Menstrual cycle and ovary alterations in women with epilepsy on antiepileptic therapy

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ABSTRACT. Impaired reproductive function is thought to frequently affect women with epilepsy, mainly when seizures originate in the temporal lobe. In this study, we evaluated menstrual cycle features and assessed ovulation by determining luteal progesterone (Pg) levels in 101 consecutive women with epilepsy (36 with idiopathic generalized epilepsy -IGE; 65 with partial epilepsy -PE), aged between 16 and 50 years, treated with various antiepileptic drugs (AED). PE originated in the temporal lobe (TLE) in 40 subjects, in the frontal lobe in 13, in the parietal lobe in 2, while the origin of focal seizures remained undetermined in 10 patients. In all patients, menstrual and reproductive history, body mass index, hair distribution and hormonal pattern were assessed. Suprapubic ovary ultrasound (US) examination was carried out in 83 patients (28 with IGE, 55 with PE). Three patients with IGE and one with PE were amenorrheic. Oligomenorrhea occurred in 16 patients, polymenorrhea in 2. Changes in menstrual cyclicity were independent from epilepsy type (19.4% in IGE; 23.1% in PE) and from origin of focal discharges (22.5% of patients with TLE; 20.0% with origin in other brain areas). Luteal Pg levels remained below 2 ng/ml in 30 patients independently of epilepsy type. Corpus luteum dysfunction was combined with hyperandrogenism in 15 of these patients. In the other cases different alterations of hypothalamus-pituitary-ovary axis were observed. Valproic acid blunted luteal Pg surge more frequently than other AED. Polycystic ovaries (PCO) were observed in 14 (16.9%) patients (21.0% with IGE; 14.5% with PE). These prevalences are not higher than those reported in the general population. Among PE patients, PCO was found in 1 case with undertemined focal origin and in 7 TLE cases, who also had ovary volume significantly larger than patients with seizures originating from the frontal or parietal lobe. Epileptic women exhibited an increased occurrence of multifollicular ovaries (MFO) found in 12 cases (14.4% *vs* 5% in the general population). However, no defined hormonal or clinical pictures were associated with this US alteration in most patients. These findings reappraise the impact of ovary alterations in women mainly affected by mild to moderate epilepsy, on differing AED regimens, with the exception of more frequent ovulatory dysfunction and PCO occurrence in patients taking VPA. (J. Endocrinol. Invest. *20:* 519-526, 1997)

INTRODUCTION

Both seizures themselves and anti-epileptic drugs (AED) may influence endocrine function and reproduction. Generalized and complex partial seizures (1), as well as interictal epileptiform discharges (2, 3) have all been found to affect the hypothalamus-pituitary system. Changes in hypothalamic control of gonadotropin secretion have also been disclosed in normally-menstruated drug-free epileptic patients (3-5). Moreover, most AED interfere with neurotransmission involved in pituitary regulation and modify sex steroid secretion, peripheral conversion and carrier-protein binding (6).

An appraisal of the occurrence of ovary dysfunction in treated epileptic women remains as yet undefined, despite the increased prevalence of men-

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strual disturbances, hyperandrogenism and polycystic ovary syndrome (PCOS) observed in women on valproic acid treatment (7).
This study was aimed at investigating the prevalence of alterations of menstrual cycle, ovary dysfunction and changes in gonadal structure in women with epilepsy on different AED regimens.

