests that women with catamenial seizure exacerbation may be more susceptible to develop POF than are women without catamenial seizure exacerbation. It also suggests an increased sensitivity of temporolimbic epileptiform tissue to gonadal hormonal effects among these women.

Biochemical confirmation of the diagnosis of POF includes the finding of low serum estrogen levels and elevated FSH. However, normal FSH levels may occur in POF (11), as was the case in three of five of the women tested in our study. Declining ovarian function is initially reflected in reduced luteal secretion of progesterone and inhibin A, a dipeptide secreted by the ovary during the luteal phase that inhibits FSH secretion by the pituitary. When secretion of progesterone, estrogen, and inhibin is low, their inhibitory influence on the hypothalamus and pituitary is removed, and the serum level of FSH increases. The reduced levels of inhibin A in two of five of our patients indicated failing endocrine function of the ovaries despite normal FSH levels.

The increased risk of POF has important consequences for clinical management of WWE. It should be considered when advising WWE about family planning during the later stages of their reproductive lives. Women with reduced fertility because of POF may need an increased level of emotional support. In addition, women with POF sustain a sex steroid hormone deficiency for longer than do naturally menopausal women. They have an almost twofold age-specific increase in mortality rate (8). In particular, they have higher risk for osteoporosis and cardiovascular disease. They therefore require careful evaluation of these risks, and of possible hormone replacement therapy and other steps aimed at preventing osteoporosis and cardiovascular disease.

In conclusion, this study shows that women with epilepsy have an increased risk for developing premature ovarian failure. This finding should be considered in counseling WWE about family planning and in clinical management of WWE.

Acknowledgment: We thank Theresa Ingram, Epilepsy Unit Coordinator, Georgetown University Hospital, for her expert technical assistance in the preparation of this article.

REFERENCES

1. Cummings LN, Giudice L, Morrell MJ. Ovulatory function in epilepsy. *Epilepsia* 1995;36:355–60.
2. Herzog AG, Seibel MM, Schomer DL, et al. Reproductive endocrine disorders in women with partial seizures of temporal lobe origin. *Arch Neurol* 1986;43:341–6.
3. Dansky LV, Andermann E, Anderman F. Marriage and fertility in epileptic patients. *Epilepsia* 1980;21:261–71.

4. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. *Maturitas* 1992;14:103–15.
5. Coulam CB, Adamson SC, Annergers JF. Incidence of premature ovarian failure. *Obstet Gynecol* 1986;67:604–6.
6. Isojarvi JIT, Laatikainen TJ, Pakarinen AJ, et al. Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. *N Engl J Med* 1993;329:1383–9.
7. Herzog AG, Klein P, Ransil BJ. Three patterns of catamenial epilepsy. *Epilepsia* 1997;38:1082–8.
8. Kalantaridou SN, Davis SR, Nelson LM. Premature ovarian failure. *Endocrinol Metab Clin North Am* 1998;27:989–1004.
9. Speroff L, Glass RH, Kase NG. *Clinical gynecologic endocrinology and infertility.* 5th ed. Baltimore: Williams & Wilkins, 1994: 583–651.
10. Harlow BL, Cramer DW, Annis KM. Association of medically treated depression and age of natural menopause. *Am J Epidemiol* 1995;80:30–6.
11. Wheatcroft N, Weetman AP. Is premature ovarian failure an autoimmune disease? *Autoimmunity* 1997;25:157–65.
12. Rebar RW, Erickson GF, Yen SSC. Idiopathic premature ovarian failure: clinical and endocrine characteristics. *Fertil Steril* 1982; 37:35–41.
13. Rebar RW, Connolly HV. Clinical features of young women with hypergonadotropic amenorrhoea. *Fertil Steril* 1990;53:804–10.
14. Moncayo J, Moncayo R, Benz R, et al. Ovarian failure and autoimmunity. *J Clin Invest* 1990;84:1857–62.
15. Richardson SJ, Senikas V, Nelson JF. Follicular depletion during the menopausal transition: evidence for accelerated loss and ultimate exhaustion. *J Clin Endocrinol Metab* 1987;65:1231–6.
16. Bilo L, Meo R, Valentino R, et al. Abnormal patterns of luteinizing hormone pulsatility in women with epilepsy. *Fertil Steril* 1991;55: 705–11.
17. Drislane FW, Coleman AE, Schomer DL, et al. Altered pulsatile secretion of luteinizing hormone in women with epilepsy. *Neurology* 1994;44:306–10.
18. Herzog AG, Coleman AE, Jacobs AR, et al. Menstrual disorders, reproductive endocrine dysfunction and interictal discharge frequency in women with temporolimbic epilepsy. *Neurology* 1999; 52(suppl 2):A24.
19. Morrell MJ, Sauer M, Guidice L, et al. Pituitary gonadotropin function in women with epilepsy. *Epilepsia* 2000;41(suppl 7):247.
20. Herzog AG, Coleman AE, Jacobs AR, et al. Acute hypothalamopituitary dysfunction following interictal unilateral temporal epileptiform discharges in women with epilepsy. *Epilepsia* 2000;41(suppl 7):167.
21. Herzog AG. Hormonal changes in epilepsy. *Epilepsia* 1995;36: 323–6.