SUBJECTS, MATERIALS AND METHODS

One-hundred and one consecutive women with idiopathic generalized epilepsy (IGE) or partial epilepsy (PE) were recruited from 187 outpatients aged between 15 and 50 years observed from March to December 1993 at the Epilepsy Centre, Department of Neurology, University of Pavia, Italy. The following exclusion criteria were adopted: epileptic syndromes differing from IGE or PE; previous ovariectomy or hysterectomy; recent (under 1 year) or ongoing pregnancy and lactation; estroprogestin and other hormonal medications (insulin included); administration of drugs interfering with the pituitary-gonadal axis, except for AED. Their age ranged from 16 to 50 years (mean age±SD, 28.4±7.9). In conformity with the Declaration of Helsinki, informed written consent was obtained from all subjects.
In accordance with the Criteria on Classification and Terminology of the International League Against Epilepsy (8), IGE was diagnosed in 36 patients and PE in 65 (cryptogenic in 45 cases; remote symptomatic in 20). The origin of localization-related seizures was identified in the temporal lobe in 40 cases (TLE) or in other brain cortex areas (not-TLE) (frontal lobe, 13 cases; parietal lobe, 2 cases). It remained undetermined in 10 patients.
Disease severity was scored by evaluating seizure frequency during the six months preceding the study according to the following scale: 1- absent (n=47); 2- sporadic =< one/monthly (n=20); 3-=< four/monthly (n=27); 4- >1/weekly (n=3); 5- >1/daily (n=4).
Nineteen patients were on monotherapy with phenobarbital -PB (50-175 mg day), 20 with carbamazepine- CBZ (400-1400 mg day), 11 with valproic acid- VPA (400-2000 mg day), 3 with phenytoin- PHT (175-450 mg day) and 1 with primidone-PRM (1125 mg day). Antiepileptic therapy with two of the above mentioned AED or ethosuximide (ESM) was being administered to 35 patients, while 12 were taking three drugs. Mean ± SD serum drug levels (µg/dl), assayed by routine fluorescence polarization immunoassay systems, were 25.4 ± 9.1 for PB; 7.1 ± 2.0 for CBZ, 13.3 ± 7.3 for PHT; 62.7 ± 23.0 for VPA; 17.3 ± 10.7 for PRM; 41.0 ± 19.6 for ESM.
Mean ± SD body weight was 60.5±11.7 kg (range: 44-103 kg). Body mass index (BMI) was calculated by the formula: kg body weight / (height in m)^2. Seven patients were obese (BMI>30), 17 overweight (BMI 25-29.9) and 9 under normal weight for females (BMI<19).
Amenorrhea was diagnosed when no menses had occurred over the last six months or more, oligomenorrhea when menstrual interval steadily exceeded 35 days, and polymenorrhea if it was shorter than 21 days.
Androgen-dependent hair (ADH) distribution and density were quantified according to Ferriman and Gallwey (9). We defined hyperandrogenism as a condition characterized by testosterone (T) and/or Δ4-Androstenedione (Δ4A) serum levels above the normal range for our laboratory (1 ng/ml for T; 2.7 ng/ml for Δ4A) in both ovarian phases, along with ADH score >4.
Since many patients declined transvaginal ultrasonography (US), morphology and size of ovaries were assessed in 83 women (28 with IGE, 55 with PE) between the 7th and 10th day of menstrual cycle by transabdominal suprapubic US using a 3.5 MHz probe. Polycystic ovaries (PCO) were diagnosed when at least 10 cysts, with diameter between 2 and 8 mm, either arranged peripherally around a dense stromal core or scattered throughout the ovary, were observed on a plane with increased amount of stroma (10). Multifollicular ovary (MFO) was distinguished from PCO by the presence of ovary cystes without increased stroma (11). Ovary volume (V) was calculated from longitudinal (a), transverse (b), and anteroposterior (c) US diameters by the formula for ellipse: V= 0.5233 x a x b x c (12).
Hormonal evaluation was performed between the 7th-10th and the 20th-23rd day of one ovarian cycle in menstruating women and twice at 14 days' interval in amenorrheic patients. Three blood samples were drawn from an arm vein every 15 min between 8:00 and 9:30, after overnight fasting. Blood was centrifuged and sera obtained in each subject were pooled and maintained at 20 C until assayed in duplicate. Sex steroid peripheral patterns, SHBG, LH, FSH and PRL serum levels were determined by currently available RIA or IRMA methods by reagents purchased from DPC (Los Angeles, CA) for E2 and Pg; from RADIM (Pomezia, Italy) for T; from Amersham (Arlington Heights, IL) for Δ4A; from Farmos Group Ltd. (Oulunsalo, Finland) for SHBG; from Ares Serono (Milan, Italy) for LH, FSH, and PRL.
SAS Statistic package was used throughout for data analysis. SAS 6.04 Univariate process was used for descriptive statistics of data and to evaluate their skewness and distribution. Data are reported as mean±SD values except for disease severity,

Table 1 - *Clinical data, body mass index (BMI), androgen-dependent hirsutism score (ADH) and ultrasonographic ovary, volume in 101 women with epilepsy, evaluated as an all or divided according to IGE or PE diagnosis and to seizure origin in the temporal lobe (TLE) and in the frontal or parietal lobes (not-TLE). Data are expressed as mean±SD values, except for disease severity reported as median and QI-Q3.*

	Age (yrs)	Menarche (yrs)	Onset (yr)	Disease Duration (yr)	Severity	BMI	ADH	Ovary volume (ml)
All patients (n=101)	28.4 ±7.9	12.4 ±1.4	13.5 ±7.1	14.9 ±8.7	2.0 1-3	24.1 ±4.1	3.3 ±3.7	10.0 (n=83) ±4.6
IGE (n=36)	25.4a ±6.6	12.6 ±1.3	12.2 ±4.9	13.1 ±8.6	1.0 c 1-2	23.2 ±3.7	3.4 ±3.4	10.1 (n=28) ±4.9
PE (n 65)	30.0a ±8.2	12.3 ±1.4	14.5 ±8.4	16.1 ±9.0	2.0c 1-3	23.4 ±4.3	3.3 ±3.9	9.9 (n=55) ±4.5
TI.E (n=40)	31.4 b ±8.5	12.3 ±10	14.5 ±9.1	17.1 ±9.3	2.0 1-3	22.2 ±3.0	4.0 ±4.5	11.3d (n=31) ±4.9
not-TLE (n=15)	26.9 b ±6.8	12.1 ±2.0	13.9 ±6.7	13.9 ±8.0	2.0 1-2	24.7 ±5.1	2.5 ±2.7	7.4d (n=14) ±2.8

a) p=0.0023; b) p=0.0466; c) p=0.0057 (after stratification for age p=0.1416 and =0.0364 between younger and older patients, respectively); d) p=0.0018

represented by median, 25% and 75% quartiles (Q1-Q3) because of their non-parametric distribution.

Because of the scant number of subjects in some subgroups, inter-group distribution of findings was evaluated by Fisher's exact test (2-tail).

Statistical differences between multiple groups showing parametric distribution of data were analyzed by multiple criteria analysis of variance (SAS General Linear Model Procedure- GLM).

Student's t test for impaired data or Kruskal-Wallis's test for nonparametric distribution were adopted to evaluate differences between groups.

Common relative risk of having PCO in epilepsy subgroups was estimated by the Cochran-Mantel-Haenszel statistics (Frequency Procedure FREQ).

RESULTS

Clinical features of patients are summarized in Table 1. Women with PE were significantly older and exhibited more frequent seizures than those with IGE (Table 1).

Age at epilepsy onset was directly correlated with that of menarche (r= 0.368; p<0.05). However, the distribution of menstrual alterations (p=0.920; Fisher's exact test), luteal Pg levels <2 ng/ml (p=0.353), and US ovary changes (p=0.787) was not different in patients with seizures that began before or after menarche.

Features of menstrual cycle

Menstrual cyclicity was altered in 22 patients (21.8%) (secondary amenorrhea in 4 cases, oligomenorrhea in 16, polymenorrhea in 2). Seven women with menstrual irregularities had IGE (19.4%) and 15 PE (23.1%) (Table 2). Nine patients with TLE (22.5%) and 3 with not-TLE (20.0%) presented menstrual disorders (p=0.705; Fisher's exact test).

Amenorrhea was ascribed to PCO syndrome (PCOS) in 2 subjects, to PRL-secreting microadenoma combined with PCO in one case and to hypergonadotropic hypogonadism, diagnosed as premature ovarian failure, in a 38-year-old woman.

Assessment of luteal function

Luteal Pg levels were higher than 4 ng/ml and consistent with normal ovulation in 63 patients, between 2-4 ng/ml in 8, and <2 ng/ml in 30, independently of epilepsy type (p=0.275; Fisher's exact test) or origin of focal seizures in defined brain areas (p=1.000; Fisher's exact test). In 3 of these patients, LH surge higher than 30 mIU/ml suggested a later occurrence of the gonadotropin ovulatory peak.

Fifteen patients with luteal deficiency had hyperandrogenic anovulation and evidence of PCO was obtained in 6 out of 13 cases submitted to US examination. VPA was administered to 12 patients (80%) of this group. Hypogonadotropic hypoestrogenism with MFO was observed in one case, and primary hypogonadism in 2 other anovulatory patients. In 9 subjects on PB and/or CBZ treatment, luteal insufficiency occurred without evidence of basal hormonal changes.

The prevalence of impaired luteal Pg surge in patients on VPA monotherapy was statistically greater than in those on other monotherapy (p=0.0432; Fisher's exact test). No statistical difference occurred between polytherapies including or not VPA (p=1.000; Fisher's exact test) (Table 3).

Table 2 - *Prevalence of changes in menstrual pattern, clinical, biometric, and ultrasonographic findings in epileptic women with altered or normal menstrual cycles. Data are expressed as absolute and percent prevalence or as mean±SD values, except for disease severity reported as median values and Q1-Q3.*

	N° of cases	Age (yr)	Disease onset (yrs)	Epilepsy type IGE	Epilepsy type PE	Severity (score)	BMI	ADH	US finding PCO	US finding MFO	US finding NORM
Amenorrhea	4 (4.0%)	26.5 ±7.9	12.2 ±6 2	3 8.3%	1 1.5%	1 1-1.5	25.2 ±9.5	5.2 ±6.0	3 75%	-	1 25%
Oligo-or Polymenorrhea	18 (17.8%)	27.5 ±8.8	13.3 ±6.8	4 11.1%	14 21.6%	1 1-3	23.3 ±4.9	3.7 ±3.6	3 21.4%	1 7.1%	10 71.4%
Normal	79 (78.2%)	28.7 ±7.9	13.7 ±7.6	29 80.6%	50 76.9%	2 1-3	23.3 ±3.5	3.1 ±3.4	8 12.3%	11 16.9%	46 70.1%
p=		0.642	0.848	0.106		0.2544	0.667	0.7391		0.0583	

Table 3 - *Age, prevalence of menstrual cycle disturbances, mid-luteal Pg levels, and US findings, BMI and hirsutism scores (ADH) in women with epilepsy treated with single AED or with polytherapy including VPA (+ VPA) or not (- VPA). Data are expressed as absolute or percent prevalence or as mean±SD values, except for ADH score reported as median and Q1-Q3.*

Drugs	Age (yr)	Menstrual Cycle Amen.	Oligo/Poly.	Norm	Luteal Pg (ng/ml) <2	2-4	>4	US Findings PCO	MFO	NORM	BMI	ADH
Monotherapy												
PB (n=19)	28.2 ±6.5	-	1 5.3%	18 94.7%	5 26.3%	1 5.3%	13 68.4%	2 12.5%	2 12.5%	12 75.0%	23.3 ±4.0	2.5 2.9
CBZ (n=20)	28.6 ±8.0	-	4 20.0%	16 80.0%	3 15.0%	2 10.0%	15 75.0%	3 21.4%	4 28.6%	7 50.0%	22.5 ±3.4	3.3 4.2
VPA (n=11)	22.9 ±7.2	-	2 18.0%	9 82.0%	7 63.6%	-	4 36.4%	-	2 20.0%	8 80.0%	26.0 ±5.3	3.1 3.1
Polytherapy												
+VPA (n=16)	25.8 ±7.0	3 19.0%	3 19 0%	10 62.0%	6 37.5%	1 6.3%	9 56.2%	6 40.0%	2 13.0%	7 47.0%	22.5 ±3.4	4.1 4.4
-VPA (n=31)	29.9 ±7.4	1 3.5%	6 20.5%	22 76.0%	9 31.0%	4 13.8%	16 55.2%	3 13.0%	2 8.0%	19 79.0%	24.0 ±4.3	3.8 41

US findings

PCO was observed in 14 cases (16.9%) and MFO in 12 (14.4%) out of 83 patients. Age in women with PCO or MFO was significantly lower than in those with normal gonads (F=6.32; p=0.002). Patients with PCO presented both higher ADH scores (F=4.65; p=0.012) and greater ovary volume (F=9.45; p=0.001) (Table 4).

The distribution of ovary US alterations in IGE and PE patients was not significantly different (p=0.683; Fisher's exact test). PCO was found in 7 out of 31 women with TLE (right hemisphere localization in 3 cases, left hemisphere in 1, undefined side in 3), in 1 with undetermined focal origin and in none of the 14 cases with not-TLE. Patients with TLE showed significantly larger ovary volume than those with not-TLE (Table 1). Relative risk of presenting PCO in IGE and PE was 1.02 (confidence limit 95%= 0.86-1.67), while in TLE *vs* not-TLE it was 1.52 (confidence limit 95%= 0.97-2.41).

Loss or irregularities of menstrual cycles were found in 6 patients with PCO (42.8%), in 11 with normal ovaries (19.3%), and in 1 with MFO (8.3%). No patients with PCO exhibited a full-blown clinical picture of PCOS (anovulation in 8 cases, hirsutism and hyperandrogenism in 5, obesity in 3, increased LH levels in 6). Among patients with US imaging of MFO, only one case had anovulation and oligomenorrhea. Besides, BMI and ovary volume were not different as compared to those in patients with normal gonads (Table 4).

PCO was found in 40% of patients on AED polytherapy including VPA, while MFO occurred in 33.3% of cases on CBZ monotherapy (Table 3).

DISCUSSION

Despite the alleged relevance of reproductive and endocrine dysfunctions in epilepsy (13, 14), evidence for this hypothesis remains as yet scantly supported. In this study we evaluated a large group of women with IGE or PE consecutively observed as outpatients and treated with various AED. Only a minority of patients (7%) had more than one

seizure/weekly, while 66.3% of them had sporadic crises or were free from seizures.

Age of our cases with PE was higher than that of patients with IGE. Later disease onset, commonly observed for some PE cases, may justify this difference.

Time of menarche of our epileptic patients was normal and consistent with that observed in our country. The significant relationship we found between menarche and epilepsy onset emphasized the possible role of unbalanced estrogen/progestin ratio in influencing neuronal excitability in pubertal patients (13, 14). However, seizure onset before or after menarche did not modify biometric parameters and ovary function.

Alterations of menstrual cycle occurred in 21.8% of our patients, without significant differences between IGE and PE cases. In this study, we decided not to compare data obtained in epileptic women with healthy controls because we think that the selection of a "normal" group in itself may influence the prevalence of menstrual irregularities or of other changes in ovary function. On the other hand, menstrual irregularities in the general population largely depend on the selection of studied groups along with spontaneous variations in ovary cycle throughout the fertile age, besides ethnic and geographic influences. Up to 20% of apparently healthy women can be expected to have cycle irregularities (10, 15-17) so that menstrual disturbances seem to be only slightly more frequent in treated epilepsy than in the normal population. However, the occurrence of menstrual cyclicity alterations we found in our patients was equal to that found in 257 unselected healthy volunteers recruited among the staff of an English hospital (amenorrhea 4%; menstrual irregularities 18%) (18).

The prevalence of menstrual changes we found was quite similar to that observed by Isojärvi et al. (7) in 238 epileptic women (20%), without differences related to the epilepsy type (21% in IGE and in secondarily generalized PE; 18% in PE) and slightly higher than that observed in the healthy women considered as the control group (20% *vs* 16%).

Higher occurrences of menstrual irregularities have been reported only in a small group of patients with IGE (30%) (19) or in Egyptian epileptic women with psychosexual dysfunctions, long duration of disease and poor seizure control (amenorrhea 16%; hypomenorrhea, oligomenorrhea, polymenorrhea 33% as a whole), but not in those with normal sexuality (20).

Although we realize that integrated data on body temperature, changes in decidual smears, US monitoring of follicular development and repeated blood Pg assays are needed to carefully assess ovulation and to diagnose corpus luteum insufficiency (21), the large number of subjects we studied induced us to infer information on luteal function by a single-day determination of serum Pg in the luteal phase. Steroid levels higher than 4 ng/ml during mid-luteal phase were thought to be consistent with ovulation and formation of corpus luteum and those lower than 2 ng/ml with anovulation (22).

In normally menstruated healthy women, 10 to 25% of ovarian cycles are believed to be anovulatory (22). Luteal Pg levels did not significantly increase and remained lower than 2 ng/ml in 29.7% of our patients (although three of the latter possibly showed a delayed ovulation). This finding agrees with previous data reporting a higher than average number of anovulatory cycles in epilepsy (23).

We did not find significant differences between anovulation occurrence in PE or IGE. Cramer and Jones (13) describe 19% of anovulatory cycles in PE and 30% in IGE. Opposite results have recently been reported by Cummings et al. (24), who documented anovulation in 6 out of 17 TLE women and in none of their 7 patients with IGE.

Table 4 - *Prevalence of ultrasound alterations, clinical, biometric, and luteal Pg levels in 83 women with epilepsy showing Polycystic Ovaries (PCO), Multifollicular Ovaries (MFO) or normal gonads (NOR). Data are expressed as absolute and percent prevalences and mean±SD values, except for disease severity reported as median and Q1-Q3.*

	Age (yr)	onset (yr)	Disease duration (yr)	severity	IGE	PE	BMI	luteal Pg (ng/ml)	ADH	Ovary volume ml
PCO (n=14)	24.6 ±3.7	12.2 ±5.2	12.4 ±5.8	1.5 (1-3)	6 21.0%	8 14.5%	22.7 ±2.7	3.7 ±4.7	5.9 ±5.3	14.3 ±4.1
MFO (n=12)	22.3 ±4.5	12.3 ±6.2	10.0 ±6.7	2.0 (1-3)	4 14.0%	8 14.5%	24.7 ±5.4	6.9 ±4.1	2.8 ±2.9	8.2 ±2.4
NORM (n=57)	29.7 ±8.9	14.3 ±8.3	15.4 ±10.0	2.0 (1-3)	18 64.0%	39 71.0%	23.4 ±4.3	6.5 ±4.9	2.7 ±2.8	8.7 ±4.6
p=	0.002	0.506	0.109	0.652	0.683		0.432	0.1178	0.010	0.001

Seizures may affect gonadotropin secretion by interfering with limbic cortex and amygdala regulation of hypothalamic centres involved in pituitary regulation (3-5, 25-27). However, only one patient with luteal dysfunction exhibited hypogonadotropic ovarian failure. No significant alteration in basal hormonal set-up was found in about one third of cases with luteal failure taking PB and/or CBZ. These findings suggest that in these patients deranged control of ovary function might be consistent with changes in gonadotropin pulsatility (3-5). Altered follicle maturation and impaired ovulation are associated with morphological ovary changes and in most cases we ascribed luteal failure to hyperandrogenic chronic anovulation, a functional condition often combined with PCO (28).

PCO prevalence in our patients (16.7%) is not higher than that reported in non-epileptic women, who up to 23% meet the US criteria for PCO (10, 28, 29). We found US PCO in 3 out of 4 amenorrheic patients. PCO prevalence was 38.0% in patients with low luteal Pg levels and 21.4% in patients with changes of their menstrual cycles. Epileptic women with PCO have significantly increased ovary volume due to stromal hypertrophy and higher hirsutism scores, but increased androgen levels were observed only in 53% of cases with PCO. On the other hand, 12.3% of patients with normal menses showed PCO at US examination. In any case, only uncomplete PCOS was identified in our patients as previously reported in both epileptic (7) and non-epileptic population (28, 30, 31).

In our patients, changes of ovary function were related neither to clinical parameters (disease onset, duration, severity) nor to the type of epilepsy. Pharmacological effects on ovary regulation must be considered, as recently inferred (7, 27). VPA affected ovary function more frequently than other AED. A GABA-mediated interference of VPA on noradrenergic regulation of LHRH secretion, gonadotropin pulsatility and ovulatory surge can be supposed (32, 33). Our data agree with previous observations indicating a higher incidence of amenorrhea (34), PCO and hyperandrogenism during VPA treatment (7), possibly mediated by body weight gain, high fasting serum insulin concentrations and decreased serum Insulin-like Growth Factor-binding protein 1 levels (35).

We observed an increased prevalence of US MFO. This condition averages 5% in the normal population (11). However, in our epileptic patients MFO ovary appearance did not combine with a defined clinical picture. In fact, only one patient with ovary cystes without stromal hyperplasia fitted into the clinical and hormonal picture of MFO (11). It also remains uncertain whether this condition is to be considered as a preliminary step of PCO or as an independent disease assimilable to hypothalamic amenorrhea.

Impaired feedback mechanisms due to AED-induced increase of SHBG levels or spontaneously enhanced frequency of LH pulsatility observed in untreated epileptic women (4, 5) may chronically stimulate the ovary and induce gonadal changes.

It is commonly accepted that both treated and drug-free patients with TLE present menstrual irregularities, sexual dysfunction, anovulation, PCOS and hypogonadotropic hypogonadism more frequently than other epileptic subjects (25-27, 36).

We did not confirm that changes in menstrual cycle or luteal function occur more frequently in PE than in IGE. Other factors (disease severity, drug regimens, patient selection) might have influenced some findings on PE in the literature. Patients with TLE, however, showed a higher prevalence and a slightly increased risk of PCO than those with seizures originating in the frontal or parietal lobe. In these patients, we did not confirm the possible relationships between laterality of seizure origin in brain cortex and PCO or hypogonadotropic hypogonadism, as previously suggested (37).

In conclusion, an anamnestic examination of ovary cyclicity in epileptic outpatients mostly affected by mild to moderate disease or free from seizures did not prove increased prevalence of alteration of menses when compared with data from the general population. However, a deeper investigation disclosed a high frequency of anovulation due to different endocrine dysfunctions largely connected to VPA administration. Ultrasonographic PCO prevalence and its clinical features were quite similar to those observed in non-epileptic women. Our patients showed a higher incidence of MFO, but this seems to be merely a US feature rather than a definite clinical condition.

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